2.7.4.4.1.1.2 DME

主な安全性項目を，以下の内因性要因の部分集団別（2.7.4.1.1.3.11）に解析した。

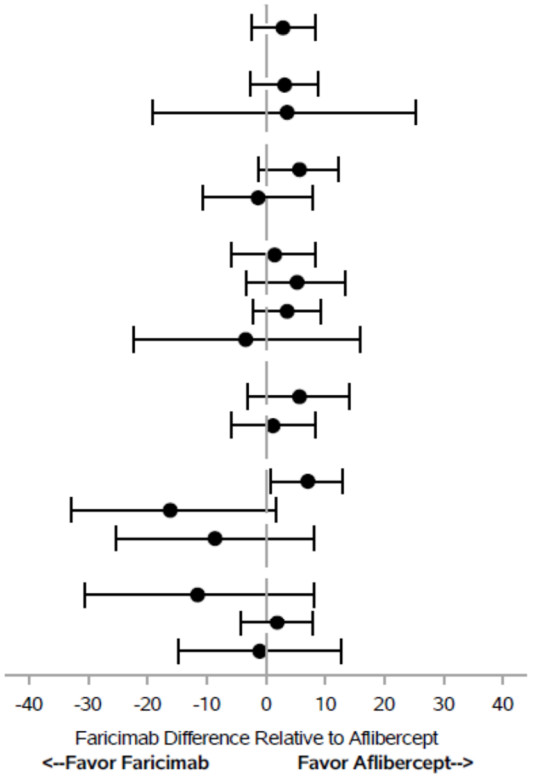
- ベースライン時の DR 重症度（53 以下及び 53 超）
- ベースライン時の HbA1c（8%以下及び 8%超）
- 年齢（65 歳未満及び 65 歳以上，並びに 75 歳未満及び 75 歳以上）
- 性別（女性及び男性）
- 人種（白人，アジア人及びその他）
- 既往歴（腎疾患，心疾患及び血管疾患）

全般的に，56週時までに試験眼に発現した有害事象，眼以外に発現した有害事象，重篤な有害事象及び試験眼に発現した AESI の発現頻度における各本剤群とアフリベルセプト Q8W 群の違いは，部分集団間（ベースライン時の DR 重症度，ベースライン時の HbA1c，年齢，性別，人種，既往歴）で一貫しており，全体の各本剤群とアフリベルセプト Q8W 群の発現頻度と一致していた。

部分集団解析は，フォレストプロットにより56週時までに試験眼に発現した有害事象（図 2.7.4.4.1.1.2-1及び図 2.7.4.4.1.1.2-2），56週時までに眼以外に発現した有害事象（5.3.5.3-nAMD-1 g_ae_sub_forest_NOCUL_AC_W56_SE_DME_HLS 及び g_ae_sub_forest_NOCUL_BC_W56_SE_DME_HLS），56週時までに発現した重篤な有害事象（5.3.5.3-nAMD-1 g_ae_sub_forest_SER_AC_W56_SE_DME_HLS 及び g_ae_sub_forest_SER_BC_W56_SE_DME_HLS），56週時までに試験眼に発現した AESI（図 2.7.4.4.1.1.2-3及び図 2.7.4.4.1.1.2-4）の発現頻度について示した。

図 2.7.4.4.1.1.2-1　56週時までに試験眼に発現した有害事象の部分集団別フォレストプロット—本剤 Q8W 群及びアフリベルセプト Q8W 群（DME 統合）

	Faricimab 6 mg Q8W n/m	%	Aflibercept 2 mg Q8W n/m	%	Difference (95% CI)
Overall	235/630	37.3%	215/625	34.4%	2.9 (-2.5, 8.3)
Baseline DR severity					
<=53	211/578	36.5%	190/568	33.5%	3.1 (-2.6, 8.7)
>53	18/42	42.9%	15/38	39.5%	3.4 (-19.2, 25.4)
Baseline HbA1c					
<=8%	161/417	38.6%	132/399	33.1%	5.5 (-1.2, 12.2)
>8%	74/210	35.2%	81/221	36.7%	-1.4 (-10.7, 7.9)
Age					
<65	132/363	36.4%	127/362	35.1%	1.3 (-5.9, 8.4)
>=65	103/267	38.6%	88/263	33.5%	5.1 (-3.3, 13.4)
<75	216/578	37.4%	193/570	33.9%	3.5 (-2.1, 9.1)
>=75	19/52	36.5%	22/55	40.0%	-3.5 (-22.3, 15.8)
Gender					
Female	100/251	39.8%	90/262	34.4%	5.5 (-3.1, 14.0)
Male	135/379	35.6%	125/363	34.4%	1.2 (-5.9, 8.2)
Race					
White	194/489	39.7%	165/504	32.7%	6.9 (0.8, 13.0)
Asian	17/65	26.2%	25/59	42.4%	-16.2 (-32.9, 1.6)
Other	24/76	31.6%	25/62	40.3%	-8.7 (-25.3, 8.1)
Medical History					
Renal Disease	26/66	39.4%	23/45	51.1%	-11.7 (-30.6, 8.1)
Cardiac Disease	188/513	36.6%	173/497	34.8%	1.8 (-4.2, 7.9)
Vascular Disease	28/91	30.8%	31/97	32.0%	-1.2 (-14.9, 12.7)

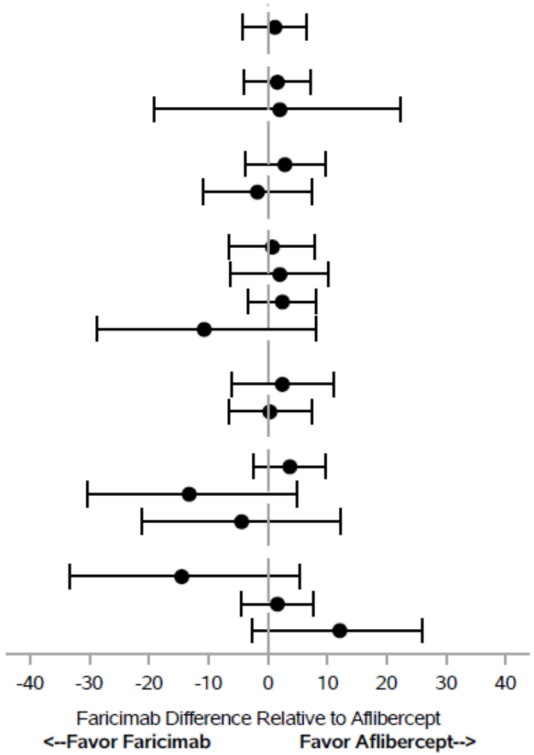


DR = Diabetic Retinopathy; HbA1c = Hemoglobin A1c; n = Number of patients with at least one ocular AE; m = Number of patients in the subgroup. Includes events with onset up to Day 405 (last day of Week 56 analysis visit window). Newcombe with continuity correction method is used for the difference and 95% CI. The bars represent 95% CI.

[5.3.5.3-nAMD-1 g_ae_sub_forest_SOCUL_AC_W56_SE_DME_HLS を改変]

図 2.7.4.4.1.1.2-2　56週時までに試験眼に発現した有害事象の部分集団別フォレストプロット—本剤 PTI 群及びアフリベルセプト Q8W 群（DME 統合）

	Faricimab 6 mg PTI n/m	%	Aflibercept 2 mg Q8W n/m	%	Difference (95% CI)
Overall	225/632	35.6%	215/625	34.4%	1.2 (-4.2, 6.6)
Baseline DR severity					
<=53	197/563	35.0%	190/568	33.5%	1.5 (-4.1, 7.2)
>53	24/58	41.4%	15/38	39.5%	1.9 (-19.3, 22.2)
Baseline HbA1c					
<=8%	145/403	36.0%	132/399	33.1%	2.9 (-3.9, 9.6)
>8%	77/221	34.8%	81/221	36.7%	-1.8 (-11.0, 7.4)
Age					
<65	126/352	35.8%	127/362	35.1%	0.7 (-6.5, 7.9)
>=65	99/280	35.4%	88/263	33.5%	1.9 (-6.3, 10.1)
<75	209/577	36.2%	193/570	33.9%	2.4 (-3.3, 8.0)
>=75	16/55	29.1%	22/55	40.0%	-10.9 (-28.8, 8.0)
Gender					
Female	87/236	36.9%	90/262	34.4%	2.5 (-6.1, 11.2)
Male	138/396	34.8%	125/363	34.4%	0.4 (-6.5, 7.3)
Race					
White	178/489	36.4%	165/504	32.7%	3.7 (-2.4, 9.7)
Asian	18/62	29.0%	25/59	42.4%	-13.3 (-30.4, 4.8)
Other	29/81	35.8%	25/62	40.3%	-4.5 (-21.2, 12.1)
Medical History					
Renal Disease	23/63	36.5%	23/45	51.1%	-14.6 (-33.5, 5.4)
Cardiac Disease	186/511	36.4%	173/497	34.8%	1.6 (-4.5, 7.6)
Vascular Disease	40/91	44.0%	31/97	32.0%	12.0 (-2.6, 26.0)

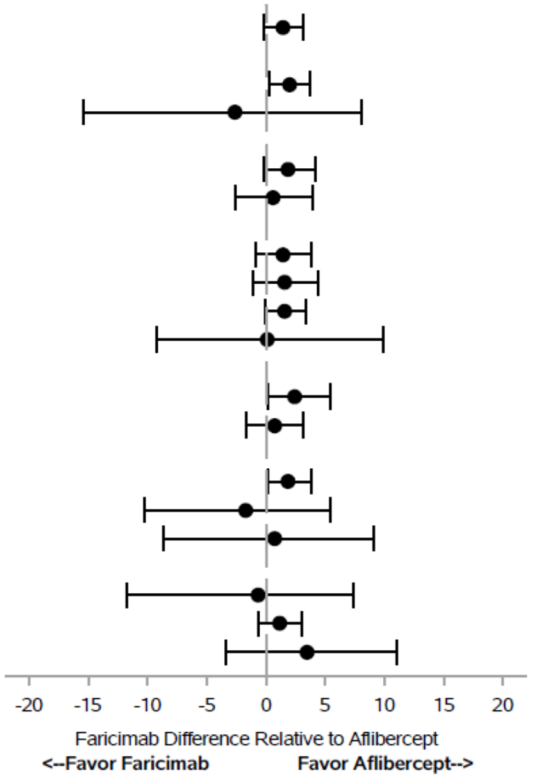


DR = Diabetic Retinopathy; HbA1c = Hemoglobin A1c; n = Number of patients with at least one ocular AE; m = Number of patients in the subgroup. PTI = Personalized Treatment Interval (from Q4W up to Q16W). Includes events with onset up to Day 405 (last day of Week 56 analysis visit window). Newcombe with continuity correction method is used for the difference and 95% CI. The bars represent 95% CI.

[5.3.5.3-nAMD-1 g_ae_sub_forest_SOCUL_BC_W56_SE_DME_HLS を改変]

図 2.7.4.4.1.1.2-3　56週時までに試験眼に発現した AESI の部分集団別フォレストプロット—本剤 Q8W 群及びアフリベルセプト Q8W 群（DME 統合）

	Faricimab 6 mg Q8W n/m	%	Aflibercept 2 mg Q8W n/m	%	Difference (95% CI)
Overall	15/630	2.4%	6/625	1.0%	1.4 (-0.2, 3.1)
Baseline DR severity					
<=53	15/578	2.6%	4/568	0.7%	1.9 (0.3, 3.7)
>53	0/42	0.0%	1/38	2.6%	-2.6 (-15.4, 8.1)
Baseline HbA1c					
<=8%	11/417	2.6%	3/399	0.8%	1.9 (-0.2, 4.1)
>8%	4/210	1.9%	3/221	1.4%	0.5 (-2.6, 3.9)
Age					
<65	9/363	2.5%	4/362	1.1%	1.4 (-0.9, 3.8)
>=65	6/267	2.2%	2/263	0.8%	1.5 (-1.1, 4.4)
<75	14/578	2.4%	5/570	0.9%	1.5 (-0.1, 3.3)
>=75	1/52	1.9%	1/55	1.8%	0.1 (-9.3, 9.9)
Gender					
Female	6/251	2.4%	0/262	0.0%	2.4 (0.1, 5.4)
Male	9/379	2.4%	6/363	1.7%	0.7 (-1.7, 3.2)
Race					
White	12/489	2.5%	3/504	0.6%	1.9 (0.2, 3.8)
Asian	0/65	0.0%	1/59	1.7%	-1.7 (-10.3, 5.4)
Other	3/76	3.9%	2/62	3.2%	0.7 (-8.7, 9.1)
Medical History					
Renal Disease	1/66	1.5%	1/45	2.2%	-0.7 (-11.8, 7.3)
Cardiac Disease	11/513	2.1%	5/497	1.0%	1.1 (-0.6, 3.0)
Vascular Disease	5/91	5.5%	2/97	2.1%	3.4 (-3.4, 11.1)

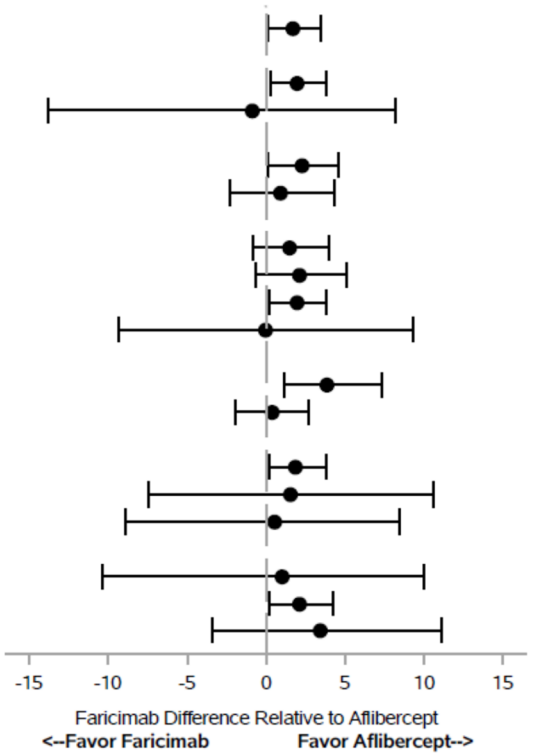


DR = Diabetic Retinopathy; HbA1c = Hemoglobin A1c; n = Number of patients with at least one ocular AE of special interest; m = Number of patients in the subgroup. Includes events with onset up to Day 405 (last day of Week 56 analysis visit window). Newcombe with continuity correction method is used for the difference and 95% CI. The bars represent 95% CI.

[5.3.5.3-nAMD-1 g_ae_sub_forest_SOCUL_AESI_AC_W56_SE_DME_HLS を改変]

図 2.7.4.4.1.1.2-4　56週時までに試験眼に発現した AESI の部分集団別フォレストプロット—本剤 PTI 群及びアフリベルセプト Q8W 群（DME 統合）

	Faricimab 6 mg PTI n/m	%	Aflibercept 2 mg Q8W n/m	%	Difference (95% CI)
Overall	17/632	2.7%	6/625	1.0%	1.7 (0.1, 3.5)
Baseline DR severity					
<=53	15/563	2.7%	4/568	0.7%	2.0 (0.3, 3.8)
>53	1/58	1.7%	1/38	2.6%	-0.9 (-13.8, 8.2)
Baseline HbA1c					
<=8%	12/403	3.0%	3/399	0.8%	2.2 (0.1, 4.6)
>8%	5/221	2.3%	3/221	1.4%	0.9 (-2.3, 4.3)
Age					
<65	9/352	2.6%	4/362	1.1%	1.5 (-0.8, 4.0)
>=65	8/280	2.9%	2/263	0.8%	2.1 (-0.6, 5.1)
<75	16/577	2.8%	5/570	0.9%	1.9 (0.2, 3.8)
>=75	1/55	1.8%	1/55	1.8%	0.0 (-9.3, 9.3)
Gender					
Female	9/236	3.8%	0/262	0.0%	3.8 (1.2, 7.4)
Male	8/396	2.0%	6/363	1.7%	0.4 (-2.0, 2.7)
Race					
White	12/489	2.5%	3/504	0.6%	1.9 (0.2, 3.8)
Asian	2/62	3.2%	1/59	1.7%	1.5 (-7.5, 10.6)
Other	3/81	3.7%	2/62	3.2%	0.5 (-8.9, 8.4)
Medical History					
Renal Disease	2/63	3.2%	1/45	2.2%	1.0 (-10.4, 10.0)
Cardiac Disease	16/511	3.1%	5/497	1.0%	2.1 (0.2, 4.2)
Vascular Disease	5/91	5.5%	2/97	2.1%	3.4 (-3.4, 11.1)



DR = Diabetic Retinopathy; HbA1c = Hemoglobin A1c; n = Number of patients with at least one ocular AE of special interest; m = Number of patients in the subgroup. PTI = Personalized Treatment Interval (from Q4W up to Q16W). Includes events with onset up to Day 405 (last day of Week 56 analysis visit window). Newcombe with continuity correction method is used for the difference and 95% CI. The bars represent 95% CI.

[5.3.5.3-nAMD-1 g_ae_sub_forest_SOCUL_AESI_BC_W56_SE_DME_HLS を改変]

2.7.4.4.1.2 ADA が安全性に及ぼす影響

nAMD 患者を対象とした第 III 相臨床試験では全体として10.4%の患者が，DME 患者を対象とした第 III 相臨床試験では全体として8.4%の患者が Treatment induced ADA 又は Treatment boosted ADA となった（2.7.2.3.11，5.3.5.3-nAMD-1 t_ada_base_IG_nAMD_HLS 及び t_ada_base_IG_DME_HLS）。

ADA 陽性の部分集団における重篤な有害事象の発現頻度は，nAMD 患者を対象とした第 III 相臨床試験の本剤群で10.7%，DME 患者を対象とした第 III 相臨床試験の本剤 Q8W 群で28.1%，本剤 PTI 群で26.8%であり，傾向は確認されなかった。ADA 陽性の部分集団における眼の有害事象のほとんどは，非重篤であり，治験薬との因果関係は否定され，30文字以上の持続的な視力低下や治験中止には至らなかった（5.3.5.3-nAMD-1 t_ae_oview_W48_ADAP_SE_nAMD_HLS, t_ae_oview_ADAP_W56_SE_DME_HLS）。

nAMD 患者を対象とした第 III 相臨床試験の本剤群で試験眼に眼内炎症を認めた患者13例（2.7.4.2.6.2.1）の内，12例で ADA の結果を入手し，眼内炎症の発現頻度は ADA 陽性患者で6.7%（5/75例），ADA 陰性患者で1.2%（7/582例）であった（表 2.7.4.4.1.2-1）。DME 患者を対象とした第 III 相臨床試験の本剤群で試験眼に眼内炎症を認めた患者17例（2.7.4.2.6.2.2）全例の ADA の結果を入手し，眼内炎症の発現頻度は ADA 陽性患者で9.7%（11/113例），ADA 陰性患者で0.5%（6/1130例）であった（表 2.7.4.4.1.2-2）。全体の約9割の患者が ADA 陰性であったものの，ADA 陽性患者における眼内炎症の発現頻度は，ADA 陰性患者に比べて高かった。

ADA による安全性への重要な影響はみられなかった。ADA 陽性患者における眼内炎症の発現頻度は ADA 陰性患者に比べて高い傾向が確認されたものの，ADA 陽性の発現頻度は低いこと，また，眼内炎症の発現頻度は低く，そのほとんどは重症度が軽度又は中等度で，回復したことから，現時点では臨床的関連性は低いと考えられた。ADA の安全性に対する影響は，引き続き注視していく。

表 2.7.4.4.1.2-1 ADA 有無別，眼内炎症の事象別発現頻度（nAMD 統合解析）

	ADA 陽性患者 N=75	ADA 陰性患者 N=582
Total patients with at least one AE	5 (6.7%)	7 (1.2%)
虹彩炎	2 (2.7%)	1 (0.2%)
ぶどう膜炎	1 (1.3%)	1 (0.2%)
虹彩毛様体炎	1 (1.3%)	2 (0.3%)
硝子体炎	1 (1.3%)	2 (0.3%)
脈絡網膜炎	0 (0.0%)	1 (0.2%)

[5.3.5.3-nAMD-1 t_ae_pt_SOCUL_IOI_W48_ADAP_SE_26OCT2020_40306, t_ae_pt_SOCUL_IOI_W48_ADAN_SE_26OCT2020_40306, t_ae_pt_SOCUL_IOI_W48_ADAP_SE_05OCT2020_40844，t_ae_pt_SOCUL_IOI_W48_ADAN_SE_05OCT2020_40844 を改変]

表 2.7.4.4.1.2-2 ADA 有無別，眼内炎症の事象別発現頻度（DME 統合解析）

	ADA 陽性患者 N=113	ADA 陰性患者 N=1130
Total patients with at least one AE	11 (9.7%)	6 (0.5%)
ぶどう膜炎	4 (3.5%)	2 (0.2%)
虹彩毛様体炎	3 (2.7%)	1 (0.1%)
虹彩炎	3 (2.7%)	2 (0.2%)
硝子体炎	3 (2.7%)	1 (0.1%)
前房の炎症	1 (0.9%)	0 (0.0%)
脈絡網膜炎	1 (0.9%)	0 (0.0%)
角膜後面沈着物	1 (0.9%)	0 (0.0%)
角膜ぶどう膜炎	1 (0.9%)	0 (0.0%)

[5.3.5.1-DME-2 t_ae_pt_SOCUL_IOI_ADAP_W56_SE_20OCT2020_40349, t_ae_pt_SOCUL_IOI_ADAN_W56_SE_20OCT2020_40349，5.3.5.1-DME-3 t_ae_pt_SOCUL_IOI_ADAP_W56_SE_19OCT2020_40398，t_ae_pt_SOCUL_IOI_ADAN_W56_SE_19OCT2020_40398 を改変]

nAMD 患者を対象とした第 III 相臨床試験の日本延長コホートを含む52週時までの ADA 有無別，眼内炎症の事象別発現頻度を表 2.7.4.4.1.2-3に示した。

表 2.7.4.4.1.2-3 52週時までの ADA 有無別，眼内炎症の事象別発現頻度（nAMD 統合解析－日本延長コホートを含む）

	ADA 陽性患者 N=84	ADA 陰性患者 N=613
Total patients with at least one AE	8 (9.5%)	7 (1.1%)
虹彩炎	3 (3.6%)	1 (0.2%)
ぶどう膜炎	3 (3.6%)	1 (0.2%)
虹彩毛様体炎	1 (1.2%)	2 (0.3%)
角膜後面沈着物	1 (1.2%)	0 (0.0%)
硝子体炎	1 (1.2%)	2 (0.3%)
脈絡網膜炎	0 (0.0%)	1 (0.2%)

[5.3.5.3-nAMD-3 t_ae_pt_SOCUL_IOI_W52_ADAP_SE_nAMD_JPN, t_ae_pt_SOCUL_IOI_W52_ADAN_SE_nAMD_JPN を改変]

nAMD 患者を対象とした第 III 相臨床試験の日本延長コホートを含む52週時までの ADA の発現状況を表 2.7.4.7-41に，ADA 陽性患者又は陰性患者における眼内炎症の Definition 2の集計を表 2.7.4.7-42及び表 2.7.4.7-43に示した。

DME 患者を対象とした第 III 相臨床試験の56週時までの ADA 陽性患者又は陰性患者における眼内炎症の Definition 2の集計を表 2.7.4.7-44及び表 2.7.4.7-45に示した。

2.7.4.4.1.3 日本部分集団

GR40306試験及び GR40349試験における日本部分集団の結果を示した。

2.7.4.4.1.3.1 nAMD（GR40306試験）

1) 患者背景

日本部分集団においてベースライン時の患者背景は投与群間で同様であった（表 2.7.4.4.1.3.1-1）。

ITT 集団の日本部分集団は計52例であり，本剤群及びアフリベルセプト群に各26例であった。

登録時の平均年齢は71.10歳（本剤群71.92歳，アフリベルセプト群70.27歳）であり，75歳未満の患者（59.6%）が半数以上であり，男性が4分の3（75.0%）を占めた。

表 2.7.4.4.1.3.1-1　人口統計学的特性の要約（nAMD，GR40306試験－日本部分集団）

Demographics in Japanese Subpopulation, Intent-to-Treat Population, Japan Subgroup
Protocol: GR40306
Clinical Cutoff Date: 26OCT2020

	Faricimab 6 mg (N=26)	Aflibercept 2 mg (N=26)	All Patients (N=52)
Region			
n	26	26	52
Asia	26 (100%)	26 (100%)	52 (100%)
Age (years)			
n	26	26	52
Mean (SD)	71.92 (8.03)	70.27 (9.81)	71.10 (8.92)
Median	72.50	70.50	71.50
Min - Max	50.0 - 91.0	53.0 - 88.0	50.0 - 91.0
Age group (years)			
n	26	26	52
<75	14 (53.8%)	17 (65.4%)	31 (59.6%)
>=75	12 (46.2%)	9 (34.6%)	21 (40.4%)
<65	4 (15.4%)	8 (30.8%)	12 (23.1%)
>=65 - <75	10 (38.5%)	9 (34.6%)	19 (36.5%)
>=75 - <85	11 (42.3%)	8 (30.8%)	19 (36.5%)
>=85	1 (3.8%)	1 (3.8%)	2 (3.8%)
SEX			
n	26	26	52
Male	22 (84.6%)	17 (65.4%)	39 (75.0%)
Female	4 (15.4%)	9 (34.6%)	13 (25.0%)

Age at randomization.

Program: root/clinical_studies/RO6867461/CDPT7716/GR40306/data_analysis/CTD_Tenaya/prod/program/t_dm.sas
Output: root/clinical_studies/RO6867461/CDPT7716/GR40306/data_analysis/CTD_Tenaya/prod/output/t_dm_IT_JP_amd.out
18FEB2021 16:43
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Demographics in Japanese Subpopulation, Intent-to-Treat Population, Japan Subgroup
Protocol: GR40306
Clinical Cutoff Date: 26OCT2020

	Faricimab 6 mg (N=26)	Aflibercept 2 mg (N=26)	All Patients (N=52)
Ethnicity			
n	26	26	52
Not Hispanic or Latino	26 (100%)	26 (100%)	52 (100%)
Race			
n	26	26	52
Asian	26 (100%)	26 (100%)	52 (100%)
Japanese	26 (100%)	26 (100%)	52 (100%)

Age at randomization.

Program: root/clinical_studies/RO6867461/CDPT7716/GR40306/data_analysis/CTD_Tenaya/prod/program/t_dm.sas
Output: root/clinical_studies/RO6867461/CDPT7716/GR40306/data_analysis/CTD_Tenaya/prod/output/t_dm_IT_JP_amd.out
18FEB2021 16:43
Page 2 of 2

[5.3.5.3-nAMD-1 t_dm_IT_JP_amd を再掲]

2)　治験薬の曝露状況

48週時までの投与期間の中央値はいずれの投与群においても48.1週であり（表 2.7.4.4.1.3.1-2），試験全体での投与期間と一致していた（2.7.4.1.1.4.1）。

表 2.7.4.4.1.3.1-2　48週時までの曝露状況（nAMD，GR40306試験－日本部分集団）

Summary of Study Treatment Exposure in the Study Eye through Week 48 in Japanese Subpopulation, Safety-Evaluable Population, Japan Subgroup
Protocol: GR40306
Clinical Cutoff Date: 26OCT2020

	Faricimab 6 mg (N=26)	Aflibercept 2 mg (N=26)
Treatment duration (weeks)		
n	26	26
Mean (SD)	44.6 (10.25)	48.2 (0.96)
Median	48.1	48.1
Min-max	4 - 49	44 - 49
Number of study drug administrations		
n	26	26
Mean (SD)	6.0 (1.04)	7.6 (0.75)
Median	6.0	8.0
Min-max	2 - 7	5 - 8
Dose interruption		
Number of doses interrupted	2	9
At least one interrupted dose	2 (7.7%)	4 (15.4%)
Intraocular inflammation	0	0
BCVA decrease	0	0
Elevated intraocular pressure	0	0
Rhegmatogenous retinal break	1 (3.8%)	0
Rhegmatogenous retinal detachment or macular hole	0	0
Active infection	1 (3.8%)	4 (15.4%)
Intraocular surgery in the study eye	0	0
On-study prohibited medications	0	0
Other	0	0
Interruptions per patient		
n	2	4
1	2 (7.7%)	3 (11.5%)
2	0	0
3	0	0
4	0	0
5	0	0
6	0	1 (3.8%)

BCVA = Best-corrected Visual Acuity.
Study drug corresponds to faricimab or aflibercept. Study treatment corresponds to faricimab, aflibercept or sham. Treatment duration is the (maximum of the date of the last dose of study treatment and the date of the last treatment dose hold) minus the date of the first dose plus one day.
Includes study treatment received and dose hold on or prior to Day 349 (last day of Week 48 analysis visit window). Percentages are based on N in the column headings. The number of study drug administrations may include any active drug administered including medication errors. The number of injections does not take into account the use of prohibited therapies.

Program: root/clinical_studies/RO6867461/CDPT7716/GR40306/data_analysis/CTD_Tenaya/prod/program/t_ex.sas
Output: root/clinical_studies/RO6867461/CDPT7716/GR40306/data_analysis/CTD_Tenaya/prod/output/t_ex_SE_JP_amd.out
16FEB2021 8:00　Page 1 of 1

[5.3.5.3-nAMD-1 t_ex_SE_JP_amd を再掲]

3)　安全性の結果

48週時までの結果を以下に記載する（表 2.7.4.4.1.3.1-3）。

- 有害事象の発現頻度は本剤群及びアフリベルセプト群でそれぞれ 73.1%（19/26 例）及び 69.2%（18/26 例）であり，投与群間で同様であった。
- 試験眼に発現した有害事象の発現頻度は本剤群及びアフリベルセプト群でそれぞれ 15.4%及び 34.6%であり，アフリベルセプト群に比べて本剤群で低かった。
- いずれかの群の 2 例以上で試験眼に発現した有害事象はドライアイであり，試験全体の結果（2.7.4.1.1.4.1）と大きな違いはなかった（表 2.7.4.4.1.3.1-4）。

- 試験眼に発現した副作用の発現頻度は本剤群及びアフリベルセプト群でそれぞれ 0.0%及び 3.8%であり，試験全体（それぞれ 2.7%及び 2.7%，表 2.7.4.1.1.4.1-1）と同様であった。
- いずれかの群の 2 例以上で試験眼に発現した副作用はなかった（表 2.7.4.4.1.3.1-5）。
- 非試験眼に発現した有害事象の発現頻度は本剤群及びアフリベルセプト群でそれぞれ 19.2%及び 23.1%であり，試験全体（22.8%及び 24.1%）と同様であった（表 2.7.4.4.1.3.1-6）。非試験眼に発現した有害事象はいずれも治験薬との因果関係は否定された（5.3.5.3-nAMD-1 t_ae_FOCUL_SREL_W48_SE_JP_amd）。
- 試験眼に発現した重症度が高度の有害事象は本剤群に認められず，アフリベルセプト群の 1 例（新生血管加齢黄斑変性）で認められた。新生血管加齢黄斑変性は治験薬との因果関係は否定された。
- 試験眼に発現した重篤な有害事象は本剤群に認められず，アフリベルセプト群の 1 例（新生血管加齢黄斑変性）で認められた。新生血管加齢黄斑変性の重症度は高度であった。
- 試験眼に発現した治験薬の投与中止に至った有害事象及び治験中止に至った有害事象はいずれの群にも認められなかった。
- 試験眼に発現した AESI は本剤群で認められず，アフリベルセプト群の 1 例（新生血管加齢黄斑変性）で認められた。新生血管加齢黄斑変性は永続的な失明を回避するために内科的/外科的介入が必要となった事象に該当した。1 時間を超える 30 文字以上の視力低下に至った AESI はいずれの群にも認められなかった。
- 眼以外に発現した有害事象の発現頻度は本剤群及びアフリベルセプト群でそれぞれ 69.2%及び 57.7%であり，本剤群では，アフリベルセプト群に比べて高く，試験全体（52.3%及び 51.8%）に比べて高かった。しかし，眼以外に発現した副作用は本剤群で認められず，アフリベルセプト群で 3.8%（1 例，高血圧）に認められた（表 2.7.4.4.1.3.1-8）。
- いずれかの群の 2 例以上で眼以外に発現した有害事象（本剤群及びアフリベルセプト群別）は，上咽頭炎［15.4%（4 例）及び 26.9%（7 例）］，関節周囲炎［7.7%（2 例）及び 0.0%（0 例）］及びインフルエンザ及び関節痛（いずれも 0.0%（0 例）及び 7.7%（2 例）］であった（表 2.7.4.4.1.3.1-7）。
- 眼以外に発現した重症度が高度の有害事象は，本剤群及びアフリベルセプト群で，それぞれ 3 例（1 例に認められた敗血症性心筋炎，細菌性関節炎及び敗血症性ショック，並びに胃癌，肺膿瘍各 1 例），及び 1 例（全身性細菌感染）であった。いずれも治験薬との因果関係は否定された。
- 眼以外に発現した重篤な有害事象の発現頻度は本剤群及びアフリベルセプト群でそれぞれ 15.4%（4 例）及び 3.8%（1 例）であり，アフリベルセプト群に比べて本剤群で高かったものの，いずれも治験薬との因果関係は否定され，発現頻度は試験全体（9.0%及び 10.1%）と同様であった。
- 死亡に至った有害事象はいずれの群にも認められなかった。
- 外部判定による APTC ATE はいずれの群にも認められなかった。

表 2.7.4.4.1.3.1-3 48週時までに発現した有害事象の概況（nAMD, GR40306試験－日本部分集団）

Safety Summary through Week 48 in Japanese Subpopulation, Safety-Evaluable Population, Japan Subgroup
Protocol: GR40306
Clinical Cutoff Date: 26OCT2020

	Faricimab 6 mg (N=26)	Aflibercept 2 mg (N=26)
Total number of patients with at least one AE	19 (73.1%)	18 (69.2%)
Total number of AEs	54	49
Total number of patients with at least one SAE	4 (15.4%)	3 (11.5%)
Total number of SAEs	5	3
Total number of deaths	0	0
Total number of patients withdrawn from study due to an AE	0	0
Total number of patients withdrawn from study treatment due to an AE	0	0
Total number of patients with at least one AESI	0	2 (7.7%)
Ocular events: study eye total number of patients with at least one		
AE	4 (15.4%)	9 (34.6%)
SAE	0	1 (3.8%)
AE leading to withdrawal from study treatment	0	0
Treatment related AEs	0	1 (3.8%)
Treatment related SAEs	0	0
AE of Special Interest	0	1 (3.8%)

AE=Adverse Event; SAE=Serious Adverse Event; AESI=Adverse Event of Special Interest; APTC=Antiplatelet Trialists' Collaboration. IOI=Intraocular Inflammation; SAE=Serious Adverse Event; VA=Visual Acuity.
APTC events are defined as non-fatal strokes or non-fatal myocardial infarctions or vascular deaths (including deaths of unknown cause).
Investigator text for AEs encoded using MedDRA version 23.1.
Drop in VA score >=30 is defined as causing a decrease of >=30 VA score (compared with the last of VA prior to the most recent assessment) lasting more than 1 hour.
Cases of potential drug-induced liver injury that include an elevated ALT or AST with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law.
Intervention req. to prevent permanent vision loss is defined as required surgical or medical intervention to prevent permanent loss of sight.
Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for the "Total number of AEs" row in which multiple occurrences of the same AE are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).

Program: root/clinical_studies/RO6867461/CDPT7716/GR40306/data_analysis/CTD_Tenaya/prod/program/t_ae_oview.sas
Output: root/clinical_studies/RO6867461/CDPT7716/GR40306/data_analysis/CTD_Tenaya/prod/output/t_ae_oview_W48_SE_JP_amd.out
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表 2.7.4.4.1.3.1-3 48週時までに発現した有害事象の概況（nAMD, GR40306試験－日本部分集団）（続）

Safety Summary through Week 48 in Japanese Subpopulation, Safety-Evaluable Population, Japan Subgroup
Protocol: GR40306
Clinical Cutoff Date: 26OCT2020

	Faricimab 6 mg (N=26)	Aflibercept 2 mg (N=26)
Drop in VA score >=30	0	0
Associated with severe IOI	0	0
Intervention req. to prevent permanent vision loss	0	1 (3.8%)
Suspected transmission of infectious agent by study drug	0	0
Ocular events: fellow eye total number of patients with at least one		
AE	5 (19.2%)	6 (23.1%)
SAE	0	1 (3.8%)
AE of Special Interest	0	1 (3.8%)
Drop in VA score >=30	0	0
Associated with severe IOI	0	0
Intervention req. to prevent permanent vision loss	0	1 (3.8%)
Suspected transmission of infectious agent by study drug	0	0

AE=Adverse Event; SAE=Serious Adverse Event; AESI=Adverse Event of Special Interest; APTC=Antiplatelet Trialists' Collaboration. IOI=Intraocular Inflammation; SAE=Serious Adverse Event; VA=Visual Acuity.
APTC events are defined as non-fatal strokes or non-fatal myocardial infarctions or vascular deaths (including deaths of unknown cause).
Investigator text for AEs encoded using MedDRA version 23.1.
Drop in VA score >=30 is defined as causing a decrease of >=30 VA score (compared with the last of VA prior to the most recent assessment) lasting more than 1 hour.
Cases of potential drug-induced liver injury that include an elevated ALT or AST with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law.
Intervention req. to prevent permanent vision loss is defined as required surgical or medical intervention to prevent permanent loss of sight.
Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for the "Total number of AEs" row in which multiple occurrences of the same AE are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).

Program: root/clinical_studies/RO6867461/CDPT7716/GR40306/data_analysis/CTD_Tenaya/prod/program/t_ae_oview.sas
Output: root/clinical_studies/RO6867461/CDPT7716/GR40306/data_analysis/CTD_Tenaya/prod/output/t_ae_oview_W48_SE_JP_amd.out
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表 2.7.4.4.1.3.1-3 48週時までに発現した有害事象の概況（nAMD, GR40306試験－日本部分集団）（続）

Safety Summary through Week 48 in Japanese Subpopulation, Safety-Evaluable Population, Japan Subgroup
Protocol: GR40306
Clinical Cutoff Date: 26OCT2020

	Faricimab 6 mg (N=26)	Aflibercept 2 mg (N=26)
Non-ocular events total number of patients with at least one		
AE	18 (69.2%)	15 (57.7%)
SAE	4 (15.4%)	1 (3.8%)
AE leading to withdrawal from study treatment	0	0
AE of Special Interest	0	0
Elevated ALT or AST with either elevated bilirubin or clinical jaundice	0	0
Adjudicated APTC events	0	0
Non-fatal MI	0	0
Non-fatal Stroke	0	0
Death	0	0

AE=Adverse Event; SAE=Serious Adverse Event; AESI=Adverse Event of Special Interest; APTC=Antiplatelet Trialists' Collaboration. IOI=Intraocular Inflammation; SAE=Serious Adverse Event; VA=Visual Acuity.
APTC events are defined as non-fatal strokes or non-fatal myocardial infarctions or vascular deaths (including deaths of unknown cause).
Investigator text for AEs encoded using MedDRA version 23.1.
Drop in VA score >=30 is defined as causing a decrease of >=30 VA score (compared with the last of VA prior to the most recent assessment) lasting more than 1 hour.
Cases of potential drug-induced liver injury that include an elevated ALT or AST with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law.
Intervention req. to prevent permanent vision loss is defined as required surgical or medical intervention to prevent permanent loss of sight.
Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for the "Total number of AEs" row in which multiple occurrences of the same AE are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).

Program: root/clinical_studies/RO6867461/CDPT7716/GR40306/data_analysis/CTD_Tenaya/prod/program/t_ae_oview.sas
Output: root/clinical_studies/RO6867461/CDPT7716/GR40306/data_analysis/CTD_Tenaya/prod/output/t_ae_oview_W48_SE_JP_amd.out
16FEB2021 7:44 Page 3 of 3

[5.3.5.3-nAMD-1 t_ae_oview_W48_SE_JP_amd を再掲]

表 2.7.4.4.1.3.1-4 48週時までに試験眼に発現した有害事象（nAMD, GR40306試験－日本部分集団）

Ocular Adverse Events in the Study Eye through Week 48 in Japanese Subpopulation, Safety-Evaluable Population, Japan Subgroup
Protocol: GR40306
Clinical Cutoff Date: 26OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg (N=26)	Aflibercept 2 mg run (N=26)
Total number of patients with at least one adverse event	4 (15.4%)	9 (34.6%)
Overall total number of events	4	12
眼障害		
Total number of patients with at least one adverse event	3 (11.5%)	7 (26.9%)
Total number of events	3	9
ドライアイ	2 (7.7%)	1 (3.8%)
加齢黄斑変性	0	1 (3.8%)
乾性加齢黄斑変性	0	1 (3.8%)
眼の異物感	0	1 (3.8%)
結膜出血	0	1 (3.8%)
結膜沈着物	0	1 (3.8%)
高眼圧症	1 (3.8%)	0
新生血管加齢黄斑変性	0	1 (3.8%)
落屑症候群	0	1 (3.8%)
流涙増加	0	1 (3.8%)
傷害、中毒および処置合併症		
Total number of patients with at least one adverse event	1 (3.8%)	1 (3.8%)
Total number of events	1	1
眼内異物	1 (3.8%)	0
投薬過誤	0	1 (3.8%)
感染症および寄生虫症		
Total number of patients with at least one adverse event	0	1 (3.8%)
Total number of events	0	1
結膜炎	0	1 (3.8%)
臨床検査		
Total number of patients with at least one adverse event	0	1 (3.8%)
Total number of events	0	1
眼圧上昇	0	1 (3.8%)

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).

Program: root/clinical_studies/RO6867461/CDPT7716/GR40306/data_analysis/CTD_Tenaya/prod/program/t_ae.sas
Output: root/clinical_studies/RO6867461/CDPT7716/GR40306/data_analysis/CTD_Tenaya/prod/output/t_ae_SOCUL_W48_SE_JP_amd.out
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[5.3.5.3-nAMD-1 t_ae_SOCUL_W48_SE_JP_amd を再掲]

表 2.7.4.4.1.3.1-5 48週時までに試験眼に発現した副作用（nAMD, GR40306試験－日本部分集団）

Ocular Adverse Events Related to Study Treatment in the Study Eye through Week 48 in Japanese Subpopulation, Safety-Evaluable Population, Japan Subgroup
Protocol: GR40306
Clinical Cutoff Date: 26OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg (N=26)	Aflibercept 2 mg run (N=26)
Total number of patients with at least one adverse event	0	1 (3.8%)
Overall total number of events	0	1
臨床検査		
Total number of patients with at least one adverse event	0	1 (3.8%)
Total number of events	0	1
眼圧上昇	0	1 (3.8%)

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).

Program: root/clinical_studies/RO6867461/CDPT7716/GR40306/data_analysis/CTD_Tenaya/prod/program/t_ae.sas
Output: root/clinical_studies/RO6867461/CDPT7716/GR40306/data_analysis/CTD_Tenaya/prod/output/t_ae_SOCUL_SREL_W48_SE_JP_amd.out
16FEB2021 7:50 Page 1 of 1

[5.3.5.3-nAMD-1 t_ae_SOCUL_SREL_W48_SE_JP_amd を再掲]

表 2.7.4.4.1.3.1-6 48週時までに非試験眼に発現した有害事象（nAMD, GR40306試験－日本部分集団）

Ocular Adverse Events in the Fellow Eye through Week 48 in Japanese Subpopulation, Safety-Evaluable Population, Japan Subgroup
Protocol: GR40306
Clinical Cutoff Date: 26OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg (N=26)	Aflibercept 2 mg run (N=26)
Total number of patients with at least one adverse event	5 (19.2%)	6 (23.1%)
Overall total number of events	7	7
眼障害		
Total number of patients with at least one adverse event	5 (19.2%)	5 (19.2%)
Total number of events	7	6
ドライアイ	2 (7.7%)	1 (3.8%)
結膜出血	1 (3.8%)	1 (3.8%)
新生血管加齢黄斑変性	1 (3.8%)	1 (3.8%)
角膜炎	1 (3.8%)	0
角膜内皮炎	1 (3.8%)	0
乾性加齢黄斑変性	0	1 (3.8%)
点状角膜炎	0	1 (3.8%)
糖尿病網膜症	1 (3.8%)	0
裂孔原性網膜剥離	0	1 (3.8%)
感染症および寄生虫症		
Total number of patients with at least one adverse event	0	1 (3.8%)
Total number of events	0	1
結膜炎	0	1 (3.8%)

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).

Program: root/clinical_studies/RO6867461/CDPT7716/GR40306/data_analysis/CTD_Tenaya/prod/program/t_ae.sas
Output: root/clinical_studies/RO6867461/CDPT7716/GR40306/data_analysis/CTD_Tenaya/prod/output/t_ae_FOCUL_W48_SE_JP_amd.out
16FEB2021 7:52 Page 1 of 1

[5.3.5.3-nAMD-1 t_ae_FOCUL_W48_SE_JP_amd を再掲]

表 2.7.4.4.1.3.1-7 48週時までに眼以外に発現した有害事象（nAMD, GR40306試験－日本部分集団）

Non-Ocular Adverse Events through Week 48 in Japanese Subpopulation, Safety-Evaluable Population, Japan Subgroup
Protocol: GR40306
Clinical Cutoff Date: 26OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg (N=26)	Aflibercept 2 mg run (N=26)
Total number of patients with at least one adverse event	18 (69.2%)	15 (57.7%)
Overall total number of events	43	30
感染症および寄生虫症		
Total number of patients with at least one adverse event	6 (23.1%)	8 (30.8%)
Total number of events	13	12
上咽頭炎	4 (15.4%)	7 (26.9%)
インフルエンザ	0	2 (7.7%)
ＣＯＶＩＤ－１９	0	1 (3.8%)
胃腸炎	1 (3.8%)	0
気管支炎	1 (3.8%)	0
細菌性関節炎	1 (3.8%)	0
歯周炎	1 (3.8%)	0
全身性細菌感染	0	1 (3.8%)
椎間板炎	1 (3.8%)	0
敗血症性ショック	1 (3.8%)	0
敗血症性心筋炎	1 (3.8%)	0
肺膿瘍	1 (3.8%)	0
腹部膿瘍	0	1 (3.8%)
筋骨格系および結合組織障害		
Total number of patients with at least one adverse event	4 (15.4%)	3 (11.5%)
Total number of events	5	3
関節周囲炎	2 (7.7%)	0
関節痛	0	2 (7.7%)
背部痛	1 (3.8%)	1 (3.8%)
関節炎	1 (3.8%)	0
筋肉痛	1 (3.8%)	0
傷害、中毒および処置合併症		
Total number of patients with at least one adverse event	4 (15.4%)	2 (7.7%)
Total number of events	6	2
ストレス骨折	0	1 (3.8%)
圧迫骨折	0	1 (3.8%)
顔面損傷	1 (3.8%)	0
節足動物咬傷	1 (3.8%)	0
足骨折	1 (3.8%)	0
転倒	1 (3.8%)	0
動物咬傷	1 (3.8%)	0
粘膜擦過傷	1 (3.8%)	0
皮膚および皮下組織障害		
Total number of patients with at least one adverse event	2 (7.7%)	3 (11.5%)
Total number of events	4	3
ざ瘡様皮膚炎	1 (3.8%)	0
そう痒症	1 (3.8%)	0
アレルギー性皮膚炎	0	1 (3.8%)
紅斑性皮疹	0	1 (3.8%)
手皮膚炎	1 (3.8%)	0
蕁麻疹	0	1 (3.8%)

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).

Program: root/clinical_studies/RO6867461/CDPT7716/GR40306/data_analysis/CTD_Tenaya/prod/program/t_ae.sas
Output: root/clinical_studies/RO6867461/CDPT7716/GR40306/data_analysis/CTD_Tenaya/prod/output/t_ae_NOCUL_W48_SE_JP_amd.out
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表 2.7.4.4.1.3.1-7 48週時までに眼以外に発現した有害事象（nAMD, GR40306試験－日本部分集団）（続）

Non-Ocular Adverse Events through Week 48 in Japanese Subpopulation, Safety-Evaluable Population, Japan Subgroup
Protocol: GR40306
Clinical Cutoff Date: 26OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg (N=26)	Aflibercept 2 mg run (N=26)
胃腸障害		
Total number of patients with at least one adverse event	3 (11.5%)	1 (3.8%)
Total number of events	3	1
口腔粘膜血腫	1 (3.8%)	0
腹痛	1 (3.8%)	0
便秘	0	1 (3.8%)
齲歯	1 (3.8%)	0
呼吸器、胸郭および縦隔障害		
Total number of patients with at least one adverse event	1 (3.8%)	2 (7.7%)
Total number of events	1	4
咳喘息	0	1 (3.8%)
口腔咽頭痛	1 (3.8%)	0
上気道の炎症	0	1 (3.8%)
血管障害		
Total number of patients with at least one adverse event	1 (3.8%)	1 (3.8%)
Total number of events	1	1
高血圧	1 (3.8%)	1 (3.8%)
神経系障害		
Total number of patients with at least one adverse event	1 (3.8%)	1 (3.8%)
Total number of events	1	1
坐骨神経痛	0	1 (3.8%)
浮動性めまい	1 (3.8%)	0
精神障害		
Total number of patients with at least one adverse event	1 (3.8%)	1 (3.8%)
Total number of events	1	1
うつ病	1 (3.8%)	0
不眠症	0	1 (3.8%)
免疫系障害		
Total number of patients with at least one adverse event	1 (3.8%)	1 (3.8%)
Total number of events	1	1
過敏症	1 (3.8%)	0
造影剤アレルギー	0	1 (3.8%)
臨床検査		
Total number of patients with at least one adverse event	2 (7.7%)	0
Total number of events	4	0
肝機能検査値上昇	1 (3.8%)	0
血中尿酸増加	1 (3.8%)	0
尿潜血陽性	1 (3.8%)	0
尿中蛋白陽性	1 (3.8%)	0
血液およびリンパ系障害		
Total number of patients with at least one adverse event	1 (3.8%)	0
Total number of events	1	0
貧血	1 (3.8%)	0

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).

Program: root/clinical_studies/RO6867461/CDPT7716/GR40306/data_analysis/CTD_Tenaya/prod/program/t_ae.sas
Output: root/clinical_studies/RO6867461/CDPT7716/GR40306/data_analysis/CTD_Tenaya/prod/output/t_ae_NOCUL_W48_SE_JP_amd.out
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表 2.7.4.4.1.3.1-7 48週時までに眼以外に発現した有害事象（nAMD, GR40306試験－日本部分集団）（続）

Non-Ocular Adverse Events through Week 48 in Japanese Subpopulation, Safety-Evaluable Population, Japan Subgroup
Protocol: GR40306
Clinical Cutoff Date: 26OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg (N=26)	Aflibercept 2 mg run (N=26)
生殖系および乳房障害		
Total number of patients with at least one adverse event	1 (3.8%)	0
Total number of events	1	0
不正子宮出血	1 (3.8%)	0
代謝および栄養障害		
Total number of patients with at least one adverse event	0	1 (3.8%)
Total number of events	0	1
糖尿病	0	1 (3.8%)
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）		
Total number of patients with at least one adverse event	1 (3.8%)	0
Total number of events	1	0
胃癌	1 (3.8%)	0

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).

Program: root/clinical_studies/RO6867461/CDPT7716/GR40306/data_analysis/CTD_Tenaya/prod/program/t_ae.sas
Output: root/clinical_studies/RO6867461/CDPT7716/GR40306/data_analysis/CTD_Tenaya/prod/output/t_ae_NOCUL_W48_SE_JP_amd.out
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[5.3.5.3-nAMD-1 t_ae_NOCUL_W48_SE_JP_amd を再掲]

表 2.7.4.4.1.3.1-8 48週時までに眼以外に発現した副作用（nAMD，GR40306試験－日本部分集団）

Non-Ocular Adverse Events Related to Study Treatment through Week 48 in Japanese Subpopulation, Safety-Evaluable Population, Japan Subgroup
Protocol: GR40306
Clinical Cutoff Date: 26OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg (N=26)	Aflibercept 2 mg run (N=26)
Total number of patients with at least one adverse event	0	1 (3.8%)
Overall total number of events	0	1
血管障害		
Total number of patients with at least one adverse event	0	1 (3.8%)
Total number of events	0	1
高血圧	0	1 (3.8%)

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).

Program: root/clinical_studies/RO6867461/CDPT7716/GR40306/data_analysis/CTD_Tenaya/prod/program/t_ae.sas
Output: root/clinical_studies/RO6867461/CDPT7716/GR40306/data_analysis/CTD_Tenaya/prod/output/t_ae_NOCUL_SREL_W48_SE_JP_amd.out
16FEB2021 7:54 Page 1 of 1

[5.3.5.3-nAMD-1 t_ae_NOCUL_SREL_W48_SE_JP_amd を再掲]

2.7.4.4.1.3.2 DME（GR40349試験）

1) 患者背景

日本部分集団においてベースライン時の患者背景は投与群間で同様であった（表 2.7.4.4.1.3.2-1）。

ITT 集団の日本部分集団は計60例であり，本剤 Q8W 群に21例，本剤 PTI 群に19例，アフリベルセプト Q8W 群に20例であった。抗 VEGF 薬未治療患者は計43例であり，本剤 Q8W 群に14例，本剤 PTI 群に14例，アフリベルセプト Q8W 群に15例であった。抗 VEGF 薬未治療患者の割合は投与群間で同様であった（5.3.5.3-nAMD-1 t_dm_TN_JP_dme）。

登録時の平均年齢は64.23歳（本剤 Q8W 群63.90歳，本剤 PTI 群62.95歳，アフリベルセプト Q8W 群65.80歳）であり，65歳未満の患者（48.3%）と65歳以上の患者（51.7%）が約半数ずつであり，男性が半分以上（55.0%）を占めた。

表 2.7.4.4.1.3.2-1 人口統計学的特性の要約（DME, GR40349試験－日本部分集団）

Demographics in Japanese Subpopulation, Intent-to-Treat Population, Japan Subgroup
Protocol: GR40349
Clinical Cutoff Date: 20OCT2020

	Faricimab 6 mg Q8W (N=21)	Faricimab 6 mg PTI (N=19)	Aflibercept 2 mg Q8W (N=20)	All Patients (N=60)
Region				
n	21	19	20	60
Asia	21 (100%)	19 (100%)	20 (100%)	60 (100%)
Age (years)				
n	21	19	20	60
Mean (SD)	63.90 (10.33)	62.95 (10.66)	65.80 (9.41)	64.23 (10.04)
Median	65.00	62.00	67.00	65.00
Min - Max	41.0 - 80.0	41.0 - 79.0	47.0 - 81.0	41.0 - 81.0
Age group (years)				
n	21	19	20	60
<65	10 (47.6%)	10 (52.6%)	9 (45.0%)	29 (48.3%)
>=65	11 (52.4%)	9 (47.4%)	11 (55.0%)	31 (51.7%)
<65	10 (47.6%)	10 (52.6%)	9 (45.0%)	29 (48.3%)
>=65 - <75	7 (33.3%)	7 (36.8%)	7 (35.0%)	21 (35.0%)
>=75 - <85	4 (19.0%)	2 (10.5%)	4 (20.0%)	10 (16.7%)
SEX				
n	21	19	20	60
Male	12 (57.1%)	10 (52.6%)	11 (55.0%)	33 (55.0%)
Female	9 (42.9%)	9 (47.4%)	9 (45.0%)	27 (45.0%)

PTI = Personalized Treatment Interval (from Q4W up to Q16W). Age is at randomization.

Program: root/clinical_studies/RO6867461/CDT70122/GR40349/data_analysis/CTD_Yosemite/prod/program/t_dm.sas
Output:
root/clinical_studies/RO6867461/CDT70122/GR40349/data_analysis/CTD_Yosemite/prod/output/t_dm_IT_JP_dme.out
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Page 1 of 2

表 2.7.4.4.1.3.2-1 人口統計学的特性の要約（DME, GR40349試験－日本部分集団）（続）

Demographics in Japanese Subpopulation, Intent-to-Treat Population, Japan Subgroup
Protocol: GR40349
Clinical Cutoff Date: 20OCT2020

	Faricimab 6 mg Q8W (N=21)	Faricimab 6 mg PTI (N=19)	Aflibercept 2 mg Q8W (N=20)	All Patients (N=60)
Ethnicity				
n	21	19	20	60
Not Hispanic or Latino	21 (100%)	19 (100%)	20 (100%)	60 (100%)
Race				
n	21	19	20	60
Asian	21 (100%)	19 (100%)	20 (100%)	60 (100%)
Chinese	0	0	0	0
Taiwanese	0	0	0	0
Asian Indian	0	0	0	0
Korean	0	0	0	0
Malaysian	0	0	0	0
Vietnamese	0	0	0	0
Japanese	21 (100%)	19 (100%)	20 (100%)	60 (100%)
Other Asian	0	0	0	0

PTI = Personalized Treatment Interval (from Q4W up to Q16W). Age is at randomization.

Program: root/clinical_studies/RO6867461/CDT70122/GR40349/data_analysis/CTD_Yosemite/prod/program/t_dm.sas
Output:
root/clinical_studies/RO6867461/CDT70122/GR40349/data_analysis/CTD_Yosemite/prod/output/t_dm_IT_JP_dme.out
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[5.3.5.3-nAMD-1 t_dm_IT_JP_dme を再掲]

2) 治験薬の曝露状況

56週時までの投与期間の中央値はいずれの投与群においても56.1週であり（表 2.7.4.4.1.3.2-2），試験全体での投与期間と一致していた（2.7.4.1.1.4.6）。

表 2.7.4.4.1.3.2-2 56週時までの曝露状況（DME, GR40349試験－日本部分集団）

Summary of Study Treatment Exposure in the Study Eye through Week 56 in Japanese Subpopulation, Safety-Evaluable Population, Japan Subgroup
Protocol: GR40349
Clinical Cutoff Date: 20OCT2020

	Faricimab 6 mg Q8W (N=21)	Faricimab 6 mg PTI (N=19)	Faricimab 6 mg All (N=40)	Aflibercept 2 mg Q8W (N=20)
Treatment duration (weeks)				
n	21	19	40	20
Mean (SD)	54.3 (9.67)	55.6 (2.08)	54.9 (7.10)	54.8 (6.28)
Median	56.1	56.1	56.1	56.1
Min-max	12 - 57	47 - 57	12 - 57	28 - 57
Number of study drug administrations				
n	21	19	40	20
Mean (SD)	9.7 (1.31)	9.1 (2.22)	9.4 (1.81)	9.7 (0.93)
Median	10.0	8.0	10.0	10.0
Min-max	4 - 10	7 - 15	4 - 15	6 - 10
Dose interruption				
Number of doses interrupted	2	4	6	1
At least one interrupted dose	2 (9.5%)	3 (15.8%)	5 (12.5%)	1 (5.0%)
Intraocular inflammation	1 (4.8%)	0	1 (2.5%)	0
BCVA decrease	0	0	0	0
Elevated intraocular pressure	0	0	0	0
Rhegmatogenous retinal break	0	0	0	0
Rhegmatogenous retinal detachment or macular hole	0	0	0	0
Active or suspected infection	0	2 (10.5%)	2 (5.0%)	0
Cataract surgery in the study eye	1 (4.8%)	0	1 (2.5%)	1 (5.0%)
Oral corticosteroids (prednisone > 10mg/day or equivalent)	0	0	0	0

PTI = Personalized Treatment Interval (from Q4W up to Q16W). Study drug corresponds to faricimab or aflibercept. Study treatment corresponds to faricimab, aflibercept or sham. Treatment duration is the (maximum of the date of the last dose of study treatment and the date of the last treatment dose hold) minus the date of the first dose plus one day. Includes study treatment received and dose hold on or prior to Day 405 (last day of Week 56 analysis visit window). Percentages are based on N in the column headings. The number of study drug administered may include any active drug administered including medication errors. The number of injections does not take into account the use of prohibited therapies.

Program: root/clinical_studies/RO6867461/CDT70122/GR40349/data_analysis/CTD_Yosemite/prod/program/t_ex.sas
Output: root/clinical_studies/RO6867461/CDT70122/GR40349/data_analysis/CTD_Yosemite/prod/output/t_ex_SE_JP_dme.out
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表 2.7.4.4.1.3.2-2 56週時までの曝露状況（DME, GR40349試験－日本部分集団）（続）

Summary of Study Treatment Exposure in the Study Eye through Week 56 in Japanese Subpopulation, Safety-Evaluable Population, Japan Subgroup
Protocol: GR40349
Clinical Cutoff Date: 20OCT2020

	Faricimab 6 mg Q8W (N=21)	Faricimab 6 mg PTI (N=19)	Faricimab 6 mg All (N=40)	Aflibercept 2 mg Q8W (N=20)
IV corticosteroids	0	0	0	0
On-study prohibited medications	0	0	0	0
Other	0	1 (5.3%)	1 (2.5%)	0
Interruptions per patient				
n	2	3	5	1
1	2 (9.5%)	2 (10.5%)	4 (10.0%)	1 (5.0%)
2	0	1 (5.3%)	1 (2.5%)	0
3	0	0	0	0
4	0	0	0	0
5	0	0	0	0
6	0	0	0	0
7	0	0	0	0
8	0	0	0	0
9	0	0	0	0
10	0	0	0	0

PTI = Personalized Treatment Interval (from Q4W up to Q16W). Study drug corresponds to faricimab or aflibercept. Study treatment corresponds to faricimab, aflibercept or sham. Treatment duration is the (maximum of the date of the last dose of study treatment and the date of the last treatment dose hold) minus the date of the first dose plus one day. Includes study treatment received and dose hold on or prior to Day 405 (last day of Week 56 analysis visit window). Percentages are based on N in the column headings. The number of study drug administered may include any active drug administered including medication errors. The number of injections does not take into account the use of prohibited therapies.

Program: root/clinical_studies/RO6867461/CDT70122/GR40349/data_analysis/CTD_Yosemite/prod/program/t_ex.sas
Output: root/clinical_studies/RO6867461/CDT70122/GR40349/data_analysis/CTD_Yosemite/prod/output/t_ex_SE_JP_dme.out
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[5.3.5.3-nAMD-1 t_ex_SE_JP_dme を再掲]

3) 安全性の結果

56週時までの結果を以下に記載する（表 2.7.4.4.1.3.2-3）。

- 有害事象の発現頻度は本剤 Q8W 群，本剤 PTI 群及びアフリベルセプト Q8W 群でそれぞれ 71.4%（15/21 例），78.9%（15/19 例）及び 90.0%（18/20 例）であり，アフリベルセプト Q8W 群に比べて本剤群で低かった。
- 試験眼に発現した有害事象の発現頻度は本剤 Q8W 群，本剤 PTI 群及びアフリベルセプト Q8W 群でそれぞれ 23.8%，31.6%及び 40.0%であり，アフリベルセプト Q8W 群に比べて本剤 Q8W 群で低かった。
- いずれかの群で 2 例以上に認められた試験眼に発現した有害事象は，結膜出血，ドライアイ及び白内障であり，試験全体の結果（2.7.4.1.1.4.6）と大きな違いはなかった（表 2.7.4.4.1.3.2-4）。
- 試験眼に発現した副作用の発現頻度は本剤 Q8W 群，本剤 PTI 群及びアフリベルセプト Q8W 群でそれぞれ 14.3%，5.3%及び 0.0%であり，試験全体（それぞれ 3.5%，2.6%及び 1.6%）と比べて本剤 Q8W 群及び本剤 PTI 群で高かった。
- いずれかの群で 2 例以上に認められた試験眼に発現した副作用はなかった（表 2.7.4.4.1.3.2-5）。
- 非試験眼に発現した有害事象の発現頻度は本剤 Q8W 群，本剤 PTI 群及びアフリベルセプト Q8W 群でそれぞれ 19.0%，57.9%及び 30.0%であり，試験全体（28.4%，33.2%及び 34.1%）と比べて，本剤 PTI 群で高く，アフリベルセプト Q8W 群で低かった（表 2.7.4.4.1.3.2-6）。
- 試験眼に発現した重症度が高度の有害事象は本剤 Q8W 群及びアフリベルセプト Q8W 群に認められず，本剤 PTI 群の 1 例（ぶどう膜炎）で認められた。ぶどう膜炎は治験薬との因果関係は否定されなかった。
- 試験眼に発現した重篤な有害事象は本剤 Q8W 群に認められず，本剤 PTI 群及びアフリベルセプト Q8W 群のそれぞれ 5.3%（1 例，ぶどう膜炎）及び 5.0%（1 例，白内障）で認められ，投与群間で発現頻度は同様であった。試験眼に発現した重篤な有害事象の内，治験薬との因果関係が否定されなかったのは本剤 PTI 群の 1 例（ぶどう膜炎）であった。
- 試験眼に発現した治験薬の投与中止に至った有害事象は本剤 Q8W 群及びアフリベルセプト Q8W 群で認められず，本剤 PTI 群の 1 例（ぶどう膜炎）で認められた。ぶどう膜炎は治験薬との因果関係は否定されなかった。
- 眼以外に発現した治験中止に至った有害事象は本剤 Q8W 群及び本剤 PTI 群で認められず，アフリベルセプト Q8W 群の 5.0%（1 例，アルツハイマー型認知症）で認められた。アルツハイマー型認知症は治験薬との因果関係は否定された。
- 試験眼に発現した AESI は本剤 Q8W 群及びアフリベルセプト Q8W 群で認められず，本剤 PTI 群の 1 例（ぶどう膜炎）で認められた。ぶどう膜炎は重症度が高度の眼内炎症に該当した。1 時間を超える 30 文字以上の視力低下に至った AESI はいずれの群にも認められなかった。
- 眼以外に発現した有害事象の発現頻度は本剤 Q8W 群，本剤 PTI 群及びアフリベルセプト Q8W 群でそれぞれ 61.9%，57.9%及び 70.0%であり（表 2.7.4.4.1.3.2-7），試験全体（65.2%，67.1%及び 65.3%）の結果と同様であった。眼以外に発現した副作用は本剤 Q8W 群及びアフリベルセプト Q8W 群で認められず，本剤 PTI 群で 5.3%（1 例，突発性難聴）に認められた（表 2.7.4.4.1.3.2-8）。
- いずれかの群の 2 例以上で眼以外に発現した有害事象（本剤 Q8W 群，本剤 PTI 群及びアフリベルセプト Q8W 群別）は，上咽頭炎［19.0%（4 例），10.5%（2 例）及び 10.0%（2 例）］，節足動物咬傷［0.0%（0 例），10.5%（2 例）及び 0.0%（0 例）］，頭痛，齲歯，糖尿病，皮膚嚢腫，咳嗽［9.5%（2 例），0.0%（0 例）及び 0.0%（0 例）］及び筋痙縮［0.0%（0 例），0.0%（0 例）及び 10.0%（2 例）］であった（表 2.7.4.4.1.3.2-7）。

- 眼以外に発現した重症度が高度の有害事象は，本剤 Q8W 群，本剤 PTI 群及びアフリベルセプト Q8W 群で，それぞれ 1 例（転倒，脛骨骨折及び肺塞栓症），1 例（大腿骨骨折）及び 1 例（うっ血性心不全及び心筋梗塞）であった。いずれも治験薬との因果関係は否定された。
- 眼以外に発現した重篤な有害事象の発現頻度は本剤 Q8W 群，本剤 PTI 群及びアフリベルセプト Q8W 群でそれぞれ 9.5%（2 例），15.8%（3 例）及び 5.0%（1 例）で，投与群間で同様であり，試験全体（24.0%，20.4%及び 16.1%）と比べて（2.7.4.1.1.4.6）本剤 Q8W 群及びアフリベルセプト Q8W 群で低かった。
- 死亡に至った有害事象はいずれの群にも認められなかった。
- 外部判定による APTC ATE はいずれの群にも認められなかった。

表 2.7.4.4.1.3.2-3 56週時までに発現した有害事象の概況（DME, GR40349試験－日本部分集団）

Safety Summary through Week 56 in Japanese Subpopulation, Safety-Evaluable Population, Japan Subgroup
Protocol: GR40349
Clinical Cutoff Date: 20OCT2020

	Faricimab 6 mg Q8W (N=21)	Faricimab 6 mg PTI (N=19)	Faricimab 6 mg All (N=40)	Aflibercept 2 mg Q8W (N=20)
Total number of patients with at least one AE	15 (71.4%)	15 (78.9%)	30 (75.0%)	18 (90.0%)
Total number of AEs	55	47	102	47
Total number of patients with at least one SAE	2 (9.5%)	5 (26.3%)	7 (17.5%)	3 (15.0%)
Total number of SAEs	3	5	8	4
Total number of deaths	0	0	0	0
Total number of patients withdrawn from study due to an AE	0	0	0	1 (5.0%)
Total number of patients withdrawn from study treatment due to an AE	0	1 (5.3%)	1 (2.5%)	1 (5.0%)
Total number of patients with at least one AESI	0	2 (10.5%)	2 (5.0%)	0
Ocular events: study eye total number of patients with at least one				
AE	5 (23.8%)	6 (31.6%)	11 (27.5%)	8 (40.0%)
SAE	0	1 (5.3%)	1 (2.5%)	1 (5.0%)
AE leading to withdrawal from study treatment	0	1 (5.3%)	1 (2.5%)	0
Treatment related AEs	3 (14.3%)	1 (5.3%)	4 (10.0%)	0
Treatment related SAEs	0	1 (5.3%)	1 (2.5%)	0
AE of Special Interest	0	1 (5.3%)	1 (2.5%)	0

AESI=Adverse Event of Special Interest; APTC = Antiplatelet Trialists" Collaboration; IOI=Intraocular Inflammation; MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W); SAE=Serious Adverse Event; VA = Visual Acuity; MedDRA = Medical Dictionary for Regulatory Activities.
APTC events are defined as non-fatal strokes or non-fatal myocardial infarctions or vascular deaths (including deaths of unknown cause). Investigator text for AEs encoded using MedDRA version 23.1.
Drop in VA score >=30 is defined as causing a decrease of >=30 VA score lasting more than 1 hour.
Intervention req. to prevent permanent vision loss is defined as required surgical or medical intervention to prevent permanent loss of sight.
Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for the "Total number of AEs" row in which multiple occurrences of the same AE are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

Program: root/clinical_studies/RO6867461/CDT70122/GR40349/data_analysis/CTD_Yosemite/prod/program/t_ae_oview.sas
Output: root/clinical_studies/RO6867461/CDT70122/GR40349/data_analysis/CTD_Yosemite/prod/output/t_ae_oview_W56_SE_JP_dme.out
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表 2.7.4.4.1.3.2-3 56週時までに発現した有害事象の概況（DME, GR40349試験－日本部分集団）（続）

Safety Summary through Week 56 in Japanese Subpopulation, Safety-Evaluable Population, Japan Subgroup
Protocol: GR40349
Clinical Cutoff Date: 20OCT2020

	Faricimab 6 mg Q8W (N=21)	Faricimab 6 mg PTI (N=19)	Faricimab 6 mg All (N=40)	Aflibercept 2 mg Q8W (N=20)
Drop in VA score >=30	0	0	0	0
Associated with severe IOI	0	1 (5.3%)	1 (2.5%)	0
Intervention req. to prevent permanent vision loss	0	0	0	0
Suspected transmission of infectious agent by study drug	0	0	0	0
Ocular events: fellow eye total number of patients with at least one				
AE	4 (19.0%)	11 (57.9%)	15 (37.5%)	6 (30.0%)
SAE	0	1 (5.3%)	1 (2.5%)	1 (5.0%)
AE of Special Interest	0	1 (5.3%)	1 (2.5%)	0
Drop in VA score >=30	0	0	0	0
Associated with severe IOI	0	0	0	0
Intervention req. to prevent permanent vision loss	0	1 (5.3%)	1 (2.5%)	0
Suspected transmission of infectious agent by study drug	0	0	0	0

AESI=Adverse Event of Special Interest; APTC = Antiplatelet Trialists" Collaboration; IOI=Intraocular Inflammation; MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W); SAE=Serious Adverse Event; VA = Visual Acuity; MedDRA = Medical Dictionary for Regulatory Activities.
APTC events are defined as non-fatal strokes or non-fatal myocardial infarctions or vascular deaths (including deaths of unknown cause). Investigator text for AEs encoded using MedDRA version 23.1.
Drop in VA score >=30 is defined as causing a decrease of >=30 VA score lasting more than 1 hour.
Intervention req. to prevent permanent vision loss is defined as required surgical or medical intervention to prevent permanent loss of sight.
Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for the "Total number of AEs" row in which multiple occurrences of the same AE are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

Program: root/clinical_studies/RO6867461/CDT70122/GR40349/data_analysis/CTD_Yosemite/prod/program/t_ae_oview.sas
Output: root/clinical_studies/RO6867461/CDT70122/GR40349/data_analysis/CTD_Yosemite/prod/output/t_ae_oview_W56_SE_JP_dme.out
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表 2.7.4.4.1.3.2-3　56週時までに発現した有害事象の概況（DME, GR40349試験－日本部分集団）（続）

Safety Summary through Week 56 in Japanese Subpopulation, Safety-Evaluable Population, Japan Subgroup
Protocol: GR40349
Clinical Cutoff Date: 20OCT2020

	Faricimab 6 mg Q8W (N=21)	Faricimab 6 mg PTI (N=19)	Faricimab 6 mg All (N=40)	Aflibercept 2 mg Q8W (N=20)
Non-ocular events total number of patients with at least one				
AE	13 (61.9%)	11 (57.9%)	24 (60.0%)	14 (70.0%)
SAE	2 (9.5%)	3 (15.8%)	5 (12.5%)	1 (5.0%)
AE leading to withdrawal from study treatment	0	0	0	1 (5.0%)
AE of Special Interest	0	0	0	0
Elevated ALT or AST with either elevated bilirubin or clinical jaundice	0	0	0	0
Adjudicated APTC events	0	0	0	0
Non-fatal MI	0	0	0	0
Non-fatal Stroke	0	0	0	0
Death	0	0	0	0

AESI=Adverse Event of Special Interest; APTC = Antiplatelet Trialists" Collaboration; IOI=Intraocular Inflammation; MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W); SAE=Serious Adverse Event; VA = Visual Acuity; MedDRA = Medical Dictionary for Regulatory Activities.
APTC events are defined as non-fatal strokes or non-fatal myocardial infarctions or vascular deaths (including deaths of unknown cause). Investigator text for AEs encoded using MedDRA version 23.1.
Drop in VA score >=30 is defined as causing a decrease of >=30 VA score lasting more than 1 hour.
Intervention req. to prevent permanent vision loss is defined as required surgical or medical intervention to prevent permanent loss of sight.
Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for the "Total number of AEs" row in which multiple occurrences of the same AE are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

Program: root/clinical_studies/RO6867461/CDT70122/GR40349/data_analysis/CTD_Yosemite/prod/program/t_ae_oview.sas
Output: root/clinical_studies/RO6867461/CDT70122/GR40349/data_analysis/CTD_Yosemite/prod/output/t_ae_oview_W56_SE_JP_dme.out
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[5.3.5.3-nAMD-1 t_ae_oview_W56_SE_JP_dme を再掲]

表 2.7.4.4.1.3.2-4　56週時までに試験眼に発現した有害事象（DME，GR40349試験－日本部分集団）

Ocular Adverse Events in the Study Eye through Week 56 in Japanese Subpopulation, Safety-Evaluable Population, Japan Subgroup
Protocol: GR40349
Clinical Cutoff Date: 20OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=21)	Faricimab 6 mg PTI (N=19)	Faricimab 6 mg All run (N=40)	Aflibercept 2 mg Q8W (N=20)
Total number of patients with at least one adverse event	5 (23.8%)	6 (31.6%)	11 (27.5%)	8 (40.0%)
Overall total number of events	9	7	16	8
眼障害				
Total number of patients with at least one adverse event	5 (23.8%)	6 (31.6%)	11 (27.5%)	8 (40.0%)
Total number of events	7	7	14	8
結膜出血	0	1 (5.3%)	1 (2.5%)	2 (10.0%)
ぶどう膜炎	1 (4.8%)	1 (5.3%)	2 (5.0%)	0
ドライアイ	2 (9.5%)	0	2 (5.0%)	0
白内障	0	0	0	2 (10.0%)
黄斑線維症	1 (4.8%)	0	1 (2.5%)	0
角膜びらん	0	1 (5.3%)	1 (2.5%)	0
角膜後面沈着物	0	1 (5.3%)	1 (2.5%)	0
眼脂	0	0	0	1 (5.0%)
眼痛	0	0	0	1 (5.0%)
眼瞼炎	1 (4.8%)	0	1 (2.5%)	0
後天性涙道狭窄	0	1 (5.3%)	1 (2.5%)	0
後嚢部混濁	1 (4.8%)	0	1 (2.5%)	0
視測障害	1 (4.8%)	0	1 (2.5%)	0
色素散乱症候群	0	1 (5.3%)	1 (2.5%)	0
点状角膜炎	0	0	0	1 (5.0%)
糖尿病網膜症	0	0	0	1 (5.0%)
網膜静脈閉塞	0	1 (5.3%)	1 (2.5%)	0
臨床検査				
Total number of patients with at least one adverse event	1 (4.8%)	0	1 (2.5%)	0
Total number of events	2	0	2	0
眼圧上昇	1 (4.8%)	0	1 (2.5%)	0

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

Program: root/clinical_studies/RO6867461/CDT70122/GR40349/data_analysis/CTD_Yosemite/prod/program/t_ae.sas
Output: root/clinical_studies/RO6867461/CDT70122/GR40349/data_analysis/CTD_Yosemite/prod/output/t_ae_SOCUL_W56_SE_JP_dme.out
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[5.3.5.3-nAMD-1 t_ae_SOCUL_W56_SE_JP_dme を再掲]

表 2.7.4.4.1.3.2-5　56週時までに試験眼に発現した副作用（DME，GR40349試験－日本部分集団）

Ocular Adverse Events Related to Study Treatment in the Study Eye through Week 56 in Japanese Subpopulation, Safety-Evaluable Population, Japan Subgroup
Protocol: GR40349
Clinical Cutoff Date: 20OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=21)	Faricimab 6 mg PTI (N=19)	Faricimab 6 mg All run (N=40)	Aflibercept 2 mg Q8W (N=20)
Total number of patients with at least one adverse event	3 (14.3%)	1 (5.3%)	4 (10.0%)	0
Overall total number of events	4	2	6	0
眼障害				
Total number of patients with at least one adverse event	2 (9.5%)	1 (5.3%)	3 (7.5%)	0
Total number of events	2	2	4	0
ぶどう膜炎	1 (4.8%)	1 (5.3%)	2 (5.0%)	0
黄斑線維症	1 (4.8%)	0	1 (2.5%)	0
角膜後面沈着物	0	1 (5.3%)	1 (2.5%)	0
臨床検査				
Total number of patients with at least one adverse event	1 (4.8%)	0	1 (2.5%)	0
Total number of events	2	0	2	0
眼圧上昇	1 (4.8%)	0	1 (2.5%)	0

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

Program: root/clinical_studies/RO6867461/CDT70122/GR40349/data_analysis/CTD_Yosemite/prod/program/t_ae.sas
Output: root/clinical_studies/RO6867461/CDT70122/GR40349/data_analysis/CTD_Yosemite/prod/output/t_ae_SOCUL_SREL_W56_SE_JP_dme.out
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[5.3.5.3-nAMD-1 t_ae_SOCUL_SREL_W56_SE_JP_dme を再掲]

表 2.7.4.4.1.3.2-6 56週時までに非試験眼に発現した有害事象（DME, GR40349試験－日本部分集団）

Ocular Adverse Events in the Fellow Eye through Week 56 in Japanese Subpopulation, Safety-Evaluable Population, Japan Subgroup
Protocol: GR40349
Clinical Cutoff Date: 20OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=21)	Faricimab 6 mg PTI (N=19)	Faricimab 6 mg All run (N=40)	Aflibercept 2 mg Q8W (N=20)
Total number of patients with at least one adverse event	4 (19.0%)	11 (57.9%)	15 (37.5%)	6 (30.0%)
Overall total number of events	4	15	19	7
眼障害				
Total number of patients with at least one adverse event	4 (19.0%)	11 (57.9%)	15 (37.5%)	5 (25.0%)
Total number of events	4	15	19	6
糖尿病性網膜浮腫	1 (4.8%)	3 (15.8%)	4 (10.0%)	1 (5.0%)
白内障	0	1 (5.3%)	1 (2.5%)	2 (10.0%)
ドライアイ	1 (4.8%)	1 (5.3%)	2 (5.0%)	0
眼瞼炎	1 (4.8%)	1 (5.3%)	2 (5.0%)	0
糖尿病網膜症	0	1 (5.3%)	1 (2.5%)	1 (5.0%)
アレルギー性眼瞼炎	0	1 (5.3%)	1 (2.5%)	0
アレルギー性結膜炎	0	1 (5.3%)	1 (2.5%)	0
黄斑線維症	0	0	0	1 (5.0%)
眼脂	0	0	0	1 (5.0%)
結膜出血	0	1 (5.3%)	1 (2.5%)	0
後天性涙道狭窄	0	1 (5.3%)	1 (2.5%)	0
後嚢部混濁	1 (4.8%)	0	1 (2.5%)	0
硝子体出血	0	1 (5.3%)	1 (2.5%)	0
硝子体剥離	0	1 (5.3%)	1 (2.5%)	0
硝子体浮遊物	0	1 (5.3%)	1 (2.5%)	0
臨床検査				
Total number of patients with at least one adverse event	0	0	0	1 (5.0%)
Total number of events	0	0	0	1
眼圧上昇	0	0	0	1 (5.0%)

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

Program: root/clinical_studies/RO6867461/CDT70122/GR40349/data_analysis/CTD_Yosemite/prod/program/t_ae.sas
Output: root/clinical_studies/RO6867461/CDT70122/GR40349/data_analysis/CTD_Yosemite/prod/output/t_ae_FOCUL_W56_SE_JP_dme.out
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[5.3.5.3-nAMD-1 t_ae_FOCUL_W56_SE_JP_dme を再掲]

表 2.7.4.4.1.3.2-7　56週時までに眼以外に発現した有害事象（DME，GR40349試験－日本部分集団）

Non-Ocular Adverse Events through Week 56 in Japanese Subpopulation, Safety-Evaluable Population, Japan Subgroup
Protocol: GR40349
Clinical Cutoff Date: 20OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=21)	Faricimab 6 mg PTI (N=19)	Faricimab 6 mg All run (N=40)	Aflibercept 2 mg Q8W (N=20)
Total number of patients with at least one adverse event	13 (61.9%)	11 (57.9%)	24 (60.0%)	14 (70.0%)
Overall total number of events	42	25	67	32
感染症および寄生虫症				
Total number of patients with at least one adverse event	5 (23.8%)	6 (31.6%)	11 (27.5%)	8 (40.0%)
Total number of events	9	8	17	10
上咽頭炎	4 (19.0%)	2 (10.5%)	6 (15.0%)	2 (10.0%)
歯肉炎	1 (4.8%)	1 (5.3%)	2 (5.0%)	0
帯状疱疹	0	1 (5.3%)	1 (2.5%)	1 (5.0%)
インフルエンザ	0	0	0	1 (5.0%)
胃腸炎	0	1 (5.3%)	1 (2.5%)	0
咽頭炎	0	0	0	1 (5.0%)
感染性皮膚嚢腫	0	0	0	1 (5.0%)
限局性感染	0	0	0	1 (5.0%)
歯髄炎	1 (4.8%)	0	1 (2.5%)	0
腎盂腎炎	0	0	0	1 (5.0%)
爪囲炎	0	1 (5.3%)	1 (2.5%)	0
糖尿病性足感染	0	0	0	1 (5.0%)
副鼻腔炎	0	1 (5.3%)	1 (2.5%)	0
膀胱炎	1 (4.8%)	0	1 (2.5%)	0
傷害、中毒および処置合併症				
Total number of patients with at least one adverse event	3 (14.3%)	4 (21.1%)	7 (17.5%)	3 (15.0%)
Total number of events	6	6	12	3
節足動物咬傷	0	2 (10.5%)	2 (5.0%)	0
転倒	1 (4.8%)	1 (5.3%)	2 (5.0%)	0
熱傷	1 (4.8%)	1 (5.3%)	2 (5.0%)	0
挫傷	0	0	0	1 (5.0%)
歯牙破折	0	0	0	1 (5.0%)
大腿骨骨折	0	1 (5.3%)	1 (2.5%)	0
皮膚擦過傷	1 (4.8%)	0	1 (2.5%)	0
皮膚裂傷	1 (4.8%)	0	1 (2.5%)	0
肋骨骨折	0	0	0	1 (5.0%)
脛骨骨折	1 (4.8%)	0	1 (2.5%)	0
神経系障害				
Total number of patients with at least one adverse event	3 (14.3%)	2 (10.5%)	5 (12.5%)	2 (10.0%)
Total number of events	5	2	7	2
糖尿病性ニューロパチー	0	1 (5.3%)	1 (2.5%)	1 (5.0%)
頭痛	2 (9.5%)	0	2 (5.0%)	0
アルツハイマー型認知症	0	0	0	1 (5.0%)
感覚鈍麻	1 (4.8%)	0	1 (2.5%)	0
坐骨神経痛	0	1 (5.3%)	1 (2.5%)	0
神経痛	1 (4.8%)	0	1 (2.5%)	0

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

Program: root/clinical_studies/RO6867461/CDT70122/GR40349/data_analysis/CTD_Yosemite/prod/program/t_ae.sas
Output: root/clinical_studies/RO6867461/CDT70122/GR40349/data_analysis/CTD_Yosemite/prod/output/t_ae_NOCUL_W56_SE_JP_dme.out
27JAN2021 14:24

表 2.7.4.4.1.3.2-7 56週時までに眼以外に発現した有害事象（DME, GR40349試験－日本部分集団）（続）

Non-Ocular Adverse Events through Week 56 in Japanese Subpopulation, Safety-Evaluable Population, Japan Subgroup
Protocol: GR40349
Clinical Cutoff Date: 20OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=21)	Faricimab 6 mg PTI (N=19)	Faricimab 6 mg All run (N=40)	Aflibercept 2 mg Q8W (N=20)
胃腸障害				
Total number of patients with at least one adverse event	3 (14.3%)	1 (5.3%)	4 (10.0%)	2 (10.0%)
Total number of events	3	1	4	2
齲歯	2 (9.5%)	0	2 (5.0%)	0
胃炎	0	0	0	1 (5.0%)
消化不良	0	1 (5.3%)	1 (2.5%)	0
上腹部痛	1 (4.8%)	0	1 (2.5%)	0
便秘	0	0	0	1 (5.0%)
筋骨格系および結合組織障害				
Total number of patients with at least one adverse event	2 (9.5%)	2 (10.5%)	4 (10.0%)	2 (10.0%)
Total number of events	3	2	5	2
筋痙縮	0	0	0	2 (10.0%)
関節周囲炎	1 (4.8%)	0	1 (2.5%)	0
筋骨格硬直	1 (4.8%)	0	1 (2.5%)	0
骨粗鬆症	0	1 (5.3%)	1 (2.5%)	0
背部痛	0	1 (5.3%)	1 (2.5%)	0
変形性関節症	1 (4.8%)	0	1 (2.5%)	0
代謝および栄養障害				
Total number of patients with at least one adverse event	3 (14.3%)	0	3 (7.5%)	2 (10.0%)
Total number of events	3	0	3	2
高脂血症	1 (4.8%)	0	1 (2.5%)	1 (5.0%)
糖尿病	2 (9.5%)	0	2 (5.0%)	0
高尿酸血症	0	0	0	1 (5.0%)
皮膚および皮下組織障害				
Total number of patients with at least one adverse event	2 (9.5%)	2 (10.5%)	4 (10.0%)	0
Total number of events	3	3	6	0
皮膚嚢腫	2 (9.5%)	0	2 (5.0%)	0
過角化	1 (4.8%)	0	1 (2.5%)	0
手皮膚炎	0	1 (5.3%)	1 (2.5%)	0
蕁麻疹	0	1 (5.3%)	1 (2.5%)	0
呼吸器、胸郭および縦隔障害				
Total number of patients with at least one adverse event	3 (14.3%)	0	3 (7.5%)	1 (5.0%)
Total number of events	4	0	4	1
咳嗽	2 (9.5%)	0	2 (5.0%)	0
口腔咽頭痛	1 (4.8%)	0	1 (2.5%)	0
上気道の炎症	0	0	0	1 (5.0%)
肺塞栓症	1 (4.8%)	0	1 (2.5%)	0
耳および迷路障害				
Total number of patients with at least one adverse event	1 (4.8%)	1 (5.3%)	2 (5.0%)	0
Total number of events	1	1	2	0
耳閉	1 (4.8%)	0	1 (2.5%)	0
突発性難聴	0	1 (5.3%)	1 (2.5%)	0

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

Program: root/clinical_studies/RO6867461/CDT70122/GR40349/data_analysis/CTD_Yosemite/prod/program/t_ae.sas
Output: root/clinical_studies/RO6867461/CDT70122/GR40349/data_analysis/CTD_Yosemite/prod/output/t_ae_NOCUL_W56_SE_JP_dme.out
27JAN2021 14:24

表 2.7.4.4.1.3.2-7 56週時までに眼以外に発現した有害事象（DME, GR40349試験－日本部分集団）（続）

Non-Ocular Adverse Events through Week 56 in Japanese Subpopulation, Safety-Evaluable Population, Japan Subgroup
Protocol: GR40349
Clinical Cutoff Date: 20OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=21)	Faricimab 6 mg PTI (N=19)	Faricimab 6 mg All run (N=40)	Aflibercept 2 mg Q8W (N=20)
免疫系障害				
Total number of patients with at least one adverse event	2 (9.5%)	0	2 (5.0%)	0
Total number of events	2	0	2	0
過敏症	1 (4.8%)	0	1 (2.5%)	0
造影剤反応	1 (4.8%)	0	1 (2.5%)	0
臨床検査				
Total number of patients with at least one adverse event	1 (4.8%)	0	1 (2.5%)	2 (10.0%)
Total number of events	1	0	1	2
ヘリコバクター検査陽性	1 (4.8%)	0	1 (2.5%)	0
血圧上昇	0	0	0	1 (5.0%)
血中尿酸増加	0	0	0	1 (5.0%)
血液およびリンパ系障害				
Total number of patients with at least one adverse event	0	1 (5.3%)	1 (2.5%)	1 (5.0%)
Total number of events	0	1	1	1
貧血	0	1 (5.3%)	1 (2.5%)	1 (5.0%)
心臓障害				
Total number of patients with at least one adverse event	1 (4.8%)	0	1 (2.5%)	1 (5.0%)
Total number of events	1	0	1	2
うっ血性心不全	0	0	0	1 (5.0%)
心筋梗塞	0	0	0	1 (5.0%)
動悸	1 (4.8%)	0	1 (2.5%)	0
腎および尿路障害				
Total number of patients with at least one adverse event	0	1 (5.3%)	1 (2.5%)	1 (5.0%)
Total number of events	0	1	1	1
頻尿	0	0	0	1 (5.0%)
夜間頻尿	0	1 (5.3%)	1 (2.5%)	0
精神障害				
Total number of patients with at least one adverse event	1 (4.8%)	0	1 (2.5%)	0
Total number of events	1	0	1	0
不眠症	1 (4.8%)	0	1 (2.5%)	0
一般・全身障害および投与部位の状態				
Total number of patients with at least one adverse event	0	0	0	1 (5.0%)
Total number of events	0	0	0	1
発熱	0	0	0	1 (5.0%)
血管障害				
Total number of patients with at least one adverse event	0	0	0	1 (5.0%)
Total number of events	0	0	0	1
高血圧	0	0	0	1 (5.0%)
生殖系および乳房障害				
Total number of patients with at least one adverse event	0	0	0	1 (5.0%)
Total number of events	0	0	0	1
良性前立腺肥大症	0	0	0	1 (5.0%)

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

Program: root/clinical_studies/RO6867461/CDT70122/GR40349/data_analysis/CTD_Yosemite/prod/program/t_ae.sas
Output: root/clinical_studies/RO6867461/CDT70122/GR40349/data_analysis/CTD_Yosemite/prod/output/t_ae_NOCUL_W56_SE_JP_dme.out
27JAN2021 14:24

表 2.7.4.4.1.3.2-7 56週時までに眼以外に発現した有害事象（DME, GR40349試験－日本部分集団）（続）

Non-Ocular Adverse Events through Week 56 in Japanese Subpopulation, Safety-Evaluable Population, Japan Subgroup
Protocol: GR40349
Clinical Cutoff Date: 20OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=21)	Faricimab 6 mg PTI (N=19)	Faricimab 6 mg All run (N=40)	Aflibercept 2 mg Q8W (N=20)
内分泌障害				
Total number of patients with at least one adverse event	0	0	0	1 (5.0%)
Total number of events	0	0	0	1
甲状腺機能低下症	0	0	0	1 (5.0%)

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

Program: root/clinical_studies/RO6867461/CDT70122/GR40349/data_analysis/CTD_Yosemite/prod/program/t_ae.sas
Output: root/clinical_studies/RO6867461/CDT70122/GR40349/data_analysis/CTD_Yosemite/prod/output/t_ae_NOCUL_W56_SE_JP_dme.out
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[5.3.5.3-nAMD-1 t_ae_NOCUL_W56_SE_JP_dme を再掲]

表 2.7.4.4.1.3.2-8 56週時までに眼以外に発現した副作用（DME, GR40349試験－日本部分集団）

Non-Ocular Adverse Events Related to Study Treatment through Week 56 in Japanese Subpopulation, Safety-Evaluable Population, Japan Subgroup
Protocol: GR40349
Clinical Cutoff Date: 20OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=21)	Faricimab 6 mg PTI (N=19)	Faricimab 6 mg All run (N=40)	Aflibercept 2 mg Q8W (N=20)
Total number of patients with at least one adverse event	0	1 (5.3%)	1 (2.5%)	0
Overall total number of events	0	1	1	0
耳および迷路障害				
Total number of patients with at least one adverse event	0	1 (5.3%)	1 (2.5%)	0
Total number of events	0	1	1	0
突発性難聴	0	1 (5.3%)	1 (2.5%)	0

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

Program: root/clinical_studies/RO6867461/CDT70122/GR40349/data_analysis/CTD_Yosemite/prod/program/t_ae.sas
Output: root/clinical_studies/RO6867461/CDT70122/GR40349/data_analysis/CTD_Yosemite/prod/output/t_ae_NOCUL_SREL_W56_SE_JP_dme.out
27JAN2021 14:25 Page 1 of 1

[5.3.5.3-nAMD-1 t_ae_NOCUL_SREL_W56_SE_JP_dme を再掲]

2.7.4.4.1.3.3 nAMD（GR40306試験の日本部分集団及び日本延長コホート）

1) 患者の内訳

グローバル登録日本部分集団（データカットオフ日：2021年1月19日）及び日本延長コホート期間中に追加登録した日本部分集団（データカットオフ日：2021年5月26日）は合計で133例であり，本剤群及びアフリベルセプト群にそれぞれ66例及び67例であった。これらの内，主要解析の日本部分集団は52例（本剤群及びアフリベルセプト群に各26例），日本延長コホートは81例（本剤群及びアフリベルセプト群にそれぞれ40例及び41例）であった。以降，本項では断りのない限り，133例での結果を記載する。

登録された全例に治験薬が投与され，本剤群の6.1%（4例）が治験薬の投与中止に至り，アフリベルセプト群では治験薬の投与中止に至った患者はいなかった。治験薬の投与中止に至った理由の内訳は，治験責任（分担）医師の判断が2例，効果不十分及び同意撤回が各1例であった。

治験中止に至った患者は，割付けられた群では本剤群に4.5%（3例）認められ，アフリベルセプト群に該当例はいなかった。治験中止に至った理由の内訳は，同意撤回が2例，治験責任（分担）医師の判断が1例であった（表 2.7.4.4.1.3.3-1）。

表 2.7.4.4.1.3.3-1　52週時までの患者の内訳（nAMD, GR40306試験－日本部分集団及び日本延長コホート）

Patient Disposition and Reason for Discontinuation through Week 52, Intent-to-Treat Population, Japanese Subpopulation
Protocol: GR40306
Clinical Cutoff Date: TENAYA 19JAN2021 (global enrollment) 26MAY2021 (Japan extension)

Status / Primary Reason for Discontinuation	GR40306(TENAYA) (N=133)	
	Faricimab 6 mg (N=66)	Aflibercept 2 mg (N=67)
Number of Patients Randomized	66 (100.0%)	67 (100.0%)
Number of Patients Treated	66 (100.0%)	67 (100.0%)
Discontinued Study Treatment in study eye through Week 52*		
Total	4 (6.1%)	0
Adverse Event	0	0
Pregnancy	0	0
Death	0	0
Lack of Efficacy	1 (1.5%)	0
Lost To Follow-up	0	0
Protocol Deviation	0	0
Withdrawal by Subject	1 (1.5%)	0
Physician decision	2 (3.0%)	0
Other	0	0
Discontinued Study through Week 52**		
Total	3 (4.5%)	0
Adverse Event	0	0
Pregnancy	0	0
Death	0	0
Lack of Efficacy	0	0
Lost To Follow-up	0	0
Protocol Deviation	0	0
Withdrawal by Subject	2 (3.0%)	0
Physician decision	1 (1.5%)	0
Other	0	0

*Percentages are based on number of patients treated.
**Percentages are based on number of patients randomized.
Includes discontinuation occurring prior to Day 350 (first day of Week 52 analysis visit window).

Program: root/clinical_studies/RO6867461/CDPT7716/share/pool_nAMD_Chugai/prod/program/t_ds.sas
Output: root/clinical_studies/RO6867461/CDPT7716/share/pool_nAMD_Chugai/prod/output/t_ds_IT_JP_nAMD_JPN.out
05JUL2021 11:08

[5.3.5.1-nAMD-5 表 4.1-1を再掲]

2) 患者背景

グローバル登録日本部分集団及び日本延長コホート期間中に追加登録した日本部分集団においてベースライン時の患者背景は投与群間で同様であった（表 2.7.4.4.1.3.3-2）。

登録時の平均年齢は本剤群72.1歳，アフリベルセプト群71.8歳であり，75歳未満の患者が半数以上（本剤群及びアフリベルセプト群でそれぞれ60.6%及び58.2%）であり，投与群間で同様であった。男性が半数以上（それぞれ81.8%及び67.2%）であった。本剤群における男性の割合はアフリベルセプト群に比べて高かった（表 2.7.4.4.1.3.3-2）。

表 2.7.4.4.1.3.3-2 人口統計学的特性の要約（nAMD，GR40306試験－日本部分集団及び日本延長コホート）

Demographics, Intent-to-Treat Population, Japanese Subpopulation
Protocol: GR40306
Clinical Cutoff Date: TENAYA 19JAN2021 (global enrollment) 26MAY2021 (Japan extension)

	GR40306(TENAYA) (N=133)	
	Faricimab 6 mg (N=66)	Aflibercept 2 mg (N=67)
Region		
n	66	67
Asia	66 (100%)	67 (100%)
Age (years)		
n	66	67
Mean (SD)	72.1 (7.5)	71.8 (9.5)
Median	72.0	72.0
Min - Max	50 - 91	53 - 90
Age group (years)		
n	66	67
<75	40 (60.6%)	39 (58.2%)
>=75	26 (39.4%)	28 (41.8%)
<65	10 (15.2%)	15 (22.4%)
>=65 - <75	30 (45.5%)	24 (35.8%)
>=75 - <85	23 (34.8%)	24 (35.8%)
>=85	3 (4.5%)	4 (6.0%)
Sex		
n	66	67
Male	54 (81.8%)	45 (67.2%)
Female	12 (18.2%)	22 (32.8%)
Ethnicity		
n	66	67
Not Hispanic or Latino	66 (100%)	67 (100%)

Age at randomization.

Program: root/clinical_studies/RO6867461/CDPT7716/share/pool_nAMD_Chugai/prod/program/t_dm.sas
Output: root/clinical_studies/RO6867461/CDPT7716/share/pool_nAMD_Chugai/prod/output/t_dm_IT_JP_nAMD_JPN.out
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表 2.7.4.4.1.3.3-2　人口統計学的特性の要約（nAMD，GR40306試験－日本部分集団及び日本延長コホート）（続）

Demographics, Intent-to-Treat Population, Japanese Subpopulation
Protocol: GR40306
Clinical Cutoff Date: TENAYA 19JAN2021 (global enrollment) 26MAY2021 (Japan extension)

	GR40306(TENAYA) (N=133)	
	Faricimab 6 mg (N=66)	Aflibercept 2 mg (N=67)
Race		
n	66	67
Asian	66 (100%)	67 (100%)
Japanese	66 (100%)	67 (100%)

Age at randomization.

Program: root/clinical_studies/RO6867461/CDPT7716/share/pool_nAMD_Chugai/prod/program/t_dm.sas
Output: root/clinical_studies/RO6867461/CDPT7716/share/pool_nAMD_Chugai/prod/output/t_dm_IT_JP_nAMD_JPN.out
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[5.3.5.1-nAMD-5 表 4.5.1-1を再掲]

3)　治験薬の曝露状況

52週時までの投与期間の中央値はいずれの投与群においても52.1週であり，投与群間で一致していた（表 2.7.4.4.1.3.3-3）。

表 2.7.4.4.1.3.3-3 52週時までの曝露状況（nAMD，GR40306試験－日本部分集団及び日本延長コホート）

Summary of Study Treatment Exposure in the Study Eye through Week 52, Safety-Evaluable Population, Japanese Subpopulation
Protocol: GR40306
Clinical Cutoff Date: TENAYA 19JAN2021 (global enrollment) 26MAY2021 (Japan extension)

	GR40306(TENAYA) (N=133)	
	Faricimab 6 mg (N=66)	Aflibercept 2 mg (N=67)
Treatment duration (weeks)		
n	66	67
Mean (SD)	49.9 (8.73)	52.2 (0.74)
Median	52.1	52.1
Min-max	4 - 53	48 - 53
Number of study drug administrations		
n	66	67
Mean (SD)	6.2 (1.17)	7.9 (0.46)
Median	6.0	8.0
Min-max	2 - 9	5 - 9
Dose interruption		
Number of doses interrupted	11	11
At least one interrupted dose	8 (12.1%)	6 (9.0%)
Intraocular inflammation	1 (1.5%)	0
BCVA decrease	1 (1.5%)	0
Rhegmatogenous retinal break	2 (3.0%)	1 (1.5%)
Active infection	3 (4.5%)	4 (6.0%)
Intraocular surgery in the study eye	1 (1.5%)	1 (1.5%)
Other	2 (3.0%)	0
Interruptions per patient		
n	8	6
1	6 (9.1%)	5 (7.5%)
2	1 (1.5%)	0
3	1 (1.5%)	0
6	0	1 (1.5%)

BCVA = Best-corrected Visual Acuity.
Study drug corresponds to faricimab or aflibercept. Study treatment corresponds to faricimab, aflibercept or sham. Treatment duration is the (maximum of the date of the last dose of study treatment and the date of the last treatment dose hold) minus the date of the first dose plus one day.
Percentages are based on N in the column headings. The number of study drug administrations may include any active drug administered including medication errors. The number of injections does not take into account the use of prohibited therapies.
Includes study treatment received and dose hold on or prior to Day 377 (last day of Week 52 analysis visit window).

Program: root/clinical_studies/RO6867461/CDPT7716/share/pool_nAMD_Chugai/prod/program/t_ex.sas
Output: root/clinical_studies/RO6867461/CDPT7716/share/pool_nAMD_Chugai/prod/output/t_ex_SE_JP_nAMD_JPN.out
05JUL2021 11:56
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[5.3.5.1-nAMD-5 表 5-1を再掲]

4) 安全性の結果

52週時までの結果を以下に記載する（表 2.7.4.4.1.3.3-4）。

- 有害事象の発現頻度は本剤群及びアフリベルセプト群でそれぞれ 71.2%（47/66 例）及び 64.2%（43/67 例）であり，投与群間で大きな違いはなかった。
- 試験眼に発現した有害事象の発現頻度は本剤群及びアフリベルセプト群でそれぞれ 21.2%及び 25.4%であり，投与群間で同様であった。
- いずれかの群の 2%以上で試験眼に発現した有害事象はアレルギー性結膜炎，新生血管加齢黄斑変性及びドライアイであり，試験全体の結果（5.3.5.3-nAMD-3 表 2.1.1-8）と大きな違いはなかった（表 2.7.4.4.1.3.3-5）。

- 試験眼に発現した副作用の発現頻度は本剤群及びアフリベルセプト群でいずれも 3.0%であり，また，試験全体（それぞれ 2.7%及び 2.7%，表 2.7.4.2.9-1）と同様であった。
- いずれかの群の 2%以上で試験眼に発現した副作用はなかった（表 2.7.4.4.1.3.3-6）。
- 非試験眼に発現した有害事象の発現頻度は本剤群及びアフリベルセプト群でそれぞれ 21.2%及び 17.9%と投与群間で大きな違いはなく，また試験全体（23.9%及び 25.7%，表 2.7.4.2.9-1）とも同様であった（表 2.7.4.4.1.3.3-7）。非試験眼に発現した有害事象はいずれも治験薬との因果関係は否定された（表 2.7.4.4.1.3.3-8）。
- 試験眼に発現した重症度が高度の有害事象は本剤群に認められず，アフリベルセプト群の 1 例（新生血管加齢黄斑変性）で認められた（表 2.7.4.4.1.3.3-9）。新生血管加齢黄斑変性は治験薬との因果関係は否定された。
- 試験眼に発現した重篤な有害事象の発現頻度は本剤群及びアフリベルセプト群でいずれも 3.0%（本剤群 2 例：白内障及び裂孔原性網膜剥離，アフリベルセプト群 2 例：嚢下白内障及び新生血管加齢黄斑変性）であり，また試験全体（いずれの群も 2.1%，表 2.7.4.2.9-1）とも同様であった（表 2.7.4.4.1.3.3-10）。これらの内，重篤な副作用はアフリベルセプト群の 1 例（嚢下白内障）であった（表 2.7.4.4.1.3.3-11）。各症例の叙述を 5.3.5.1-nAMD-5 8 に記載した。
- 試験眼に発現した治験薬の投与中止に至った有害事象（表 2.7.4.4.1.3.3-12）及び治験中止に至った有害事象はいずれの群にも認められなかった（表 2.7.4.4.1.3.3-13）。試験眼に発現した休薬に至った有害事象は本剤群及びアフリベルセプト群でそれぞれ 12.1%及び 9.0%と投与群間で大きな違いはなかった。しかし，試験全体（4.3%及び 3.2%，5.3.5.3-nAMD-3 表 2.1.1-17）と比較していずれの群も発現頻度が高かった（5.3.5.1-nAMD-5 表 6-11）。
- 試験眼に発現した AESI は本剤群及びアフリベルセプト群でそれぞれ 1 例（裂孔原性網膜剥離）及び 2 例（新生血管加齢黄斑変性及び嚢下白内障）で認められた。本剤群及びアフリベルセプト群の各 1 例（それぞれ裂孔原性網膜剥離及び嚢下白内障）が 1 時間を超える 30 文字以上の視力低下に至った AESI に該当した。アフリベルセプト群の 1 例（新生血管加齢黄斑変性）は，永続的な失明を回避するために内科的/外科的介入が必要となった事象に該当した。
- 52 週時までに試験眼に発現した眼内炎症は本剤群に 3.0%（2 例，虹彩炎及びぶどう膜炎）認められ，アフリベルセプト群では認められなかった（5.3.5.1-nAMD-5 表 6.3-1）。52 週時までに試験眼に発現した網膜血管閉塞事象は，いずれの群にも認められなかった（5.3.5.1-nAMD-5 表 6.3-2）。
- 眼以外に発現した有害事象の発現頻度は本剤群及びアフリベルセプト群でそれぞれ 65.2%及び 52.2%であり，本剤群では，アフリベルセプト群に比べて高く，試験全体（56.3%， 表 2.7.4.2.9-1）に比べてもやや高かった。しかし，眼以外に発現した副作用の発現頻度は本剤群及びアフリベルセプト群いずれも 1.5%（1 例，それぞれ虚血性小腸炎及び高血圧）であった（表 2.7.4.4.1.3.3-15）。
- いずれかの群の 2%以上で眼以外に発現した有害事象（本剤群及びアフリベルセプト群別）は，上咽頭炎［10.6%（7 例）及び 13.4%（9 例）］，齲歯［10.6%（7 例）及び 3.0%（2 例）］，関節痛［6.1%（4 例）及び 4.5%（3 例）］，高血圧［4.5%（3 例）及び 3.0%（2 例）］，背部痛［3.0%（2 例）及び 3.0%（2 例）］，歯周炎，節足動物咬傷，頭痛［3.0%（2 例）及び 1.5%（1 例）］，便秘［1.5%（1 例）及び 4.5%（3 例）］，湿疹，浮動性めまい［4.5%（3 例）及び 0.0%（0 例）］，気管支炎，胃腸炎，腹痛，筋肉痛，関節周囲炎，転倒，手皮膚炎，肝機能検査値上昇［いずれも 3.0%（2 例）及び 0.0%（0 例）］，インフルエンザ，大腸ポリープ，挫傷［（いずれも 0.0%（0 例）及び 3.0%（2 例）］であった（表 2.7.4.4.1.3.3-14）。
- 眼以外に発現した重篤な有害事象の発現頻度は本剤群及びアフリベルセプト群でそれぞれ 13.6%（9 例）及び 6.0%（4 例）であり，本剤群の発現頻度はアフリベルセプト群に比べて

高かったものの，いずれかの群の 2%以上で眼以外に発現した重篤な有害事象はなかった（表 2.7.4.4.1.3.3-16）。眼以外に発現した重篤な副作用はアフリベルセプト群で認められず，本剤群で 1 例（虚血性小腸炎）認められた（表 2.7.4.4.1.3.3-17）。

- 死亡例又は死亡に至った有害事象はいずれの群にも認められなかった。
- 外部判定による APTC ATE（Anti-platelet Trialists' Collaboration で定義された動脈血栓塞栓事象）はいずれの群にも認められなかった（表 2.7.4.4.1.3.3-18）。

表 2.7.4.4.1.3.3-4　52週時までに発現した有害事象の概況（nAMD，GR40306試験－日本部分集団及び日本延長コホート）

Safety Summary through Week 52, Safety-Evaluable Population, Japanese Subpopulation
Protocol: GR40306
Clinical Cutoff Date: TENAYA 19JAN2021 (global enrollment) 26MAY2021 (Japan extension)

	GR40306(TENAYA) (N=133)	
	Faricimab 6 mg (N=66)	Aflibercept 2 mg (N=67)
Total number of patients with at least one AE	47 (71.2%)	43 (64.2%)
Total number of AEs	158	102
Total number of patients with at least one SAE	11 (16.7%)	8 (11.9%)
Total number of SAEs	14	8
Total number of deaths	0	0
Total number of patients withdrawn from study due to an AE	0	0
Total number of patients withdrawn from study treatment due to an AE	0	0
Total number of patients with at least one AESI	1 (1.5%)	3 (4.5%)
Ocular events: study eye total number of patients with at least one		
AE	14 (21.2%)	17 (25.4%)
SAE	2 (3.0%)	2 (3.0%)
AE leading to withdrawal from study treatment	0	0
Treatment related AEs	2 (3.0%)	2 (3.0%)
Treatment related SAEs	0	1 (1.5%)
AE of Special Interest	1 (1.5%)	2 (3.0%)
Drop in VA score >=30	1 (1.5%)	1 (1.5%)
Associated with severe IOI	0	0
Intervention req. to prevent permanent vision loss	0	1 (1.5%)
Suspected transmission of infectious agent by study drug	0	0

AE=Adverse Event; SAE=Serious Adverse Event; AESI=Adverse Event of Special Interest; APTC=Anti-Platelet Trialists' Collaboration. IOI=Intraocular Inflammation; VA=Visual Acuity.
APTC events are defined as non-fatal strokes or non-fatal myocardial infarctions or vascular deaths (including deaths of unknown cause).
Investigator text for AEs encoded using MedDRA version 24.0.
Drop in VA score >=30 is defined as causing a decrease of >=30 VA score (compared with the last of VA prior to the most recent assessment) lasting more than 1 hour.
Cases of potential drug-induced liver injury that include an elevated ALT or AST with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law.
Intervention req. to prevent permanent vision loss is defined as required surgical or medical intervention to prevent permanent loss of sight.
Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for the "Total number of AEs" row in which multiple occurrences of the same AE are counted separately.
Includes AEs with onset up to Day 377 (last day of Week 52 analysis visit window).

Program: root/clinical_studies/RO6867461/CDPT7716/share/pool_nAMD_Chugai/prod/program/t_ae_oview.sas
Output: root/clinical_studies/RO6867461/CDPT7716/share/pool_nAMD_Chugai/prod/output/t_ae_oview_W52_SE_JP_nAMD_JPN.out
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表 2.7.4.4.1.3.3-4　52週時までに発現した有害事象の概況（nAMD, GR40306試験－日本部分集団及び日本延長コホート）（続）

Safety Summary through Week 52, Safety-Evaluable Population, Japanese Subpopulation
Protocol: GR40306
Clinical Cutoff Date: TENAYA 19JAN2021 (global enrollment) 26MAY2021 (Japan extension)

	GR40306(TENAYA) (N=133)	
	Faricimab 6 mg (N=66)	Aflibercept 2 mg (N=67)
Ocular events: fellow eye total number of patients with at least one		
AE	14 (21.2%)	12 (17.9%)
SAE	1 (1.5%)	2 (3.0%)
AE of Special Interest	0	1 (1.5%)
Drop in VA score >=30	0	0
Associated with severe IOI	0	0
Intervention req. to prevent permanent vision loss	0	1 (1.5%)
Suspected transmission of infectious agent by study drug	0	0
Non-ocular events total number of patients with at least one		
AE	43 (65.2%)	35 (52.2%)
SAE	9 (13.6%)	4 (6.0%)
AE leading to withdrawal from study treatment	0	0
AE of Special Interest	0	0
Elevated ALT or AST with either elevated bilirubin or clinical jaundice	0	0

AE=Adverse Event; SAE=Serious Adverse Event; AESI=Adverse Event of Special Interest; APTC=Anti-Platelet Trialists' Collaboration. IOI=Intraocular Inflammation; VA=Visual Acuity.
APTC events are defined as non-fatal strokes or non-fatal myocardial infarctions or vascular deaths (including deaths of unknown cause).
Investigator text for AEs encoded using MedDRA version 24.0.
Drop in VA score >=30 is defined as causing a decrease of >=30 VA score (compared with the last of VA prior to the most recent assessment) lasting more than 1 hour.
Cases of potential drug-induced liver injury that include an elevated ALT or AST with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law.
Intervention req. to prevent permanent vision loss is defined as required surgical or medical intervention to prevent permanent loss of sight.
Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for the "Total number of AEs" row in which multiple occurrences of the same AE are counted separately.
Includes AEs with onset up to Day 377 (last day of Week 52 analysis visit window).

Program: root/clinical_studies/RO6867461/CDPT7716/share/pool_nAMD_Chugai/prod/program/t_ae_oview.sas
Output: root/clinical_studies/RO6867461/CDPT7716/share/pool_nAMD_Chugai/prod/output/t_ae_oview_W52_SE_JP_nAMD_JPN.out
21JUL2021 17:06

表 2.7.4.4.1.3.3-4　52週時までに発現した有害事象の概況（nAMD，GR40306試験－日本部分集団及び日本延長コホート）（続）

Safety Summary through Week 52, Safety-Evaluable Population, Japanese Subpopulation
Protocol: GR40306
Clinical Cutoff Date: TENAYA 19JAN2021 (global enrollment) 26MAY2021 (Japan extension)

	GR40306(TENAYA) (N=133)	
	Faricimab 6 mg (N=66)	Aflibercept 2 mg (N=67)
Adjudicated APTC events	0	0
Non-fatal MI	0	0
Non-fatal Stroke	0	0
Death	0	0

AE=Adverse Event; SAE=Serious Adverse Event; AESI=Adverse Event of Special Interest; APTC=Anti-Platelet Trialists' Collaboration. IOI=Intraocular Inflammation; VA=Visual Acuity.
APTC events are defined as non-fatal strokes or non-fatal myocardial infarctions or vascular deaths (including deaths of unknown cause).
Investigator text for AEs encoded using MedDRA version 24.0.
Drop in VA score >=30 is defined as causing a decrease of >=30 VA score (compared with the last of VA prior to the most recent assessment) lasting more than 1 hour.
Cases of potential drug-induced liver injury that include an elevated ALT or AST with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law.
Intervention req. to prevent permanent vision loss is defined as required surgical or medical intervention to prevent permanent loss of sight.
Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for the "Total number of AEs" row in which multiple occurrences of the same AE are counted separately.
Includes AEs with onset up to Day 377 (last day of Week 52 analysis visit window).

Program: root/clinical_studies/RO6867461/CDPT7716/share/pool_nAMD_Chugai/prod/program/t_ae_oview.sas
Output: root/clinical_studies/RO6867461/CDPT7716/share/pool_nAMD_Chugai/prod/output/t_ae_oview_W52_SE_JP_nAMD_JPN.out
21JUL2021 17:06

[5.3.5.1-nAMD-5 表 6-1を再掲]

表 2.7.4.4.1.3.3-5　52週時までに試験眼に発現した有害事象（nAMD，GR40306試験－日本部分集団及び日本延長コホート）

MedDRA Preferred Term	GR40306(TENAYA) (N=133) Faricimab 6 mg (N=66)	GR40306(TENAYA) (N=133) Aflibercept 2 mg (N=67)
Total number of patients with at least one adverse event	14 (21.2%)	17 (25.4%)
Total number of events	17	23
アレルギー性結膜炎	2 (3.0%)	2 (3.0%)
新生血管加齢黄斑変性	2 (3.0%)	2 (3.0%)
ドライアイ	2 (3.0%)	1 (1.5%)
白内障	1 (1.5%)	1 (1.5%)
結膜沈着物	1 (1.5%)	1 (1.5%)
結膜出血	1 (1.5%)	1 (1.5%)
点状角膜炎	1 (1.5%)	1 (1.5%)

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 24.0. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
AE reported as neovascular age-related macular degeneration in the study eye indicates an accelerated worsening of the condition, as judged by the investigator.
Includes AEs with onset up to Day 377 (last day of Week 52 analysis visit window).

表 2.7.4.4.1.3.3-5　52週時までに試験眼に発現した有害事象（nAMD，GR40306試験－日本部分集団及び日本延長コホート）（続）

MedDRA Preferred Term	GR40306(TENAYA) (N=133) Faricimab 6 mg (N=66)	GR40306(TENAYA) (N=133) Aflibercept 2 mg (N=67)
加齢黄斑変性	0	1 (1.5%)
嚢下白内障	0	1 (1.5%)
結膜炎	0	1 (1.5%)
角膜擦過傷	0	1 (1.5%)
乾性加齢黄斑変性	0	1 (1.5%)
落屑症候群	0	1 (1.5%)
眼内異物	1 (1.5%)	0
眼の異物感	0	1 (1.5%)
眼圧上昇	0	1 (1.5%)
虹彩炎	1 (1.5%)	0
流涙増加	0	1 (1.5%)
投薬過誤	0	1 (1.5%)
高眼圧症	1 (1.5%)	0
眼窩周囲血腫	1 (1.5%)	0
網膜裂孔	0	1 (1.5%)
裂孔原性網膜剥離	1 (1.5%)	0
ぶどう膜炎	1 (1.5%)	0
硝子体浮遊物	0	1 (1.5%)

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 24.0. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
AE reported as neovascular age-related macular degeneration in the study eye indicates an accelerated worsening of the condition, as judged by the investigator.
Includes AEs with onset up to Day 377 (last day of Week 52 analysis visit window).

[5.3.5.1-nAMD-5 表 6-2を再掲]

表 2.7.4.4.1.3.3-6　52週時までに試験眼に発現した副作用（nAMD，GR40306試験－日本部分集団及び日本延長コホート）

MedDRA Preferred Term	GR40306(TENAYA) (N=133) Faricimab 6 mg (N=66)	GR40306(TENAYA) (N=133) Aflibercept 2 mg (N=67)
Total number of patients with at least one adverse event	2 (3.0%)	2 (3.0%)
Total number of events	2	2
嚢下白内障	0	1 (1.5%)
眼圧上昇	0	1 (1.5%)
虹彩炎	1 (1.5%)	0
ぶどう膜炎	1 (1.5%)	0

MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 24.0.
Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 377 (last day of Week 52 analysis visit window).

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[5.3.5.1-nAMD-5 表 6-3を再掲]

表 2.7.4.4.1.3.3-7　52週時までに非試験眼に発現した有害事象（nAMD，GR40306試験－日本部分集団及び日本延長コホート）

MedDRA Preferred Term	GR40306(TENAYA) (N=133) Faricimab 6 mg (N=66)	GR40306(TENAYA) (N=133) Aflibercept 2 mg (N=67)
Total number of patients with at least one adverse event	14 (21.2%)	12 (17.9%)
Total number of events	16	14
新生血管加齢黄斑変性	3 (4.5%)	2 (3.0%)
アレルギー性結膜炎	2 (3.0%)	2 (3.0%)
ドライアイ	3 (4.5%)	1 (1.5%)
白内障	1 (1.5%)	1 (1.5%)
結膜出血	1 (1.5%)	1 (1.5%)
点状角膜炎	1 (1.5%)	1 (1.5%)
眼精疲労	0	1 (1.5%)
結膜炎	0	1 (1.5%)
角膜内皮炎	1 (1.5%)	0
糖尿病網膜症	1 (1.5%)	0
乾性加齢黄斑変性	0	1 (1.5%)
眼内注射合併症	1 (1.5%)	0
角膜炎	1 (1.5%)	0
瞼裂斑	0	1 (1.5%)
翼状片	0	1 (1.5%)
高血圧性網膜症	1 (1.5%)	0
裂孔原性網膜剥離	0	1 (1.5%)

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 24.0. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
AE reported as neovascular age-related macular degeneration in the study eye indicates an accelerated worsening of the condition, as judged by the investigator.
Includes AEs with onset up to Day 377 (last day of Week 52 analysis visit window).

[5.3.5.1-nAMD-5 表 6-4を再掲]

表 2.7.4.4.1.3.3-8　52週時までに非試験眼に発現した副作用（nAMD，GR40306試験－日本部分集団及び日本延長コホート）

Ocular Adverse Events Related to Study Treatment in the Fellow Eye through Week 52, Safety-Evaluable Population, Japanese Subpopulation
Protocol: GR40306
Clinical Cutoff Date: TENAYA 19JAN2021 (global enrollment) 26MAY2021 (Japan extension)

Null Report: No observations met the reporting criteria for inclusion in this output.

MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 24.0.
Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 377 (last day of Week 52 analysis visit window).

Program: root/clinical_studies/RO6867461/CDPT7716/share/pool_nAMD_Chugai/prod/program/t_ae_pt.sas
Output: root/clinical_studies/RO6867461/CDPT7716/share/pool_nAMD_Chugai/prod/output/t_ae_pt_FOCUL_SREL_W52_SE_JP_nAMD_JPN.out
05JUL2021 11:48 Page 1 of 1

[5.3.5.1-nAMD-5 表 6-5を再掲]

表 2.7.4.4.1.3.3-9　52週時までに眼に発現した重症度が高度の有害事象（nAMD，GR40306試験－日本部分集団及び日本延長コホート）

MedDRA Preferred Term	GR40306(TENAYA) (N=133)	
	Faricimab 6 mg (N=66)	Aflibercept 2 mg (N=67)
Total number of patients with at least one adverse event	0	1 (1.5%)
Total number of events	0	1
新生血管加齢黄斑変性	0	1 (1.5%)

MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 24.0.
AE reported as neovascular age-related macular degeneration in the study eye indicate an accelerated worsening of the condition, as judged by the investigator.
Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 377 (last day of Week 52 analysis visit window).
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[5.3.5.1-nAMD-5 表 6-6を再掲]

表 2.7.4.4.1.3.3-10　52週時までに眼に発現した重篤な有害事象（nAMD，GR40306試験－日本部分集団及び日本延長コホート）

MedDRA Preferred Term	GR40306(TENAYA) (N=133) Faricimab 6 mg (N=66)	GR40306(TENAYA) (N=133) Aflibercept 2 mg (N=67)
Total number of patients with at least one adverse event	2 (3.0%)	2 (3.0%)
Total number of events	2	2
白内障	1 (1.5%)	0
嚢下白内障	0	1 (1.5%)
新生血管加齢黄斑変性	0	1 (1.5%)
裂孔原性網膜剥離	1 (1.5%)	0

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 24.0. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
AE reported as neovascular age-related macular degeneration in the study eye indicates an accelerated worsening of the condition, as judged by the investigator.
Includes AEs with onset up to Day 377 (last day of Week 52 analysis visit window).

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[5.3.5.1-nAMD-5 表 6-7を再掲]

表 2.7.4.4.1.3.3-11　52週時までに眼に発現した重篤な副作用（nAMD，GR40306試験－日本部分集団及び日本延長コホート）

MedDRA Preferred Term	GR40306(TENAYA) (N=133) Faricimab 6 mg (N=66)	GR40306(TENAYA) (N=133) Aflibercept 2 mg (N=67)
Total number of patients with at least one adverse event	0	1 (1.5%)
Total number of events	0	1
嚢下白内障	0	1 (1.5%)

MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 24.0.
Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 377 (last day of Week 52 analysis visit window).

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[5.3.5.1-nAMD-5 表 6-8を再掲]

表 2.7.4.4.1.3.3-12　52週時までに治験薬の投与中止に至った有害事象（nAMD，GR40306試験－日本部分集団及び日本延長コホート）

Adverse Events Leading to Study Treatment Discontinuation through Week 52, Safety-Evaluable Population, Japanese Subpopulation
Protocol: GR40306
Clinical Cutoff Date: TENAYA 19JAN2021 (global enrollment) 26MAY2021 (Japan extension)

Null Report: No observations met the reporting criteria for inclusion in this output.

MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 24.0.
Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 377 (last day of Week 52 analysis visit window).

Program: root/clinical_studies/RO6867461/CDPT7716/share/pool_nAMD_Chugai/prod/program/t_ae.sas
Output: root/clinical_studies/RO6867461/CDPT7716/share/pool_nAMD_Chugai/prod/output/t_ae_SDSC_W52_SE_JP_nAMD_JPN.out
05JUL2021 11:45

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[5.3.5.1-nAMD-5 表 6-9を再掲]

表 2.7.4.4.1.3.3-13　52週時までに治験中止に至った有害事象（nAMD，GR40306試験－日本部分集団及び日本延長コホート）

Adverse Events Leading to Study Discontinuation through Week 52, Safety-Evaluable Population, Japanese Subpopulation
Protocol: GR40306
Clinical Cutoff Date: TENAYA 19JAN2021 (global enrollment) 26MAY2021 (Japan extension)

Null Report: No observations met the reporting criteria for inclusion in this output.

MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 24.0.
AE reported as neovascular age-related macular degeneration in the study eye indicate an accelerated worsening of the condition, as judged by the investigator.
Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 377 (last day of Week 52 analysis visit window).

Program: root/clinical_studies/RO6867461/CDPT7716/share/pool_nAMD_Chugai/prod/program/t_ae.sas
Output: root/clinical_studies/RO6867461/CDPT7716/share/pool_nAMD_Chugai/prod/output/t_ae_DSC_W52_SE_JP_nAMD_JPN.out
05JUL2021 11:47 Page 1 of 1

[5.3.5.1-nAMD-5 表 6-10を再掲]

表 2.7.4.4.1.3.3-14　52週時までに眼以外に発現した有害事象（nAMD，GR40306試験－日本部分集団及び日本延長コホート）

MedDRA System Organ Class MedDRA Preferred Term	GR40306(TENAYA) (N=133) Faricimab 6 mg (N=66)	 Aflibercept 2 mg (N=67)
Total number of patients with at least one adverse event	43 (65.2%)	35 (52.2%)
Overall total number of events	125	65
感染症および寄生虫症		
Total number of patients with at least one adverse event	16 (24.2%)	12 (17.9%)
Total number of events	30	16
上咽頭炎	7 (10.6%)	9 (13.4%)
歯周炎	2 (3.0%)	1 (1.5%)
気管支炎	2 (3.0%)	0
胃腸炎	2 (3.0%)	0
インフルエンザ	0	2 (3.0%)
腹部膿瘍	0	1 (1.5%)
細菌性関節炎	1 (1.5%)	0
ＣＯＶＩＤ－１９	0	1 (1.5%)
蜂巣炎	1 (1.5%)	0
膀胱炎	1 (1.5%)	0
毛包炎	1 (1.5%)	0
せつ	1 (1.5%)	0
歯肉炎	1 (1.5%)	0
椎間板炎	1 (1.5%)	0
肺膿瘍	1 (1.5%)	0
敗血症性心筋炎	1 (1.5%)	0
中耳炎	0	1 (1.5%)
咽頭炎	1 (1.5%)	0
敗血症性ショック	1 (1.5%)	0

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 24.0. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 377 (last day of Week 52 analysis visit window).

表 2.7.4.4.1.3.3-14　52週時までに眼以外に発現した有害事象（nAMD，GR40306試験－日本部分集団及び日本延長コホート）（続）

MedDRA System Organ Class MedDRA Preferred Term	GR40306(TENAYA) (N=133) Faricimab 6 mg (N=66)	 Aflibercept 2 mg (N=67)
副鼻腔炎	1 (1.5%)	0
ＣＯＶＩＤ－１９の疑い	1 (1.5%)	0
全身性細菌感染	0	1 (1.5%)
足部白癬	1 (1.5%)	0
上気道感染	1 (1.5%)	0
胃腸障害		
Total number of patients with at least one adverse event	16 (24.2%)	8 (11.9%)
Total number of events	18	9
齲歯	7 (10.6%)	2 (3.0%)
便秘	1 (1.5%)	3 (4.5%)
腹部不快感	1 (1.5%)	1 (1.5%)
腹痛	2 (3.0%)	0
大腸ポリープ	0	2 (3.0%)
上腹部痛	1 (1.5%)	0
慢性胃炎	1 (1.5%)	0
下痢	0	1 (1.5%)
胃食道逆流性疾患	1 (1.5%)	0
虚血性小腸炎	1 (1.5%)	0
口腔粘膜血腫	1 (1.5%)	0
嘔吐	1 (1.5%)	0

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 24.0. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 377 (last day of Week 52 analysis visit window).

表 2.7.4.4.1.3.3-14　52週時までに眼以外に発現した有害事象（nAMD，GR40306試験－日本部分集団及び日本延長コホート）（続）

MedDRA System Organ Class MedDRA Preferred Term	GR40306(TENAYA) (N=133) Faricimab 6 mg (N=66)	 Aflibercept 2 mg (N=67)
筋骨格系および結合組織障害		
Total number of patients with at least one adverse event	12 (18.2%)	6 (9.0%)
Total number of events	17	6
関節痛	4 (6.1%)	3 (4.5%)
背部痛	2 (3.0%)	2 (3.0%)
筋肉痛	2 (3.0%)	0
関節周囲炎	2 (3.0%)	0
関節炎	1 (1.5%)	0
椎間板突出	1 (1.5%)	0
腰部脊柱管狭窄症	1 (1.5%)	0
筋骨格硬直	1 (1.5%)	0
筋炎	0	1 (1.5%)
変形性関節症	1 (1.5%)	0
四肢痛	1 (1.5%)	0
腱鞘炎	1 (1.5%)	0

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 24.0. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 377 (last day of Week 52 analysis visit window).

表 2.7.4.4.1.3.3-14　52週時までに眼以外に発現した有害事象（nAMD，GR40306試験－日本部分集団及び日本延長コホート）（続）

MedDRA System Organ Class MedDRA Preferred Term	GR40306(TENAYA) (N=133) Faricimab 6 mg (N=66)	 Aflibercept 2 mg (N=67)
傷害、中毒および処置合併症		
Total number of patients with at least one adverse event	7 (10.6%)	7 (10.4%)
Total number of events	12	7
節足動物咬傷	2 (3.0%)	1 (1.5%)
動物咬傷	1 (1.5%)	1 (1.5%)
挫傷	0	2 (3.0%)
転倒	2 (3.0%)	0
圧迫骨折	0	1 (1.5%)
顔面損傷	1 (1.5%)	0
腓骨骨折	1 (1.5%)	0
足骨折	1 (1.5%)	0
四肢損傷	1 (1.5%)	0
粘膜擦過傷	1 (1.5%)	0
脊椎圧迫骨折	0	1 (1.5%)
ストレス骨折	0	1 (1.5%)
脛骨骨折	1 (1.5%)	0
創傷	1 (1.5%)	0

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 24.0. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 377 (last day of Week 52 analysis visit window).

表 2.7.4.4.1.3.3-14　52週時までに眼以外に発現した有害事象（nAMD，GR40306試験－日本部分集団及び日本延長コホート）（続）

MedDRA System Organ Class MedDRA Preferred Term	GR40306(TENAYA) (N=133) Faricimab 6 mg (N=66)	 Aflibercept 2 mg (N=67)
皮膚および皮下組織障害		
Total number of patients with at least one adverse event	9 (13.6%)	3 (4.5%)
Total number of events	14	3
湿疹	3 (4.5%)	0
手皮膚炎	2 (3.0%)	0
脱毛症	1 (1.5%)	0
皮膚炎	1 (1.5%)	0
ざ瘡様皮膚炎	1 (1.5%)	0
アレルギー性皮膚炎	0	1 (1.5%)
皮脂欠乏性湿疹	1 (1.5%)	0
貨幣状湿疹	1 (1.5%)	0
そう痒症	1 (1.5%)	0
紅斑性皮疹	0	1 (1.5%)
蕁麻疹	0	1 (1.5%)
呼吸器、胸郭および縦隔障害		
Total number of patients with at least one adverse event	6 (9.1%)	3 (4.5%)
Total number of events	6	5
アレルギー性鼻炎	1 (1.5%)	1 (1.5%)
慢性閉塞性肺疾患	1 (1.5%)	0
咳嗽	1 (1.5%)	0
咳喘息	0	1 (1.5%)
鼻茸	1 (1.5%)	0
口腔咽頭痛	1 (1.5%)	0
湿性咳嗽	1 (1.5%)	0
上気道の炎症	0	1 (1.5%)

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 24.0. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 377 (last day of Week 52 analysis visit window).

表 2.7.4.4.1.3.3-14　52週時までに眼以外に発現した有害事象（nAMD，GR40306試験－日本部分集団及び日本延長コホート）（続）

MedDRA System Organ Class MedDRA Preferred Term	GR40306(TENAYA) (N=133) Faricimab 6 mg (N=66)	 Aflibercept 2 mg (N=67)
神経系障害		
Total number of patients with at least one adverse event	5 (7.6%)	3 (4.5%)
Total number of events	5	3
浮動性めまい	3 (4.5%)	0
頭痛	2 (3.0%)	1 (1.5%)
自律神経失調	0	1 (1.5%)
坐骨神経痛	0	1 (1.5%)
代謝および栄養障害		
Total number of patients with at least one adverse event	1 (1.5%)	4 (6.0%)
Total number of events	2	4
糖尿病	0	1 (1.5%)
耐糖能障害	0	1 (1.5%)
高尿酸血症	0	1 (1.5%)
低亜鉛血症	0	1 (1.5%)
ビタミンＢ１欠乏	1 (1.5%)	0
亜鉛欠乏	1 (1.5%)	0
血管障害		
Total number of patients with at least one adverse event	3 (4.5%)	2 (3.0%)
Total number of events	3	3
高血圧	3 (4.5%)	2 (3.0%)
血行不全	0	1 (1.5%)

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 24.0. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 377 (last day of Week 52 analysis visit window).

表 2.7.4.4.1.3.3-14　52週時までに眼以外に発現した有害事象（nAMD，GR40306試験－日本部分集団及び日本延長コホート）（続）

MedDRA System Organ Class MedDRA Preferred Term	GR40306(TENAYA) (N=133) Faricimab 6 mg (N=66)	 Aflibercept 2 mg (N=67)
臨床検査		
Total number of patients with at least one adverse event	3 (4.5%)	1 (1.5%)
Total number of events	5	1
肝機能検査値上昇	2 (3.0%)	0
血圧上昇	0	1 (1.5%)
血中尿酸増加	1 (1.5%)	0
尿中蛋白陽性	1 (1.5%)	0
尿潜血陽性	1 (1.5%)	0
精神障害		
Total number of patients with at least one adverse event	3 (4.5%)	1 (1.5%)
Total number of events	3	1
不眠症	1 (1.5%)	1 (1.5%)
うつ病	1 (1.5%)	0
精神疲労	1 (1.5%)	0
一般・全身障害および投与部位の状態		
Total number of patients with at least one adverse event	2 (3.0%)	1 (1.5%)
Total number of events	2	2
胸痛	1 (1.5%)	0
末梢性浮腫	1 (1.5%)	0
発熱	0	1 (1.5%)

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 24.0. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 377 (last day of Week 52 analysis visit window).

表 2.7.4.4.1.3.3-14 52週時までに眼以外に発現した有害事象（nAMD，GR40306試験－日本部分集団及び日本延長コホート）（続）

MedDRA System Organ Class MedDRA Preferred Term	GR40306(TENAYA) (N=133) Faricimab 6 mg (N=66)	 Aflibercept 2 mg (N=67)
免疫系障害		
Total number of patients with at least one adverse event	2 (3.0%)	1 (1.5%)
Total number of events	2	1
造影剤アレルギー	1 (1.5%)	1 (1.5%)
アナフィラキシーショック	1 (1.5%)	0
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）		
Total number of patients with at least one adverse event	2 (3.0%)	1 (1.5%)
Total number of events	2	2
前立腺の良性新生物	0	1 (1.5%)
大腸腺腫	0	1 (1.5%)
胃癌	1 (1.5%)	0
脂漏性角化症	1 (1.5%)	0
血液およびリンパ系障害		
Total number of patients with at least one adverse event	1 (1.5%)	1 (1.5%)
Total number of events	1	1
貧血	1 (1.5%)	0
鉄欠乏性貧血	0	1 (1.5%)
心臓障害		
Total number of patients with at least one adverse event	1 (1.5%)	0
Total number of events	2	0
心房細動	1 (1.5%)	0
心不全	1 (1.5%)	0

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 24.0. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 377 (last day of Week 52 analysis visit window).

表 2.7.4.4.1.3.3-14　52週時までに眼以外に発現した有害事象（nAMD，GR40306試験－日本部分集団及び日本延長コホート）（続）

MedDRA System Organ Class MedDRA Preferred Term	GR40306(TENAYA) (N=133) Faricimab 6 mg (N=66)	 Aflibercept 2 mg (N=67)
腎および尿路障害		
Total number of patients with at least one adverse event	0	1 (1.5%)
Total number of events	0	1
緊張性膀胱	0	1 (1.5%)
生殖系および乳房障害		
Total number of patients with at least one adverse event	1 (1.5%)	0
Total number of events	1	0
月経中間期出血	1 (1.5%)	0

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 24.0. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 377 (last day of Week 52 analysis visit window).

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[5.3.5.1-nAMD-5 表 7-1を再掲]

表 2.7.4.4.1.3.3-15　52週時までに眼以外に発現した副作用（nAMD，GR40306試験－日本部分集団及び日本延長コホート）

MedDRA System Organ Class MedDRA Preferred Term	GR40306(TENAYA) (N=133) Faricimab 6 mg (N=66)	 Aflibercept 2 mg (N=67)
Total number of patients with at least one adverse event	1 (1.5%)	1 (1.5%)
Overall total number of events	1	1
胃腸障害		
Total number of patients with at least one adverse event	1 (1.5%)	0
Total number of events	1	0
虚血性小腸炎	1 (1.5%)	0
血管障害		
Total number of patients with at least one adverse event	0	1 (1.5%)
Total number of events	0	1
高血圧	0	1 (1.5%)

MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 24.0. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 377 (last day of Week 52 analysis visit window).

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[5.3.5.1-nAMD-5 表 7-2を再掲]

表 2.7.4.4.1.3.3-16　52週時までに眼以外に発現した重篤な有害事象（nAMD，GR40306試験－日本部分集団及び日本延長コホート）

MedDRA System Organ Class MedDRA Preferred Term	GR40306(TENAYA) (N=133) Faricimab 6 mg (N=66)	 Aflibercept 2 mg (N=67)
Total number of patients with at least one adverse event	9 (13.6%)	4 (6.0%)
Overall total number of events	11	4
感染症および寄生虫症		
Total number of patients with at least one adverse event	2 (3.0%)	1 (1.5%)
Total number of events	3	1
細菌性関節炎	1 (1.5%)	0
肺膿瘍	1 (1.5%)	0
敗血症性ショック	1 (1.5%)	0
全身性細菌感染	0	1 (1.5%)
傷害、中毒および処置合併症		
Total number of patients with at least one adverse event	2 (3.0%)	1 (1.5%)
Total number of events	3	1
節足動物咬傷	1 (1.5%)	0
腓骨骨折	1 (1.5%)	0
脊椎圧迫骨折	0	1 (1.5%)
脛骨骨折	1 (1.5%)	0
胃腸障害		
Total number of patients with at least one adverse event	1 (1.5%)	1 (1.5%)
Total number of events	1	1
虚血性小腸炎	1 (1.5%)	0
大腸ポリープ	0	1 (1.5%)

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 24.0. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 377 (last day of Week 52 analysis visit window).

表 2.7.4.4.1.3.3-16　52週時までに眼以外に発現した重篤な有害事象（nAMD，GR40306試験－日本部分集団及び日本延長コホート）（続）

MedDRA System Organ Class MedDRA Preferred Term	GR40306(TENAYA) (N=133) Faricimab 6 mg (N=66)	 Aflibercept 2 mg (N=67)
心臓障害		
Total number of patients with at least one adverse event	1 (1.5%)	0
Total number of events	1	0
心不全	1 (1.5%)	0
免疫系障害		
Total number of patients with at least one adverse event	1 (1.5%)	0
Total number of events	1	0
アナフィラキシーショック	1 (1.5%)	0
筋骨格系および結合組織障害		
Total number of patients with at least one adverse event	1 (1.5%)	0
Total number of events	1	0
腰部脊柱管狭窄症	1 (1.5%)	0
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）		
Total number of patients with at least one adverse event	1 (1.5%)	0
Total number of events	1	0
胃癌	1 (1.5%)	0
神経系障害		
Total number of patients with at least one adverse event	0	1 (1.5%)
Total number of events	0	1
自律神経失調	0	1 (1.5%)

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 24.0. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 377 (last day of Week 52 analysis visit window).

[5.3.5.1-nAMD-5 表 6-12を再掲]

表 2.7.4.4.1.3.3-17　52週時までに眼以外に発現した重篤な副作用（nAMD，GR40306試験－日本部分集団及び日本延長コホート）

MedDRA System Organ Class MedDRA Preferred Term	GR40306(TENAYA) (N=133) Faricimab 6 mg (N=66)	 Aflibercept 2 mg (N=67)
Total number of patients with at least one adverse event	1 (1.5%)	0
Overall total number of events	1	0
胃腸障害		
Total number of patients with at least one adverse event	1 (1.5%)	0
Total number of events	1	0
虚血性小腸炎	1 (1.5%)	0

MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 24.0. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 377 (last day of Week 52 analysis visit window).

[5.3.5.1-nAMD-5 表 6-13を再掲]

表 2.7.4.4.1.3.3-18　52週時までの外部判定による APTC ATE（nAMD 統合，GR40306試験－日本部分集団及び日本延長コホート）

Adjudicated APTC-Defined Adverse Events through Week 52, Safety-Evaluable Population, Japanese Subpopulation
Protocol: GR40306
Clinical Cutoff Date: TENAYA 19JAN2021 (global enrollment) 26MAY2021 (Japan extension)

Null Report: No observations met the reporting criteria for inclusion in this output.

APTC = Anti-Platelet Trialists' Collaboration; MedDRA = Medical Dictionary for Regulatory Activities.
APTC events are defined as non-fatal strokes or non-fatal myocardial infarctions or vascular deaths (including deaths of unknown cause).
Investigator text for AEs encoded using MedDRA version 24.0.
Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.
For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes events with onset up to Day 377 (last day of Week 52 analysis visit window).

Program: root/clinical_studies/RO6867461/CDPT7716/share/pool_nAMD_Chugai/prod/program/t_ae.sas
Output: root/clinical_studies/RO6867461/CDPT7716/share/pool_nAMD_Chugai/prod/output/t_ae_APTC_W52_SE_JP_nAMD_JPN.out
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[5.3.5.1-nAMD-5 表 6.5-1を再掲]

2.7.4.4.2 外因性要因

外因性要因について，安全性の解析は実施されていない。

2.7.4.4.3 薬物相互作用

薬物相互作用試験は実施されていない。

2.7.4.4.4 妊娠及び授乳時の使用

妊娠を対象とした試験は実施されていない。本剤が胎盤を通過するか，あるいは妊婦に投与されたときに胎児に害を及ぼすかは不明である。眼に投与した後の全身的な曝露はとても低いものの，妊婦又は妊娠している可能性のある女性には，治療上の有益性が危険性を上回ると判断される場合にのみ投与されるべきである。

本剤が人において母乳中に分泌されるかは不明である。母乳の生成又は母乳中への分泌に対する本剤の影響を評価する試験は実施されていない。

多くの薬は母乳中に分泌されるため，乳児において吸収され，乳児の成長と発達に対する影響が否定できないことから，本剤を授乳中に投与されることは推奨されない。

nAMD 患者を対象とした GR40306試験及び GR40844試験では妊娠例は報告されず，DME 患者を対象とした GR40349試験及び GR40398試験で妊娠が計2例（本剤 PTI 群及びアフリベルセプト Q8W 群で各1例）報告された。

本剤 PTI 群の1例は，治験薬を4回投与された後に，妊娠が確認され，治験薬の投与を中止した。本患者は妊娠36週と6日で出産し，10分後のアプガースコアは8/9で正常であった。詳細は5.3.5.1-DME-2 Narratives p. 1655参照。

アフリベルセプト Q8W 群の1例は，治験薬を8回投与された後に，自然流産並びに治験薬の休薬及び投与中止に至った。治験責任医師は自然流産と治験薬との因果関係はなく，他の原因（経口避妊薬の中止）に関連があると判断した。詳細は5.3.5.1-DME-3 Narratives p. 1632参照。

2.7.4.4.5 過量投与

推奨される用法及び用量を超える投与量の評価は行われていない。

推奨される投与量を超える過量投与は眼圧を上昇させる可能性がある。過量投与が行われた際には，眼圧を測定し，担当医により必要と考えられる場合は，適切な治療を開始する。

nAMD 患者及び DME 患者を対象とした本剤の第 I 相から第Ⅲ相臨床試験において，偶発的過量投与の発現例は認められなかった

2.7.4.4.6 薬物乱用

現時点では情報は得られていない。本剤が薬物乱用の可能性を有する兆候は認められていない。

2.7.4.4.7 離脱症状及び反跳現象

現時点では情報は得られていない。本剤による離脱症状及び反跳現象の兆候は認められていない。

2.7.4.4.8 自動車運転及び機械操作に対する影響又は精神機能の障害

硝子体内投与及び関連する眼の検査により一時的な視覚障害が誘発され，運転や機械の使用能力に影響を及ぼす可能性がある。これらの症状を経験した患者には，視機能が十分に回復するまで機械類の操作や自動車等の運転には従事させないよう注意すること。

2.7.4.5 市販後データ

本剤は未承認薬であるため，現時点では本項に記載すべき市販後データはない。

2.7.4.6 参考文献

該当資料なし

2.7.4.7 付録

表 2.7.4.7-1 データカットオフ日までに試験眼に発現した有害事象（nAMD 統合）

	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
MedDRA Preferred Term	Onset after Week 48	Overall	Onset after Week 48	Overall
Total number of patients with at least one adverse event	52 (7.8%)	272 (41.0%)	44 (6.6%)	265 (40.0%)
Total number of events	77	596	50	539
結膜出血	3 (0.5%)	48 (7.2%)	2 (0.3%)	52 (7.9%)
新生血管加齢黄斑変性	7 (1.1%)	41 (6.2%)	6 (0.9%)	39 (5.9%)
硝子体剥離	4 (0.6%)	26 (3.9%)	1 (0.2%)	21 (3.2%)
ドライアイ	5 (0.8%)	18 (2.7%)	3 (0.5%)	25 (3.8%)
白内障	6 (0.9%)	26 (3.9%)	2 (0.3%)	16 (2.4%)
眼痛	2 (0.3%)	19 (2.9%)	0	20 (3.0%)
眼圧上昇	2 (0.3%)	18 (2.7%)	3 (0.5%)	18 (2.7%)
硝子体浮遊物	0	20 (3.0%)	1 (0.2%)	12 (1.8%)
網膜色素上皮裂孔	0	19 (2.9%)	0	9 (1.4%)
眼の異物感	0	10 (1.5%)	0	13 (2.0%)
眼瞼炎	3 (0.5%)	12 (1.8%)	2 (0.3%)	10 (1.5%)
点状角膜炎	0	9 (1.4%)	0	13 (2.0%)
乾性加齢黄斑変性	2 (0.3%)	10 (1.5%)	2 (0.3%)	10 (1.5%)
後嚢部混濁	2 (0.3%)	12 (1.8%)	1 (0.2%)	8 (1.2%)
流涙増加	1 (0.2%)	6 (0.9%)	1 (0.2%)	9 (1.4%)
光視症	0	6 (0.9%)	1 (0.2%)	9 (1.4%)
角膜擦過傷	1 (0.2%)	5 (0.8%)	0	8 (1.2%)
眼刺激	2 (0.3%)	9 (1.4%)	0	4 (0.6%)
眼部不快感	3 (0.5%)	8 (1.2%)	1 (0.2%)	4 (0.6%)
変視症	1 (0.2%)	5 (0.8%)	2 (0.3%)	5 (0.8%)
眼充血	3 (0.5%)	5 (0.8%)	1 (0.2%)	5 (0.8%)
麦粒腫	0	6 (0.9%)	0	3 (0.5%)
投薬過誤	1 (0.2%)	4 (0.6%)	0	5 (0.8%)
高眼圧症	1 (0.2%)	4 (0.6%)	0	5 (0.8%)
眼そう痒症	0	5 (0.8%)	0	3 (0.5%)
緑内障	1 (0.2%)	3 (0.5%)	1 (0.2%)	5 (0.8%)
黄斑線維症	1 (0.2%)	4 (0.6%)	1 (0.2%)	4 (0.6%)
網膜下線維症	0	5 (0.8%)	1 (0.2%)	3 (0.5%)
視力低下	1 (0.2%)	2 (0.3%)	2 (0.3%)	6 (0.9%)
結膜炎	0	2 (0.3%)	1 (0.2%)	5 (0.8%)
霧視	1 (0.2%)	4 (0.6%)	0	3 (0.5%)

AE= Adverse Event; MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
AE reported as neovascular age-related macular degeneration in the study eye indicates an accelerated worsening of the condition, as judged by the investigator.

表 2.7.4.7-1 データカットオフ日までに試験眼に発現した有害事象（nAMD 統合）（続）

	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
MedDRA Preferred Term	Onset after Week 48	Overall	Onset after Week 48	Overall
核性白内障	1 (0.2%)	3 (0.5%)	0	3 (0.5%)
虹彩炎	1 (0.2%)	4 (0.6%)	0	2 (0.3%)
視神経乳頭出血	0	2 (0.3%)	0	4 (0.6%)
硝子体網膜牽引症候群	0	1 (0.2%)	1 (0.2%)	5 (0.8%)
アレルギー性結膜炎	0	1 (0.2%)	0	4 (0.6%)
黄斑網膜色素上皮剥離	0	3 (0.5%)	0	2 (0.3%)
虹彩毛様体炎	0	3 (0.5%)	0	2 (0.3%)
硝子体炎	1 (0.2%)	4 (0.6%)	0	1 (0.2%)
境界域緑内障	0	4 (0.6%)	0	0
霰粒腫	1 (0.2%)	1 (0.2%)	0	3 (0.5%)
角膜びらん	0	3 (0.5%)	0	1 (0.2%)
不快感	0	1 (0.2%)	0	3 (0.5%)
回避された投薬過誤	0	4 (0.6%)	0	0
黄斑円孔	0	2 (0.3%)	0	2 (0.3%)
疼痛	2 (0.3%)	3 (0.5%)	0	1 (0.2%)
そう痒症	1 (0.2%)	3 (0.5%)	0	1 (0.2%)
ぶどう膜炎	0	2 (0.3%)	0	2 (0.3%)
ウイルス性ぶどう膜炎	1 (0.2%)	4 (0.6%)	0	0
視力障害	0	2 (0.3%)	0	2 (0.3%)
硝子体出血	0	1 (0.2%)	0	3 (0.5%)
加齢黄斑変性	0	0	1 (0.2%)	3 (0.5%)
皮質白内障	0	1 (0.2%)	1 (0.2%)	2 (0.3%)
結膜充血	0	0	1 (0.2%)	3 (0.5%)
複視	0	1 (0.2%)	0	2 (0.3%)
眼瞼下垂	0	1 (0.2%)	0	2 (0.3%)
網膜滲出物	0	0	0	3 (0.5%)
網膜出血	1 (0.2%)	2 (0.3%)	0	1 (0.2%)

AE= Adverse Event; MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
AE reported as neovascular age-related macular degeneration in the study eye indicates an accelerated worsening of the condition, as judged by the investigator.

表 2.7.4.7-1 データカットオフ日までに試験眼に発現した有害事象（nAMD 統合）（続）

	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
MedDRA Preferred Term	Onset after Week 48	Overall	Onset after Week 48	Overall
角膜リポイド環	0	2 (0.3%)	0	0
眼精疲労	0	0	1 (0.2%)	2 (0.3%)
角膜ジストロフィー	0	0	1 (0.2%)	2 (0.3%)
角膜浮腫	0	0	0	2 (0.3%)
後天性涙道狭窄	0	0	0	2 (0.3%)
眼脂	2 (0.3%)	2 (0.3%)	0	0
顔面痛	0	0	0	2 (0.3%)
眼内異物	0	2 (0.3%)	0	0
黄斑部瘢痕	0	0	0	2 (0.3%)
マイボーム腺機能不全	0	1 (0.2%)	0	1 (0.2%)
開放隅角緑内障	1 (0.2%)	1 (0.2%)	0	1 (0.2%)
処置後炎症	0	0	1 (0.2%)	2 (0.3%)
処置による疼痛	0	2 (0.3%)	0	0
網膜障害	0	0	1 (0.2%)	2 (0.3%)
眼瞼腫脹	1 (0.2%)	2 (0.3%)	0	0
硝子体変性	0	1 (0.2%)	0	1 (0.2%)
アレルギー性角膜炎	0	0	0	1 (0.2%)
閉塞隅角緑内障	0	1 (0.2%)	0	0
基底細胞癌	0	0	0	1 (0.2%)
両眼球運動障害	0	0	0	1 (0.2%)
眼瞼乳頭腫	0	0	0	1 (0.2%)
一過性失明	0	0	0	1 (0.2%)
眉毛下垂	0	0	1 (0.2%)	1 (0.2%)
灼熱感	0	1 (0.2%)	0	0
白内障手術合併症	0	0	1 (0.2%)	1 (0.2%)
嚢下白内障	0	0	0	1 (0.2%)
外傷性白内障	0	0	1 (0.2%)	1 (0.2%)
脈絡網膜炎	0	1 (0.2%)	0	0
結膜沈着物	0	0	0	1 (0.2%)
結膜びらん	0	1 (0.2%)	0	0
結膜浮腫	0	0	0	1 (0.2%)
ウイルス性結膜炎	0	1 (0.2%)	0	0
角膜浸潤	0	0	0	1 (0.2%)
角膜瘢痕	0	1 (0.2%)	0	0
眼瞼皮膚弛緩症	0	1 (0.2%)	0	0
網膜色素上皮剥離	0	1 (0.2%)	0	0
薬物過敏症	1 (0.2%)	1 (0.2%)	0	0

AE= Adverse Event; MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
AE reported as neovascular age-related macular degeneration in the study eye indicates an accelerated worsening of the condition, as judged by the investigator.

表 2.7.4.7-1 データカットオフ日までに試験眼に発現した有害事象（nAMD 統合）（続）

	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
MedDRA Preferred Term	Onset after Week 48	Overall	Onset after Week 48	Overall
薬物不耐性	0	0	0	1 (0.2%)
眼内炎	0	0	0	1 (0.2%)
眼瞼紅斑	0	1 (0.2%)	0	0
落屑緑内障	0	1 (0.2%)	0	0
落屑症候群	0	0	0	1 (0.2%)
眼球突出症	0	0	0	1 (0.2%)
眼のアレルギー	0	0	0	1 (0.2%)
眼の母斑	0	0	0	1 (0.2%)
眼部腫脹	0	0	0	1 (0.2%)
眼瞼挫傷	0	0	0	1 (0.2%)
眼瞼血腫	1 (0.2%)	1 (0.2%)	0	0
眼瞼浮腫	0	0	0	1 (0.2%)
眼瞼痛	0	0	0	1 (0.2%)
眼瞼腫瘍	0	1 (0.2%)	0	0
顔面骨骨折	0	0	0	1 (0.2%)
転倒	0	0	0	1 (0.2%)
頭部損傷	0	0	0	1 (0.2%)
頭痛	0	1 (0.2%)	0	0
星状硝子体症	0	1 (0.2%)	0	0
遠視	0	1 (0.2%)	0	0
眼の知覚低下	0	0	0	1 (0.2%)
低眼圧	0	0	0	1 (0.2%)
涙道の炎症	0	1 (0.2%)	0	0
注射部位出血	1 (0.2%)	1 (0.2%)	0	0
注射部位疼痛	0	0	0	1 (0.2%)
虹彩徹照異常	0	1 (0.2%)	0	0
角膜後面沈着物	0	1 (0.2%)	0	0
角膜炎	0	1 (0.2%)	0	0
涙液分泌低下	0	1 (0.2%)	0	0
水晶体混濁	0	1 (0.2%)	0	0
黄斑変性	0	1 (0.2%)	0	0
メラノサイト性母斑	0	0	0	1 (0.2%)
前兆を伴う片頭痛	0	0	1 (0.2%)	1 (0.2%)
前房狭隅角	0	1 (0.2%)	0	0
非感染性眼内炎	0	0	1 (0.2%)	1 (0.2%)
正常眼圧緑内障	0	1 (0.2%)	0	0
黄疸眼	0	0	0	1 (0.2%)

AE= Adverse Event; MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
AE reported as neovascular age-related macular degeneration in the study eye indicates an accelerated worsening of the condition, as judged by the investigator.

表 2.7.4.7-1 データカットオフ日までに試験眼に発現した有害事象（nAMD 統合）（続）

	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
MedDRA Preferred Term	Onset after Week 48	Overall	Onset after Week 48	Overall
眼部単純ヘルペス	1 (0.2%)	1 (0.2%)	0	0
視神経乳頭陥凹	0	0	0	1 (0.2%)
眼窩周囲痛	1 (0.2%)	1 (0.2%)	0	0
末梢血管障害	0	0	0	1 (0.2%)
瞼裂斑	0	1 (0.2%)	0	0
そう痒性皮疹	0	1 (0.2%)	0	0
読字障害	0	1 (0.2%)	0	0
先天性網膜異常	0	1 (0.2%)	0	0
網膜動脈塞栓症	0	1 (0.2%)	0	0
網膜変性	0	0	1 (0.2%)	1 (0.2%)
網膜ドルーゼン	0	0	0	1 (0.2%)
高血圧性網膜症	0	1 (0.2%)	0	0
網膜分離症	1 (0.2%)	1 (0.2%)	0	0
裂孔原性網膜剥離	1 (0.2%)	1 (0.2%)	0	0
皮膚病変	0	0	0	1 (0.2%)
皮膚乳頭腫	0	1 (0.2%)	0	0
斜視	0	1 (0.2%)	0	0
外傷性出血	0	0	0	1 (0.2%)
睫毛乱生	0	0	1 (0.2%)	1 (0.2%)
潰瘍性角膜炎	0	1 (0.2%)	0	0

AE= Adverse Event; MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
AE reported as neovascular age-related macular degeneration in the study eye indicates an accelerated worsening of the condition, as judged by the investigator.

[5.3.5.3-nAMD-1 t_ae_pt_cod_SOCUL_SE_nAMD_HLS を改変]

表 2.7.4.7-2 データカットオフ日までに試験眼に発現した副作用（nAMD 統合）

	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
MedDRA Preferred Term	Onset after Week 48	Overall	Onset after Week 48	Overall
Total number of patients with at least one adverse event	0	19 (2.9%)	2 (0.3%)	19 (2.9%)
Total number of events	0	22	2	20
網膜色素上皮裂孔	0	8 (1.2%)	0	2 (0.3%)
眼圧上昇	0	2 (0.3%)	1 (0.2%)	4 (0.6%)
ぶどう膜炎	0	2 (0.3%)	0	2 (0.3%)
硝子体炎	0	3 (0.5%)	0	1 (0.2%)
虹彩毛様体炎	0	2 (0.3%)	0	1 (0.2%)
虹彩炎	0	1 (0.2%)	0	1 (0.2%)
高眼圧症	0	0	0	2 (0.3%)
硝子体浮遊物	0	1 (0.2%)	0	1 (0.2%)
角膜びらん	0	0	0	1 (0.2%)
乾性加齢黄斑変性	0	0	0	1 (0.2%)
星状硝子体症	0	1 (0.2%)	0	0
非感染性眼内炎	0	0	1 (0.2%)	1 (0.2%)
処置後炎症	0	0	0	1 (0.2%)
点状角膜炎	0	1 (0.2%)	0	0
視力低下	0	0	0	1 (0.2%)

MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

[5.3.5.3-nAMD-1 t_ae_pt_cod_SOCUL_SREL_SE_nAMD_HLS を改変]

表 2.7.4.7-3 データカットオフ日までに試験眼に発現した有害事象（DME 統合）

Pooled(YOSEMITE and RHINE)
(N=1887)

MedDRA Preferred Term	Faricimab 6 mg Q8W (N=630) Onset after Week 56	Faricimab 6 mg Q8W (N=630) Overall	Faricimab 6 mg PTI (N=632) Onset after Week 56	Faricimab 6 mg PTI (N=632) Overall	Faricimab 6 mg All (N=1262) Onset after Week 56	Faricimab 6 mg All (N=1262) Overall	Aflibercept 2 mg Q8W (N=625) Onset after Week 56	Aflibercept 2 mg Q8W (N=625) Overall
Total number of patients with at least one adverse event	67 (10.6%)	261 (41.4%)	81 (12.8%)	263 (41.6%)	148 (11.7%)	524 (41.5%)	55 (8.8%)	240 (38.4%)
Total number of events	97	543	106	525	203	1068	71	421
白内障	14 (2.2%)	46 (7.3%)	14 (2.2%)	40 (6.3%)	28 (2.2%)	86 (6.8%)	11 (1.8%)	41 (6.6%)
結膜出血	4 (0.6%)	48 (7.6%)	1 (0.2%)	39 (6.2%)	5 (0.4%)	87 (6.9%)	1 (0.2%)	39 (6.2%)
硝子体剥離	2 (0.3%)	25 (4.0%)	7 (1.1%)	24 (3.8%)	9 (0.7%)	49 (3.9%)	2 (0.3%)	22 (3.5%)
ドライアイ	4 (0.6%)	25 (4.0%)	5 (0.8%)	19 (3.0%)	9 (0.7%)	44 (3.5%)	5 (0.8%)	16 (2.6%)
硝子体浮遊物	1 (0.2%)	30 (4.8%)	1 (0.2%)	14 (2.2%)	2 (0.2%)	44 (3.5%)	5 (0.8%)	15 (2.4%)
眼圧上昇	2 (0.3%)	24 (3.8%)	5 (0.8%)	18 (2.8%)	7 (0.6%)	42 (3.3%)	2 (0.3%)	14 (2.2%)
眼痛	1 (0.2%)	13 (2.1%)	4 (0.6%)	19 (3.0%)	5 (0.4%)	32 (2.5%)	1 (0.2%)	20 (3.2%)
糖尿病性網膜浮腫	3 (0.5%)	9 (1.4%)	8 (1.3%)	14 (2.2%)	11 (0.9%)	23 (1.8%)	7 (1.1%)	13 (2.1%)
嚢下白内障	10 (1.6%)	16 (2.5%)	3 (0.5%)	9 (1.4%)	13 (1.0%)	25 (2.0%)	5 (0.8%)	7 (1.1%)
結膜炎	0	8 (1.3%)	3 (0.5%)	12 (1.9%)	3 (0.2%)	20 (1.6%)	1 (0.2%)	8 (1.3%)
眼瞼炎	4 (0.6%)	14 (2.2%)	4 (0.6%)	7 (1.1%)	8 (0.6%)	21 (1.7%)	3 (0.5%)	5 (0.8%)
皮質白内障	2 (0.3%)	6 (1.0%)	1 (0.2%)	10 (1.6%)	3 (0.2%)	16 (1.3%)	1 (0.2%)	10 (1.6%)
後嚢部混濁	3 (0.5%)	10 (1.6%)	1 (0.2%)	5 (0.8%)	4 (0.3%)	15 (1.2%)	0	8 (1.3%)
点状角膜炎	1 (0.2%)	9 (1.4%)	2 (0.3%)	8 (1.3%)	3 (0.2%)	17 (1.3%)	0	6 (1.0%)
投薬過誤	1 (0.2%)	9 (1.4%)	0	9 (1.4%)	1 (<0.1%)	18 (1.4%)	0	4 (0.6%)
核性白内障	4 (0.6%)	10 (1.6%)	1 (0.2%)	7 (1.1%)	5 (0.4%)	17 (1.3%)	0	3 (0.5%)
糖尿病網膜症	1 (0.2%)	5 (0.8%)	3 (0.5%)	10 (1.6%)	4 (0.3%)	15 (1.2%)	1 (0.2%)	4 (0.6%)
硝子体出血	2 (0.3%)	9 (1.4%)	1 (0.2%)	7 (1.1%)	3 (0.2%)	16 (1.3%)	0	3 (0.5%)

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-3 データカットオフ日までに試験眼に発現した有害事象（DME 統合）（続）

Pooled(YOSEMITE and RHINE)
(N=1887)

MedDRA Preferred Term	Faricimab 6 mg Q8W (N=630) Onset after Week 56	Faricimab 6 mg Q8W (N=630) Overall	Faricimab 6 mg PTI (N=632) Onset after Week 56	Faricimab 6 mg PTI (N=632) Overall	Faricimab 6 mg All (N=1262) Onset after Week 56	Faricimab 6 mg All (N=1262) Overall	Aflibercept 2 mg Q8W (N=625) Onset after Week 56	Aflibercept 2 mg Q8W (N=625) Overall
霧視	3 (0.5%)	6 (1.0%)	1 (0.2%)	3 (0.5%)	4 (0.3%)	9 (0.7%)	0	9 (1.4%)
眼そう痒症	0	5 (0.8%)	0	4 (0.6%)	0	9 (0.7%)	0	5 (0.8%)
流涙増加	1 (0.2%)	2 (0.3%)	2 (0.3%)	8 (1.3%)	3 (0.2%)	10 (0.8%)	1 (0.2%)	4 (0.6%)
網膜滲出物	1 (0.2%)	5 (0.8%)	0	6 (0.9%)	1 (<0.1%)	11 (0.9%)	1 (0.2%)	3 (0.5%)
眼刺激	0	5 (0.8%)	0	3 (0.5%)	0	8 (0.6%)	0	5 (0.8%)
網膜出血	0	3 (0.5%)	1 (0.2%)	5 (0.8%)	1 (<0.1%)	8 (0.6%)	2 (0.3%)	5 (0.8%)
視力障害	0	3 (0.5%)	1 (0.2%)	6 (0.9%)	1 (<0.1%)	9 (0.7%)	1 (0.2%)	4 (0.6%)
黄斑線維症	0	2 (0.3%)	0	1 (0.2%)	0	3 (0.2%)	2 (0.3%)	9 (1.4%)
角膜擦過傷	0	3 (0.5%)	1 (0.2%)	6 (0.9%)	1 (<0.1%)	9 (0.7%)	0	2 (0.3%)
眼部不快感	1 (0.2%)	4 (0.6%)	0	5 (0.8%)	1 (<0.1%)	9 (0.7%)	0	2 (0.3%)
高眼圧症	1 (0.2%)	2 (0.3%)	1 (0.2%)	8 (1.3%)	2 (0.2%)	10 (0.8%)	0	1 (0.2%)
霰粒腫	1 (0.2%)	4 (0.6%)	2 (0.3%)	3 (0.5%)	3 (0.2%)	7 (0.6%)	0	3 (0.5%)
麦粒腫	1 (0.2%)	2 (0.3%)	0	3 (0.5%)	1 (<0.1%)	5 (0.4%)	0	5 (0.8%)
異物感	0	6 (1.0%)	0	1 (0.2%)	0	7 (0.6%)	0	3 (0.5%)
眼充血	1 (0.2%)	5 (0.8%)	0	2 (0.3%)	1 (<0.1%)	7 (0.6%)	1 (0.2%)	2 (0.3%)
光視症	1 (0.2%)	5 (0.8%)	0	2 (0.3%)	1 (<0.1%)	7 (0.6%)	2 (0.3%)	2 (0.3%)
角膜びらん	1 (0.2%)	5 (0.8%)	0	1 (0.2%)	1 (<0.1%)	6 (0.5%)	0	2 (0.3%)
虹彩炎	1 (0.2%)	2 (0.3%)	1 (0.2%)	4 (0.6%)	2 (0.2%)	6 (0.5%)	0	2 (0.3%)
緑内障	0	2 (0.3%)	1 (0.2%)	2 (0.3%)	1 (<0.1%)	4 (0.3%)	0	3 (0.5%)
ぶどう膜炎	0	2 (0.3%)	2 (0.3%)	5 (0.8%)	2 (0.2%)	7 (0.6%)	0	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-3 データカットオフ日までに試験眼に発現した有害事象（DME 統合）（続）

Pooled(YOSEMITE and RHINE)
(N=1887)

	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
MedDRA Preferred Term	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
アレルギー性結膜炎	1 (0.2%)	4 (0.6%)	0	1 (0.2%)	1 (<0.1%)	5 (0.4%)	0	1 (0.2%)
嚢胞様黄斑浮腫	0	4 (0.6%)	0	1 (0.2%)	0	5 (0.4%)	0	1 (0.2%)
眼内炎	0	2 (0.3%)	1 (0.2%)	3 (0.5%)	1 (<0.1%)	5 (0.4%)	0	1 (0.2%)
視力低下	1 (0.2%)	2 (0.3%)	1 (0.2%)	3 (0.5%)	2 (0.2%)	5 (0.4%)	1 (0.2%)	1 (0.2%)
硝子体炎	0	3 (0.5%)	0	1 (0.2%)	0	4 (0.3%)	0	2 (0.3%)
動脈瘤	0	0	1 (0.2%)	3 (0.5%)	1 (<0.1%)	3 (0.2%)	0	2 (0.3%)
角膜障害	0	2 (0.3%)	0	1 (0.2%)	0	3 (0.2%)	1 (0.2%)	2 (0.3%)
虹彩毛様体炎	0	2 (0.3%)	0	2 (0.3%)	0	4 (0.3%)	1 (0.2%)	1 (0.2%)
角膜炎	0	1 (0.2%)	1 (0.2%)	3 (0.5%)	1 (<0.1%)	4 (0.3%)	0	1 (0.2%)
潰瘍性角膜炎	0	2 (0.3%)	2 (0.3%)	3 (0.5%)	2 (0.2%)	5 (0.4%)	0	0
硝子体障害	0	0	1 (0.2%)	4 (0.6%)	1 (<0.1%)	4 (0.3%)	0	1 (0.2%)
アデノウイルス結膜炎	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	2 (0.3%)
眼瞼皮膚弛緩症	0	2 (0.3%)	1 (0.2%)	1 (0.2%)	1 (<0.1%)	3 (0.2%)	1 (0.2%)	1 (0.2%)
羞明	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	2 (0.3%)
眼瞼腫脹	1 (0.2%)	1 (0.2%)	0	1 (0.2%)	1 (<0.1%)	2 (0.2%)	1 (0.2%)	2 (0.3%)
一過性視力低下	0	2 (0.3%)	0	1 (0.2%)	0	3 (0.2%)	0	1 (0.2%)
視野欠損	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	1 (0.2%)	3 (0.5%)
硝子体網膜牽引症候群	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	3 (0.5%)

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-3 データカットオフ日までに試験眼に発現した有害事象（DME 統合）（続）

Pooled(YOSEMITE and RHINE)
(N=1887)

	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
MedDRA Preferred Term	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
結膜充血	0	0	0	2 (0.3%)	0	2 (0.2%)	0	1 (0.2%)
角膜ジストロフィー	0	0	0	2 (0.3%)	0	2 (0.2%)	0	1 (0.2%)
角膜上皮欠損	1 (0.2%)	1 (0.2%)	0	1 (0.2%)	1 (<0.1%)	2 (0.2%)	0	1 (0.2%)
角膜浮腫	0	1 (0.2%)	1 (0.2%)	2 (0.3%)	1 (<0.1%)	3 (0.2%)	0	0
不快感	1 (0.2%)	2 (0.3%)	0	1 (0.2%)	1 (<0.1%)	3 (0.2%)	0	0
眼脂	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	2 (0.3%)
眼瞼浮腫	0	0	0	2 (0.3%)	0	2 (0.2%)	0	1 (0.2%)
眼瞼下垂	0	1 (0.2%)	0	0	0	1 (<0.1%)	1 (0.2%)	2 (0.3%)
眼瞼そう痒症	1 (0.2%)	3 (0.5%)	0	0	1 (<0.1%)	3 (0.2%)	0	0
眼内異物	1 (0.2%)	1 (0.2%)	0	1 (0.2%)	1 (<0.1%)	2 (0.2%)	0	1 (0.2%)
眼の異物感	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	1 (0.2%)
黄斑虚血	0	2 (0.3%)	0	1 (0.2%)	0	3 (0.2%)	0	0
マイボーム腺機能不全	0	2 (0.3%)	0	0	0	2 (0.2%)	1 (0.2%)	1 (0.2%)
開放隅角緑内障	1 (0.2%)	1 (0.2%)	0	2 (0.3%)	1 (<0.1%)	3 (0.2%)	0	0
眼窩周囲痛	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	1 (0.2%)
そう痒症	0	1 (0.2%)	1 (0.2%)	2 (0.3%)	1 (<0.1%)	3 (0.2%)	0	0
網膜裂孔	0	0	1 (0.2%)	3 (0.5%)	1 (<0.1%)	3 (0.2%)	0	0
網膜静脈閉塞	0	1 (0.2%)	0	2 (0.3%)	0	3 (0.2%)	0	0
強膜炎	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	1 (0.2%)
硝子体混濁	0	0	0	2 (0.3%)	0	2 (0.2%)	0	1 (0.2%)
眼の異常感	0	2 (0.3%)	0	0	0	2 (0.2%)	0	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-3 データカットオフ日までに試験眼に発現した有害事象（DME 統合）（続）

Pooled(YOSEMITE and RHINE)
(N=1887)

MedDRA Preferred Term	Faricimab 6 mg Q8W (N=630) Onset after Week 56	Faricimab 6 mg Q8W (N=630) Overall	Faricimab 6 mg PTI (N=632) Onset after Week 56	Faricimab 6 mg PTI (N=632) Overall	Faricimab 6 mg All (N=1262) Onset after Week 56	Faricimab 6 mg All (N=1262) Overall	Aflibercept 2 mg Q8W (N=625) Onset after Week 56	Aflibercept 2 mg Q8W (N=625) Overall
境界域緑内障	0	0	1 (0.2%)	2 (0.3%)	1 (<0.1%)	2 (0.2%)	0	0
灼熱感	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	0
結膜浮腫	0	0	0	2 (0.3%)	0	2 (0.2%)	0	0
ウイルス性結膜炎	0	2 (0.3%)	0	0	0	2 (0.2%)	0	0
角膜刺激	0	2 (0.3%)	0	0	0	2 (0.2%)	0	0
斑状出血	0	0	1 (0.2%)	2 (0.3%)	1 (<0.1%)	2 (0.2%)	0	0
上強膜炎	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	0
眼のアレルギー	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	1 (0.2%)
眼挫傷	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	1 (0.2%)
眼出血	0	0	0	1 (0.2%)	0	1 (<0.1%)	1 (0.2%)	1 (0.2%)
充血	0	0	0	2 (0.3%)	0	2 (0.2%)	0	0
回避された投薬過誤	1 (0.2%)	2 (0.3%)	0	0	1 (<0.1%)	2 (0.2%)	0	0
虹彩癒着	0	0	0	0	0	0	0	2 (0.3%)
ウイルス性角膜炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	1 (0.2%)
黄斑浮腫	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	1 (0.2%)
瞼板腺炎	0	0	0	2 (0.3%)	0	2 (0.2%)	0	0
視神経乳頭出血	0	0	1 (0.2%)	2 (0.3%)	1 (<0.1%)	2 (0.2%)	0	0
視神経乳頭陥凹	1 (0.2%)	1 (0.2%)	1 (0.2%)	1 (0.2%)	2 (0.2%)	2 (0.2%)	0	0
疼痛	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	0
色素散乱症候群	1 (0.2%)	1 (0.2%)	0	1 (0.2%)	1 (<0.1%)	2 (0.2%)	0	0
瞼裂斑	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-3 データカットオフ日までに試験眼に発現した有害事象（DME 統合）（続）

Pooled(YOSEMITE and RHINE)
(N=1887)

MedDRA Preferred Term	Faricimab 6 mg Q8W (N=630) Onset after Week 56	Faricimab 6 mg Q8W (N=630) Overall	Faricimab 6 mg PTI (N=632) Onset after Week 56	Faricimab 6 mg PTI (N=632) Overall	Faricimab 6 mg All (N=1262) Onset after Week 56	Faricimab 6 mg All (N=1262) Overall	Aflibercept 2 mg Q8W (N=625) Onset after Week 56	Aflibercept 2 mg Q8W (N=625) Overall
処置後炎症	0	0	0	0	0	0	2 (0.3%)	2 (0.3%)
網膜血管瘤	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	1 (0.2%)
網膜動脈閉塞	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	1 (0.2%)
網膜嚢胞	0	0	0	2 (0.3%)	0	2 (0.2%)	0	0
高血圧性網膜症	0	0	0	0	0	0	0	2 (0.3%)
腫脹	0	0	1 (0.2%)	2 (0.3%)	1 (<0.1%)	2 (0.2%)	0	0
角膜生体染色陽性	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	1 (0.2%)
化学物質アレルギー	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
動物による引っかき傷	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
前房の炎症	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
眼瞼の良性新生物	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
眼瞼痙攣	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
白内障手術合併症	0	0	0	0	0	0	0	1 (0.2%)
眼部化学熱傷	0	0	0	0	0	0	0	1 (0.2%)
脈絡網膜炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
脈絡膜血管新生	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
結膜障害	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
結膜乳頭	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
細菌性結膜炎	0	0	0	0	0	0	0	1 (0.2%)
造影剤アレルギー	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-3 データカットオフ日までに試験眼に発現した有害事象（DME 統合）（続）

Pooled(YOSEMITE and RHINE)
(N=1887)

MedDRA Preferred Term	Faricimab 6 mg Q8W (N=630) Onset after Week 56	Faricimab 6 mg Q8W (N=630) Overall	Faricimab 6 mg PTI (N=632) Onset after Week 56	Faricimab 6 mg PTI (N=632) Overall	Faricimab 6 mg All (N=1262) Onset after Week 56	Faricimab 6 mg All (N=1262) Overall	Aflibercept 2 mg Q8W (N=625) Onset after Week 56	Aflibercept 2 mg Q8W (N=625) Overall
角膜血管新生	0	0	0	0	0	0	0	1 (0.2%)
後天性涙道狭窄	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
角膜縁凹窩	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
接触皮膚炎	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
網膜色素上皮剥離	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
医療機器位置異常	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
糖尿病性眼病変	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
複視	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
薬物過敏症	0	0	0	0	0	0	0	1 (0.2%)
視測障害	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
眼瞼湿疹	0	0	0	0	0	0	0	1 (0.2%)
眼瞼内反	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
紅斑	0	0	0	0	0	0	0	1 (0.2%)
眼瞼紅斑	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
血液溢出	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
眼運動障害	0	0	0	0	0	0	0	1 (0.2%)
眼部腫脹	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
眼瞼縁痂皮	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
グレア	0	0	0	0	0	0	0	1 (0.2%)
緑内障性視神経乳頭萎縮	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-3 データカットオフ日までに試験眼に発現した有害事象（DME 統合）（続）

Pooled(YOSEMITE and RHINE)
(N=1887)

MedDRA Preferred Term	Faricimab 6 mg Q8W (N=630) Onset after Week 56	Faricimab 6 mg Q8W (N=630) Overall	Faricimab 6 mg PTI (N=632) Onset after Week 56	Faricimab 6 mg PTI (N=632) Overall	Faricimab 6 mg All (N=1262) Onset after Week 56	Faricimab 6 mg All (N=1262) Overall	Aflibercept 2 mg Q8W (N=625) Onset after Week 56	Aflibercept 2 mg Q8W (N=625) Overall
帯状疱疹	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
星状硝子体症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
過敏症	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
低眼圧	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
第３脳神経麻痺	0	0	0	0	0	0	0	1 (0.2%)
インフルエンザ	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
内方発育毛	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
注射部位出血	0	0	0	0	0	0	0	1 (0.2%)
注射部位疼痛	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
眼圧変動	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
虹彩血管新生	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
角膜後面沈着物	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
細菌性角膜炎	0	0	0	0	0	0	0	1 (0.2%)
角膜症	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
角膜ぶどう膜炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
涙液分泌低下	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
水晶体混濁	0	0	0	0	0	0	0	1 (0.2%)
結石症	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
黄斑嚢胞	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
黄斑円孔	0	0	0	0	0	0	0	1 (0.2%)
黄斑色素沈着	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-3 データカットオフ日までに試験眼に発現した有害事象（DME 統合）（続）

Pooled(YOSEMITE and RHINE)
(N=1887)

MedDRA Preferred Term	Faricimab 6 mg Q8W (N=630) Onset after Week 56	Faricimab 6 mg Q8W (N=630) Overall	Faricimab 6 mg PTI (N=632) Onset after Week 56	Faricimab 6 mg PTI (N=632) Overall	Faricimab 6 mg All (N=1262) Onset after Week 56	Faricimab 6 mg All (N=1262) Overall	Aflibercept 2 mg Q8W (N=625) Onset after Week 56	Aflibercept 2 mg Q8W (N=625) Overall
黄斑肥厚	0	0	0	0	0	0	0	1 (0.2%)
前房狭隅角	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
神経血管コンフリクト	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
眼虚血症候群	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
視神経萎縮	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
視神経乳頭障害	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
視神経乳頭陥凹／乳頭比増加	0	0	0	0	0	0	0	1 (0.2%)
視神経乳頭浮腫	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
錯感覚	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
眼窩周囲蜂巣炎	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
処置による疼痛	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
製品投与の欠落の問題	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
瞳孔不同	0	0	0	0	0	0	0	1 (0.2%)
化膿性肉芽腫	0	0	0	0	0	0	0	1 (0.2%)
網膜動脈塞栓症	0	0	0	0	0	0	0	1 (0.2%)
網膜変性	0	0	0	0	0	0	0	1 (0.2%)
網膜障害	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
網膜血管新生	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
網膜色素沈着	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
網膜肥厚	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-3 データカットオフ日までに試験眼に発現した有害事象（DME 統合）（続）

Pooled(YOSEMITE and RHINE)
(N=1887)

MedDRA Preferred Term	Faricimab 6 mg Q8W (N=630) Onset after Week 56	Faricimab 6 mg Q8W (N=630) Overall	Faricimab 6 mg PTI (N=632) Onset after Week 56	Faricimab 6 mg PTI (N=632) Overall	Faricimab 6 mg All (N=1262) Onset after Week 56	Faricimab 6 mg All (N=1262) Overall	Aflibercept 2 mg Q8W (N=625) Onset after Week 56	Aflibercept 2 mg Q8W (N=625) Overall
網膜分離症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
裂孔原性網膜剥離	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
瘢痕	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
シェーグレン症候群	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
ぶどう膜炎性緑内障	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
ウイルス性角膜ぶどう膜炎	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
硝子体癒着	0	0	0	0	0	0	0	1 (0.2%)
硝子体変性	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

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[5.3.5.3-nAMD-1 t_ae_pt_cod_SOCUL_SE_DME_HLS を改変]

表 2.7.4.7-4　データカットオフ日までに試験眼に発現した副作用（DME 統合）

Pooled(YOSEMITE and RHINE)
(N=1887)

MedDRA Preferred Term	Faricimab 6 mg Q8W (N=630) Onset after Week 56	Faricimab 6 mg Q8W (N=630) Overall	Faricimab 6 mg PTI (N=632) Onset after Week 56	Faricimab 6 mg PTI (N=632) Overall	Faricimab 6 mg All (N=1262) Onset after Week 56	Faricimab 6 mg All (N=1262) Overall	Aflibercept 2 mg Q8W (N=625) Onset after Week 56	Aflibercept 2 mg Q8W (N=625) Overall
Total number of patients with at least one adverse event	2 (0.3%)	21 (3.3%)	3 (0.5%)	18 (2.8%)	5 (0.4%)	39 (3.1%)	0	19 (3.0%)
Total number of events	2	25	4	26	6	51	0	21
眼圧上昇	0	7 (1.1%)	0	3 (0.5%)	0	10 (0.8%)	0	4 (0.6%)
硝子体浮遊物	0	6 (1.0%)	0	1 (0.2%)	0	7 (0.6%)	0	4 (0.6%)
白内障	1 (0.2%)	1 (0.2%)	2 (0.3%)	4 (0.6%)	3 (0.2%)	5 (0.4%)	0	1 (0.2%)
ぶどう膜炎	0	1 (0.2%)	1 (0.2%)	3 (0.5%)	1 (<0.1%)	4 (0.3%)	0	0
虹彩炎	0	0	0	2 (0.3%)	0	2 (0.2%)	0	1 (0.2%)
高眼圧症	0	0	0	3 (0.5%)	0	3 (0.2%)	0	0
硝子体炎	0	2 (0.3%)	0	0	0	2 (0.2%)	0	1 (0.2%)
結膜出血	0	0	0	0	0	0	0	2 (0.3%)
糖尿病性網膜浮腫	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	1 (0.2%)
眼痛	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	1 (0.2%)
角膜炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	1 (0.2%)
脈絡網膜炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
角膜擦過傷	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
角膜浮腫	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
眼内炎	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
角膜後面沈着物	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
角膜ぶどう膜炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
黄斑線維症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
眼部不快感	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
シェーグレン症候群	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
霧視	0	0	0	0	0	0	0	1 (0.2%)
視力障害	0	0	0	0	0	0	0	1 (0.2%)
硝子体剥離	0	0	0	0	0	0	0	1 (0.2%)

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

[5.3.5.3-nAMD-1 t_ae_pt_cod_SOCUL_SREL_SE_DME_HLS を改変]

表 2.7.4.7-5 データカットオフ日までに非試験眼に発現した有害事象（nAMD 統合）

	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
MedDRA Preferred Term	Onset after Week 48	Overall	Onset after Week 48	Overall
Total number of patients with at least one adverse event	39 (5.9%)	194 (29.2%)	32 (4.8%)	178 (26.9%)
Total number of events	50	287	37	282
新生血管加齢黄斑変性	14 (2.1%)	68 (10.2%)	7 (1.1%)	58 (8.8%)
白内障	6 (0.9%)	20 (3.0%)	3 (0.5%)	14 (2.1%)
硝子体剥離	2 (0.3%)	11 (1.7%)	0	20 (3.0%)
ドライアイ	3 (0.5%)	14 (2.1%)	1 (0.2%)	15 (2.3%)
結膜出血	2 (0.3%)	14 (2.1%)	3 (0.5%)	14 (2.1%)
眼瞼炎	2 (0.3%)	13 (2.0%)	2 (0.3%)	11 (1.7%)
後嚢部混濁	0	7 (1.1%)	0	6 (0.9%)
乾性加齢黄斑変性	1 (0.2%)	4 (0.6%)	3 (0.5%)	7 (1.1%)
点状角膜炎	0	4 (0.6%)	0	7 (1.1%)
硝子体浮遊物	0	7 (1.1%)	0	3 (0.5%)
結膜炎	2 (0.3%)	4 (0.6%)	1 (0.2%)	5 (0.8%)
緑内障	1 (0.2%)	2 (0.3%)	0	7 (1.1%)
眼圧上昇	1 (0.2%)	4 (0.6%)	1 (0.2%)	5 (0.8%)
アレルギー性結膜炎	1 (0.2%)	2 (0.3%)	1 (0.2%)	4 (0.6%)
眼そう痒症	0	3 (0.5%)	0	3 (0.5%)
流涙増加	0	4 (0.6%)	0	2 (0.3%)
霰粒腫	1 (0.2%)	3 (0.5%)	1 (0.2%)	2 (0.3%)
眼の異物感	0	4 (0.6%)	0	1 (0.2%)
麦粒腫	0	3 (0.5%)	0	2 (0.3%)
網膜出血	0	1 (0.2%)	1 (0.2%)	4 (0.6%)
霧視	0	2 (0.3%)	0	3 (0.5%)
眼痛	0	2 (0.3%)	1 (0.2%)	2 (0.3%)
高眼圧症	0	2 (0.3%)	0	2 (0.3%)
光視症	0	1 (0.2%)	1 (0.2%)	3 (0.5%)
境界域緑内障	0	3 (0.5%)	0	0
結膜充血	0	0	1 (0.2%)	3 (0.5%)
嚢胞様黄斑浮腫	0	0	0	3 (0.5%)
黄斑網膜色素上皮剥離	0	1 (0.2%)	0	2 (0.3%)
黄斑線維症	0	0	0	3 (0.5%)
視神経乳頭出血	1 (0.2%)	3 (0.5%)	0	0
処置後炎症	0	2 (0.3%)	0	1 (0.2%)
視力障害	0	1 (0.2%)	0	2 (0.3%)
硝子体出血	0	2 (0.3%)	0	1 (0.2%)

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
AE reported as neovascular age-related macular degeneration in the study eye indicates an accelerated worsening of the condition, as judged by the investigator.

表 2.7.4.7-5 データカットオフ日までに非試験眼に発現した有害事象（nAMD 統合）（続）

	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
MedDRA Preferred Term	Onset after Week 48	Overall	Onset after Week 48	Overall
眼精疲労	0	0	0	2 (0.3%)
皮質白内障	0	0	0	2 (0.3%)
嚢下白内障	0	2 (0.3%)	0	0
細菌性結膜炎	0	2 (0.3%)	0	0
ウイルス性結膜炎	0	2 (0.3%)	0	0
角膜擦過傷	0	1 (0.2%)	0	1 (0.2%)
角膜ジストロフィー	0	0	1 (0.2%)	2 (0.3%)
後天性涙道狭窄	0	0	0	2 (0.3%)
眼瞼皮膚弛緩症	0	2 (0.3%)	0	0
糖尿病網膜症	0	2 (0.3%)	0	0
眼内炎	1 (0.2%)	1 (0.2%)	0	1 (0.2%)
眼の母斑	0	1 (0.2%)	1 (0.2%)	1 (0.2%)
眼瞼下垂	0	0	0	2 (0.3%)
虹彩炎	0	1 (0.2%)	0	1 (0.2%)
角膜炎	0	1 (0.2%)	0	1 (0.2%)
黄斑変性	0	1 (0.2%)	0	1 (0.2%)
マイボーム腺機能不全	0	1 (0.2%)	0	1 (0.2%)
メラノサイト性母斑	0	1 (0.2%)	0	1 (0.2%)
変視症	0	0	2 (0.3%)	2 (0.3%)
眼充血	1 (0.2%)	2 (0.3%)	0	0
開放隅角緑内障	1 (0.2%)	1 (0.2%)	0	1 (0.2%)
疼痛	0	1 (0.2%)	0	1 (0.2%)
網膜嚢胞	0	1 (0.2%)	0	1 (0.2%)
網膜変性	0	1 (0.2%)	0	1 (0.2%)
網膜ドルーゼン	0	0	0	2 (0.3%)
網膜色素上皮裂孔	1 (0.2%)	2 (0.3%)	0	0
網膜静脈閉塞	1 (0.2%)	2 (0.3%)	0	0
網膜分離症	0	2 (0.3%)	0	0
裂孔原性網膜剥離	0	0	1 (0.2%)	2 (0.3%)
視力低下	2 (0.3%)	2 (0.3%)	0	0
硝子体網膜牽引症候群	0	0	0	2 (0.3%)
光線角化症	0	1 (0.2%)	0	0
加齢黄斑変性	0	1 (0.2%)	0	0
閉塞隅角緑内障	0	1 (0.2%)	0	0
角膜リポイド環	0	1 (0.2%)	0	0
眉毛下垂	0	0	1 (0.2%)	1 (0.2%)
核性白内障	0	0	0	1 (0.2%)

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
AE reported as neovascular age-related macular degeneration in the study eye indicates an accelerated worsening of the condition, as judged by the investigator.

表 2.7.4.7-5 データカットオフ日までに非試験眼に発現した有害事象（nAMD 統合）（続）

	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
MedDRA Preferred Term	Onset after Week 48	Overall	Onset after Week 48	Overall
角膜内皮炎	0	1 (0.2%)	0	0
角膜浸潤	0	0	1 (0.2%)	1 (0.2%)
角膜浮腫	0	1 (0.2%)	0	0
角膜瘢痕	0	1 (0.2%)	0	0
複視	0	1 (0.2%)	0	0
薬物過敏症	1 (0.2%)	1 (0.2%)	0	0
薬物不耐性	0	0	0	1 (0.2%)
眼球陥入	0	0	0	1 (0.2%)
落屑緑内障	0	1 (0.2%)	0	0
眼脂	1 (0.2%)	1 (0.2%)	0	0
眼感染	0	0	0	1 (0.2%)
眼刺激	0	1 (0.2%)	0	0
眼瞼血腫	0	1 (0.2%)	0	0
出血	0	0	0	1 (0.2%)
ヘルペス眼感染	0	0	0	1 (0.2%)
星状硝子体症	0	1 (0.2%)	0	0
虹彩毛様体炎	0	0	0	1 (0.2%)
虹彩障害	0	0	0	1 (0.2%)
虹彩徹照異常	0	1 (0.2%)	0	0
涙液分泌低下	0	1 (0.2%)	0	0
水晶体脱臼	1 (0.2%)	1 (0.2%)	0	0
水晶体混濁	1 (0.2%)	1 (0.2%)	0	0
黄斑円孔	0	0	0	1 (0.2%)
黄斑浮腫	0	0	0	1 (0.2%)
黄斑偽円孔	0	0	0	1 (0.2%)
筋攣縮	0	0	0	1 (0.2%)
前房狭隅角	0	1 (0.2%)	0	0
非感染性結膜炎	0	0	0	1 (0.2%)
正常眼圧緑内障	0	1 (0.2%)	0	0
眼部不快感	0	0	0	1 (0.2%)
黄疸眼	0	0	0	1 (0.2%)
乳頭腫	0	0	0	1 (0.2%)
眼窩周囲出血	0	0	0	1 (0.2%)
羞明	0	0	1 (0.2%)	1 (0.2%)
瞼裂斑	0	1 (0.2%)	0	0
そう痒症	0	0	0	1 (0.2%)
翼状片	0	0	1 (0.2%)	1 (0.2%)
読字障害	0	1 (0.2%)	0	0
先天性網膜異常	0	1 (0.2%)	0	0
網膜動脈閉塞	0	0	1 (0.2%)	1 (0.2%)
網膜滲出物	0	0	0	1 (0.2%)
網膜裂孔	0	1 (0.2%)	0	0
高血圧性網膜症	0	1 (0.2%)	0	0
斜視	0	1 (0.2%)	0	0
網膜下線維症	0	1 (0.2%)	0	0
縫合関連合併症	0	1 (0.2%)	0	0
ぶどう膜炎	0	0	0	1 (0.2%)
ウイルス性ぶどう膜炎	0	0	0	1 (0.2%)
硝子体変性	0	1 (0.2%)	0	0
硝子体混濁	0	1 (0.2%)	0	0
硝子体脱出	0	0	0	1 (0.2%)

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
AE reported as neovascular age-related macular degeneration in the study eye indicates an accelerated worsening of the condition, as judged by the investigator.

[5.3.5.3-nAMD-1 PR11375_t_ae_pt_cod_FOCUL_SE_nAMD_HLS を改変]

表 2.7.4.7-6 データカットオフ日までに非試験眼に発現した副作用（nAMD 統合）

	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
MedDRA Preferred Term	Onset after Week 48	Overall	Onset after Week 48	Overall
Total number of patients with at least one adverse event	0	0	0	3 (0.5%)
Total number of events	0	0	0	3
ぶどう膜炎	0	0	0	1 (0.2%)
硝子体浮遊物	0	0	0	1 (0.2%)
硝子体出血	0	0	0	1 (0.2%)

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
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[5.3.5.3-nAMD-1 PR11375_t_ae_pt_cod_FOCUL_FREL_SE_nAMD_HLS を改変]

表 2.7.4.7-7 データカットオフ日までに非試験眼に発現した有害事象（DME 統合）

Pooled(YOSEMITE and RHINE)
(N=1887)

MedDRA Preferred Term	Faricimab 6 mg Q8W (N=630) Onset after Week 56	Faricimab 6 mg Q8W (N=630) Overall	Faricimab 6 mg PTI (N=632) Onset after Week 56	Faricimab 6 mg PTI (N=632) Overall	Faricimab 6 mg All (N=1262) Onset after Week 56	Faricimab 6 mg All (N=1262) Overall	Aflibercept 2 mg Q8W (N=625) Onset after Week 56	Aflibercept 2 mg Q8W (N=625) Overall
Total number of patients with at least one adverse event	62 (9.8%)	239 (37.9%)	73 (11.6%)	232 (36.7%)	135 (10.7%)	471 (37.3%)	60 (9.6%)	244 (39.0%)
Total number of events	92	463	100	422	192	885	70	404
糖尿病性網膜浮腫	5 (0.8%)	37 (5.9%)	8 (1.3%)	42 (6.6%)	13 (1.0%)	79 (6.3%)	13 (2.1%)	45 (7.2%)
白内障	9 (1.4%)	42 (6.7%)	14 (2.2%)	36 (5.7%)	23 (1.8%)	78 (6.2%)	9 (1.4%)	38 (6.1%)
硝子体剥離	2 (0.3%)	17 (2.7%)	4 (0.6%)	16 (2.5%)	6 (0.5%)	33 (2.6%)	2 (0.3%)	19 (3.0%)
ドライアイ	3 (0.5%)	17 (2.7%)	5 (0.8%)	18 (2.8%)	8 (0.6%)	35 (2.8%)	4 (0.6%)	16 (2.6%)
糖尿病網膜症	3 (0.5%)	14 (2.2%)	6 (0.9%)	17 (2.7%)	9 (0.7%)	31 (2.5%)	1 (0.2%)	17 (2.7%)
結膜出血	1 (0.2%)	16 (2.5%)	2 (0.3%)	17 (2.7%)	3 (0.2%)	33 (2.6%)	1 (0.2%)	14 (2.2%)
硝子体出血	3 (0.5%)	17 (2.7%)	2 (0.3%)	9 (1.4%)	5 (0.4%)	26 (2.1%)	7 (1.1%)	15 (2.4%)
眼圧上昇	1 (0.2%)	11 (1.7%)	4 (0.6%)	10 (1.6%)	5 (0.4%)	21 (1.7%)	3 (0.5%)	10 (1.6%)
網膜出血	0	6 (1.0%)	2 (0.3%)	15 (2.4%)	2 (0.2%)	21 (1.7%)	3 (0.5%)	9 (1.4%)
後嚢部混濁	2 (0.3%)	8 (1.3%)	2 (0.3%)	10 (1.6%)	4 (0.3%)	18 (1.4%)	2 (0.3%)	8 (1.3%)
網膜滲出物	1 (0.2%)	8 (1.3%)	0	9 (1.4%)	1 (<0.1%)	17 (1.3%)	1 (0.2%)	9 (1.4%)
結膜炎	0	11 (1.7%)	2 (0.3%)	5 (0.8%)	2 (0.2%)	16 (1.3%)	0	9 (1.4%)
黄斑浮腫	2 (0.3%)	7 (1.1%)	2 (0.3%)	10 (1.6%)	4 (0.3%)	17 (1.3%)	0	8 (1.3%)
硝子体浮遊物	2 (0.3%)	5 (0.8%)	1 (0.2%)	8 (1.3%)	3 (0.2%)	13 (1.0%)	1 (0.2%)	12 (1.9%)
皮質白内障	1 (0.2%)	6 (1.0%)	1 (0.2%)	10 (1.6%)	2 (0.2%)	16 (1.3%)	1 (0.2%)	8 (1.3%)
眼痛	1 (0.2%)	7 (1.1%)	0	4 (0.6%)	1 (<0.1%)	11 (0.9%)	0	10 (1.6%)
眼瞼炎	3 (0.5%)	10 (1.6%)	2 (0.3%)	5 (0.8%)	5 (0.4%)	15 (1.2%)	2 (0.3%)	5 (0.8%)
嚢下白内障	4 (0.6%)	10 (1.6%)	1 (0.2%)	6 (0.9%)	5 (0.4%)	16 (1.3%)	1 (0.2%)	3 (0.5%)

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-7 データカットオフ日までに非試験眼に発現した有害事象（DME 統合）（続）

Pooled(YOSEMITE and RHINE)
(N=1887)

	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
MedDRA Preferred Term	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
点状角膜炎	0	7 (1.1%)	1 (0.2%)	6 (0.9%)	1 (<0.1%)	13 (1.0%)	0	4 (0.6%)
黄斑線維症	1 (0.2%)	5 (0.8%)	3 (0.5%)	8 (1.3%)	4 (0.3%)	13 (1.0%)	0	3 (0.5%)
核性白内障	2 (0.3%)	5 (0.8%)	1 (0.2%)	8 (1.3%)	3 (0.2%)	13 (1.0%)	0	2 (0.3%)
眼そう痒症	0	4 (0.6%)	1 (0.2%)	5 (0.8%)	1 (<0.1%)	9 (0.7%)	0	4 (0.6%)
網膜血管新生	2 (0.3%)	4 (0.6%)	1 (0.2%)	3 (0.5%)	3 (0.2%)	7 (0.6%)	0	6 (1.0%)
嚢胞様黄斑浮腫	2 (0.3%)	5 (0.8%)	0	2 (0.3%)	2 (0.2%)	7 (0.6%)	1 (0.2%)	5 (0.8%)
霧視	2 (0.3%)	4 (0.6%)	1 (0.2%)	3 (0.5%)	3 (0.2%)	7 (0.6%)	0	5 (0.8%)
視力低下	2 (0.3%)	5 (0.8%)	1 (0.2%)	5 (0.8%)	3 (0.2%)	10 (0.8%)	0	2 (0.3%)
角膜擦過傷	1 (0.2%)	3 (0.5%)	1 (0.2%)	4 (0.6%)	2 (0.2%)	7 (0.6%)	0	4 (0.6%)
光視症	2 (0.3%)	5 (0.8%)	0	2 (0.3%)	2 (0.2%)	7 (0.6%)	2 (0.3%)	3 (0.5%)
緑内障	1 (0.2%)	3 (0.5%)	2 (0.3%)	2 (0.3%)	3 (0.2%)	5 (0.4%)	1 (0.2%)	4 (0.6%)
眼充血	2 (0.3%)	6 (1.0%)	0	2 (0.3%)	2 (0.2%)	8 (0.6%)	0	1 (0.2%)
アレルギー性結膜炎	1 (0.2%)	4 (0.6%)	0	2 (0.3%)	1 (<0.1%)	6 (0.5%)	0	1 (0.2%)
流涙増加	1 (0.2%)	2 (0.3%)	1 (0.2%)	3 (0.5%)	2 (0.2%)	5 (0.4%)	0	2 (0.3%)
視力障害	1 (0.2%)	4 (0.6%)	0	0	1 (<0.1%)	4 (0.3%)	1 (0.2%)	3 (0.5%)
虹彩炎	1 (0.2%)	3 (0.5%)	1 (0.2%)	2 (0.3%)	2 (0.2%)	5 (0.4%)	1 (0.2%)	1 (0.2%)
高眼圧症	1 (0.2%)	1 (0.2%)	1 (0.2%)	2 (0.3%)	2 (0.2%)	3 (0.2%)	2 (0.3%)	3 (0.5%)
眼刺激	1 (0.2%)	1 (0.2%)	0	1 (0.2%)	1 (<0.1%)	2 (0.2%)	0	3 (0.5%)
麦粒腫	3 (0.5%)	4 (0.6%)	0	0	3 (0.2%)	4 (0.3%)	0	1 (0.2%)

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-7 データカットオフ日までに非試験眼に発現した有害事象（DME 統合）（続）

Pooled(YOSEMITE and RHINE)
(N=1887)

MedDRA Preferred Term	Faricimab 6 mg Q8W (N=630) Onset after Week 56	Faricimab 6 mg Q8W (N=630) Overall	Faricimab 6 mg PTI (N=632) Onset after Week 56	Faricimab 6 mg PTI (N=632) Overall	Faricimab 6 mg All (N=1262) Onset after Week 56	Faricimab 6 mg All (N=1262) Overall	Aflibercept 2 mg Q8W (N=625) Onset after Week 56	Aflibercept 2 mg Q8W (N=625) Overall
境界域緑内障	0	0	1 (0.2%)	4 (0.6%)	1 (<0.1%)	4 (0.3%)	0	0
霰粒腫	0	1 (0.2%)	1 (0.2%)	2 (0.3%)	1 (<0.1%)	3 (0.2%)	0	1 (0.2%)
角膜びらん	0	1 (0.2%)	0	2 (0.3%)	0	3 (0.2%)	0	1 (0.2%)
眼瞼皮膚弛緩症	0	2 (0.3%)	1 (0.2%)	1 (0.2%)	1 (<0.1%)	3 (0.2%)	1 (0.2%)	1 (0.2%)
黄斑肥厚	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	3 (0.5%)
血管新生	0	2 (0.3%)	1 (0.2%)	2 (0.3%)	1 (<0.1%)	4 (0.3%)	0	0
眼部不快感	0	4 (0.6%)	0	0	0	4 (0.3%)	0	0
網膜肥厚	0	2 (0.3%)	0	1 (0.2%)	0	3 (0.2%)	0	1 (0.2%)
ぶどう膜炎	1 (0.2%)	1 (0.2%)	0	1 (0.2%)	1 (<0.1%)	2 (0.2%)	0	2 (0.3%)

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-7 データカットオフ日までに非試験眼に発現した有害事象（DME 統合）（続）

Pooled(YOSEMITE and RHINE)
(N=1887)

MedDRA Preferred Term	Faricimab 6 mg Q8W (N=630) Onset after Week 56	Faricimab 6 mg Q8W (N=630) Overall	Faricimab 6 mg PTI (N=632) Onset after Week 56	Faricimab 6 mg PTI (N=632) Overall	Faricimab 6 mg All (N=1262) Onset after Week 56	Faricimab 6 mg All (N=1262) Overall	Aflibercept 2 mg Q8W (N=625) Onset after Week 56	Aflibercept 2 mg Q8W (N=625) Overall
アデノウイルス結膜炎	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	2 (0.3%)
動脈瘤	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	2 (0.3%)
ウイルス性結膜炎	0	2 (0.3%)	0	1 (0.2%)	0	3 (0.2%)	0	0
角膜ジストロフィー	0	0	0	2 (0.3%)	0	2 (0.2%)	0	1 (0.2%)
眼出血	0	2 (0.3%)	0	1 (0.2%)	0	3 (0.2%)	0	0
眼瞼痛	0	2 (0.3%)	0	1 (0.2%)	0	3 (0.2%)	0	0
眼瞼下垂	0	2 (0.3%)	0	0	0	2 (0.2%)	1 (0.2%)	1 (0.2%)
黄斑虚血	0	2 (0.3%)	0	1 (0.2%)	0	3 (0.2%)	0	0
開放隅角緑内障	1 (0.2%)	1 (0.2%)	0	1 (0.2%)	1 (<0.1%)	2 (0.2%)	0	1 (0.2%)
羞明	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	1 (0.2%)
そう痒症	0	2 (0.3%)	1 (0.2%)	1 (0.2%)	1 (<0.1%)	3 (0.2%)	0	0
網膜変性	0	1 (0.2%)	1 (0.2%)	2 (0.3%)	1 (<0.1%)	3 (0.2%)	0	0
角膜生体染色陽性	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	2 (0.3%)
硝子体変性	0	1 (0.2%)	1 (0.2%)	1 (0.2%)	1 (<0.1%)	2 (0.2%)	1 (0.2%)	1 (0.2%)
硝子体炎	0	0	0	0	0	0	0	3 (0.5%)
外傷性白内障	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	0
脈絡膜血管新生	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	0
結膜充血	1 (0.2%)	1 (0.2%)	0	1 (0.2%)	1 (<0.1%)	2 (0.2%)	0	0
角膜上皮欠損	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	1 (0.2%)
角膜浮腫	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	1 (0.2%)	1 (0.2%)
皮膚嚢腫	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	1 (0.2%)

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-7 データカットオフ日までに非試験眼に発現した有害事象（DME 統合）（続）

Pooled(YOSEMITE and RHINE)
(N=1887)

MedDRA Preferred Term	Faricimab 6 mg Q8W (N=630) Onset after Week 56	Faricimab 6 mg Q8W (N=630) Overall	Faricimab 6 mg PTI (N=632) Onset after Week 56	Faricimab 6 mg PTI (N=632) Overall	Faricimab 6 mg All (N=1262) Onset after Week 56	Faricimab 6 mg All (N=1262) Overall	Aflibercept 2 mg Q8W (N=625) Onset after Week 56	Aflibercept 2 mg Q8W (N=625) Overall
不快感	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	1 (0.2%)
眼脂	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	1 (0.2%)
眼の母斑	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	1 (0.2%)
眼瞼縁痂皮	1 (0.2%)	2 (0.3%)	0	0	1 (<0.1%)	2 (0.2%)	0	0
眼瞼そう痒症	1 (0.2%)	2 (0.3%)	0	0	1 (<0.1%)	2 (0.2%)	0	0
眼内異物	0	1 (0.2%)	1 (0.2%)	1 (0.2%)	1 (<0.1%)	2 (0.2%)	0	0
虹彩毛様体炎	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	1 (0.2%)
角膜炎	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	0
ウイルス性角膜炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	1 (0.2%)
水晶体混濁	0	0	1 (0.2%)	2 (0.3%)	1 (<0.1%)	2 (0.2%)	0	0
黄斑円孔	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	1 (0.2%)
投薬過誤	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	0
視神経乳頭出血	0	0	0	1 (0.2%)	0	1 (<0.1%)	1 (0.2%)	1 (0.2%)
疼痛	0	2 (0.3%)	0	0	0	2 (0.2%)	0	0
眼窩周囲蜂巣炎	0	0	0	0	0	0	0	2 (0.3%)
瞼裂斑	1 (0.2%)	2 (0.3%)	0	0	1 (<0.1%)	2 (0.2%)	0	0
処置による疼痛	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	1 (0.2%)
網膜血管瘤	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	1 (0.2%)
網膜動脈塞栓症	0	0	0	1 (0.2%)	0	1 (<0.1%)	1 (0.2%)	1 (0.2%)
網膜障害	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	0
網膜血管障害	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	1 (0.2%)

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-7 データカットオフ日までに非試験眼に発現した有害事象（DME 統合）（続）

Pooled(YOSEMITE and RHINE)
(N=1887)

MedDRA Preferred Term	Faricimab 6 mg Q8W (N=630) Onset after Week 56	Faricimab 6 mg Q8W (N=630) Overall	Faricimab 6 mg PTI (N=632) Onset after Week 56	Faricimab 6 mg PTI (N=632) Overall	Faricimab 6 mg All (N=1262) Onset after Week 56	Faricimab 6 mg All (N=1262) Overall	Aflibercept 2 mg Q8W (N=625) Onset after Week 56	Aflibercept 2 mg Q8W (N=625) Overall
高血圧性網膜症	0	0	0	0	0	0	0	2 (0.3%)
網膜分離症	0	2 (0.3%)	0	0	0	2 (0.2%)	0	0
異物感	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	1 (0.2%)
牽引性網膜剥離	1 (0.2%)	2 (0.3%)	0	0	1 (<0.1%)	2 (0.2%)	0	0
硝子体網膜牽引症候群	1 (0.2%)	1 (0.2%)	0	1 (0.2%)	1 (<0.1%)	2 (0.2%)	0	0
硝子体混濁	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	1 (0.2%)
眼の異常感	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
閉塞隅角緑内障	0	0	0	0	0	0	0	1 (0.2%)
前嚢破裂	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
前眼房混濁	0	0	0	0	0	0	0	1 (0.2%)
動脈硬化症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
アレルギー性眼瞼炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
一過性失明	0	0	0	0	0	0	0	1 (0.2%)
灼熱感	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
眼部化学熱傷	0	0	0	0	0	0	0	1 (0.2%)
結膜刺激	0	0	0	0	0	0	0	1 (0.2%)
結膜浮腫	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
細菌性結膜炎	0	0	0	0	0	0	0	1 (0.2%)
造影剤アレルギー	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
角膜瘢痕	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
後天性涙道狭窄	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-7 データカットオフ日までに非試験眼に発現した有害事象（DME 統合）（続）

Pooled(YOSEMITE and RHINE)
(N=1887)

MedDRA Preferred Term	Faricimab 6 mg Q8W (N=630) Onset after Week 56	Faricimab 6 mg Q8W (N=630) Overall	Faricimab 6 mg PTI (N=632) Onset after Week 56	Faricimab 6 mg PTI (N=632) Overall	Faricimab 6 mg All (N=1262) Onset after Week 56	Faricimab 6 mg All (N=1262) Overall	Aflibercept 2 mg Q8W (N=625) Onset after Week 56	Aflibercept 2 mg Q8W (N=625) Overall
接触皮膚炎	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
糖尿病性眼病変	0	0	0	0	0	0	0	1 (0.2%)
薬物過敏症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
斑状出血	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
眼内炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
上強膜炎	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
紅斑	0	0	0	0	0	0	0	1 (0.2%)
眼瞼紅斑	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
眼のアレルギー	0	0	0	0	0	0	0	1 (0.2%)
眼挫傷	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
眼外傷	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
眼運動障害	0	0	0	0	0	0	0	1 (0.2%)
眼瞼血腫	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
眼瞼刺激	0	0	0	0	0	0	0	1 (0.2%)
眼瞼浮腫	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
グレア	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
緑内障性視神経乳頭萎縮	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
出血	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
半盲	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
星状硝子体症	0	0	0	0	0	0	0	1 (0.2%)
第３脳神経麻痺	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-7 データカットオフ日までに非試験眼に発現した有害事象（DME 統合）（続）

Pooled(YOSEMITE and RHINE)
(N=1887)

	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
MedDRA Preferred Term	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
眼内レンズ挿入	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
眼圧変動	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
虹彩血管新生	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
細菌性角膜炎	0	0	0	0	0	0	0	1 (0.2%)
涙液分泌低下	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
限局性浮腫	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
黄斑剥離	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
黄斑症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
瞼板腺炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
変視症	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
前兆を伴う片頭痛	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
前房狭隅角	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
神経血管コンフリクト	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
非感染性結膜炎	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
視神経萎縮	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
視神経乳頭ドルーゼン	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
視神経乳頭陥凹／乳頭比増加	0	0	0	0	0	0	0	1 (0.2%)
視神経乳頭陥凹	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
視神経乳頭浮腫	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
乳頭腫	0	0	0	0	0	0	0	1 (0.2%)

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-7 データカットオフ日までに非試験眼に発現した有害事象（DME 統合）（続）

Pooled(YOSEMITE and RHINE)
(N=1887)

MedDRA Preferred Term	Faricimab 6 mg Q8W (N=630) Onset after Week 56	Faricimab 6 mg Q8W (N=630) Overall	Faricimab 6 mg PTI (N=632) Onset after Week 56	Faricimab 6 mg PTI (N=632) Overall	Faricimab 6 mg All (N=1262) Onset after Week 56	Faricimab 6 mg All (N=1262) Overall	Aflibercept 2 mg Q8W (N=625) Onset after Week 56	Aflibercept 2 mg Q8W (N=625) Overall
錯感覚	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
眼窩周囲血腫	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
眼窩周囲出血	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
点状出血	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
処置後炎症	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
網膜動脈閉塞	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
網膜嚢胞	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
網膜色素脱失	0	0	0	0	0	0	0	1 (0.2%)
網膜浮腫	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
網膜色素沈着	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
網膜裂孔	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
網膜静脈閉塞	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
網膜症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
強膜色素沈着	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
強膜炎	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
シェーグレン症候群	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
斜視	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
網膜下液	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
腫脹	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
第６脳神経麻痺	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
一過性視力低下	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-7 データカットオフ日までに非試験眼に発現した有害事象（DME 統合）（続）

Pooled(YOSEMITE and RHINE)
(N=1887)

MedDRA Preferred Term	Faricimab 6 mg Q8W (N=630) Onset after Week 56	Faricimab 6 mg Q8W (N=630) Overall	Faricimab 6 mg PTI (N=632) Onset after Week 56	Faricimab 6 mg PTI (N=632) Overall	Faricimab 6 mg All (N=1262) Onset after Week 56	Faricimab 6 mg All (N=1262) Overall	Aflibercept 2 mg Q8W (N=625) Onset after Week 56	Aflibercept 2 mg Q8W (N=625) Overall
視野欠損	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
硝子体癒着	0	0	0	0	0	0	0	1 (0.2%)
硝子体障害	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

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[5.3.5.3-nAMD-1 PR11375_t_ae_pt_cod_FOCUL_SE_DME_HLS を改変]

表 2.7.4.7-8 データカットオフ日までに非試験眼に発現した副作用（DME 統合）

Pooled(YOSEMITE and RHINE)
(N=1887)

MedDRA Preferred Term	Faricimab 6 mg Q8W (N=630) Onset after Week 56	Faricimab 6 mg Q8W (N=630) Overall	Faricimab 6 mg PTI (N=632) Onset after Week 56	Faricimab 6 mg PTI (N=632) Overall	Faricimab 6 mg All (N=1262) Onset after Week 56	Faricimab 6 mg All (N=1262) Overall	Aflibercept 2 mg Q8W (N=625) Onset after Week 56	Aflibercept 2 mg Q8W (N=625) Overall
Total number of patients with at least one adverse event	1 (0.2%)	11 (1.7%)	1 (0.2%)	7 (1.1%)	2 (0.2%)	18 (1.4%)	1 (0.2%)	13 (2.1%)
Total number of events	1	12	1	8	2	20	1	16
眼圧上昇	0	2 (0.3%)	1 (0.2%)	3 (0.5%)	1 (<0.1%)	5 (0.4%)	1 (0.2%)	2 (0.3%)
結膜出血	0	4 (0.6%)	0	1 (0.2%)	0	5 (0.4%)	0	1 (0.2%)
硝子体浮遊物	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	2 (0.3%)
白内障	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	1 (0.2%)
眼痛	0	0	0	0	0	0	0	2 (0.3%)
眼内炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
眼刺激	0	0	0	0	0	0	0	1 (0.2%)
眼そう痒症	0	0	0	0	0	0	0	1 (0.2%)
虹彩炎	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
角膜炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
流涙増加	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
黄斑線維症	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
黄斑円孔	0	0	0	0	0	0	0	1 (0.2%)
疼痛	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
シェーグレン症候群	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
霧視	0	0	0	0	0	0	0	1 (0.2%)
硝子体剥離	0	0	0	0	0	0	0	1 (0.2%)
硝子体出血	0	0	0	0	0	0	0	1 (0.2%)
硝子体炎	0	0	0	0	0	0	0	1 (0.2%)

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

[5.3.5.3-nAMD-1 PR11375_t_ae_pt_cod_FOCUL_FREL_SE_DME_HLS を改変]

表 2.7.4.7-9 データカットオフ日までに試験眼に発現した重篤な有害事象（nAMD 統合）

Pooled(TENAYA and LUCERNE)
(N=1326)

MedDRA Preferred Term	Faricimab 6 mg (N=664) Onset after Week 48	Faricimab 6 mg (N=664) Overall	Aflibercept 2 mg (N=662) Onset after Week 48	Aflibercept 2 mg (N=662) Overall
Total number of patients with at least one adverse event	3 (0.5%)	14 (2.1%)	6 (0.9%)	18 (2.7%)
Total number of events	3	18	7	20
新生血管加齢黄斑変性	1 (0.2%)	3 (0.5%)	1 (0.2%)	4 (0.6%)
網膜色素上皮裂孔	0	4 (0.6%)	0	0
ぶどう膜炎	0	2 (0.3%)	0	1 (0.2%)
白内障	0	1 (0.2%)	1 (0.2%)	1 (0.2%)
ウイルス性ぶどう膜炎	0	2 (0.3%)	0	0
視力低下	1 (0.2%)	1 (0.2%)	1 (0.2%)	1 (0.2%)
硝子体炎	0	2 (0.3%)	0	0
加齢黄斑変性	0	0	0	1 (0.2%)
皮質白内障	0	0	0	1 (0.2%)
白内障手術合併症	0	0	1 (0.2%)	1 (0.2%)
外傷性白内障	0	0	1 (0.2%)	1 (0.2%)
脈絡網膜炎	0	1 (0.2%)	0	0
角膜擦過傷	0	0	0	1 (0.2%)
角膜浮腫	0	0	0	1 (0.2%)
眼内炎	0	0	0	1 (0.2%)
眼のアレルギー	0	0	0	1 (0.2%)
顔面骨骨折	0	0	0	1 (0.2%)
眼圧上昇	0	1 (0.2%)	0	0
非感染性眼内炎	0	0	1 (0.2%)	1 (0.2%)
網膜変性	0	0	1 (0.2%)	1 (0.2%)
裂孔原性網膜剥離	1 (0.2%)	1 (0.2%)	0	0
網膜下線維症	0	0	0	1 (0.2%)
硝子体出血	0	0	0	1 (0.2%)

AE = Adverse Event; MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
AE reported as neovascular age-related macular degeneration in the study eye indicates an accelerated worsening of the condition, as judged by the investigator.

[5.3.5.3-nAMD-1 t_ae_pt_cod_SOCUL_SER_SE_nAMD_HLS を改変]

表 2.7.4.7-10　データカットオフ日までに試験眼に発現した重篤な副作用（nAMD 統合）

	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
MedDRA Preferred Term	Onset after Week 48	Overall	Onset after Week 48	Overall
Total number of patients with at least one adverse event	0	8 (1.2%)	1 (0.2%)	2 (0.3%)
Total number of events	0	8	1	2
網膜色素上皮裂孔	0	4 (0.6%)	0	0
ぶどう膜炎	0	2 (0.3%)	0	1 (0.2%)
硝子体炎	0	2 (0.3%)	0	0
非感染性眼内炎	0	0	1 (0.2%)	1 (0.2%)

MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
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[5.3.5.3-nAMD-1 t_ae_pt_cod_SOCUL_SER_SREL_SE_nAMD_HLS を改変]

表 2.7.4.7-11 データカットオフ日までに試験眼に発現した重篤な有害事象一覧（GR40306試験及び GR40844試験）

Study: GR40306(TENAYA)
Treatment: Faricimab 6 mg

Center/Patient - Age/Sex/Race Adverse Event MedDRA Preferred Term	Number of Study Drug Administered prior to event	Date of First Study Drug Administration	Study Day of Onset	AE Duration in Days	Serious	Most Extreme Intensity	Caused by Study Drug	Outcome (1)	Treatment for AE	Action Taken with Study Drug (2)
319088/[redacted] - 7[redacted]/M/White 網膜色素上皮裂孔	2	10OCT2019	27		Yes	MODERATE	Yes	2	No	1
319418/[redacted] - 6[redacted]/M/White 網膜色素上皮裂孔	5	07MAR2019	167		Yes	MILD	Yes	2	No	1
319587/[redacted]- 7[redacted]/F/White ぶどう膜炎	6	16OCT2019	330		Yes	SEVERE	Yes	5	Yes	2
319609/[redacted] - 7[redacted]/F/White 視力低下	7	13AUG2019	361	35	Yes	MODERATE	No	3	No	1
319612/[redacted] - 6[redacted]/F/White 裂孔原性網膜剥離	9	30AUG2019	368	32	Yes	SEVERE	No	3	No	2
320823/[redacted] - 7[redacted]/M/White 新生血管加齢黄斑変性 ウイルス性ぶどう膜炎	5 6	30SEP2019 30SEP2019	232 316	29	Yes Yes	MODERATE SEVERE	No No	4 5	No Yes	1 2

MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Only treatment emergent AEs are displayed.
(1) Outcome: 1 = fatal; 2 = not recovered/not resolved; 3 = recovered/resolved; 4 = recovered/resolved with sequelae; 5 = recovering/resolving; 6 = unknown.
(2) Action taken with study drug: 1 = dose not changed; 2 = drug interrupt; 3 = drug withdrawn; 4 = not applicable; 5 = unknown.
* Study day derived from imputed onset date.
** Duration derived from imputed onset date and/or end date.

表 2.7.4.7-11 データカットオフ日までに試験眼に発現した重篤な有害事象一覧（GR40306試験及び GR40844試験）（続）

Study: GR40306(TENAYA)
Treatment: Aflibercept 2 mg

Center/Patient - Age/Sex/Race Adverse Event MedDRA Preferred Term	Number of Study Drug Administered prior to event	Date of First Study Drug Administration	Study Day of Onset	AE Duration in Days	Serious	Most Extreme Intensity	Caused by Study Drug	Outcome (1)	Treatment for AE	Action Taken with Study Drug (2)
319098/[redacted] - 7[redacted]/F/White										
加齢黄斑変性	8	09SEP2019	337	32	Yes	MILD	No	3	No	1
319418/[redacted] - 8[redacted]/M/White										
新生血管加齢黄斑変性	4	19AUG2019	116	29	Yes	MODERATE	No	3	No	1
319473/[redacted] - 8[redacted]/F/White										
網膜下線維症	3	20SEP2019	91		Yes	SEVERE	No	2	No	1
319587/[redacted]- 8[redacted]/F/White										
新生血管加齢黄斑変性	4	02OCT2019	113	29	Yes	MILD	No	3	No	1
319602/[redacted]- 6[redacted]/M/White										
新生血管加齢黄斑変性	10	01MAR2019	483		Yes	MODERATE	No	2	No	1
319624/[redacted] - 7[redacted]/M/White										
角膜擦過傷	1	01MAY2019	1	6	Yes	MILD	No	3	Yes	1
320820/[redacted] - 7[redacted]/F/White										
白内障	8	13JUN2019	364	120	Yes	MODERATE	No	3	No	1
網膜変性	8	13JUN2019	364		Yes	MODERATE	No	2	No	1
322179/[redacted] - 8[redacted]/F/Asian										
新生血管加齢黄斑変性	7	18NOV2019	298		Yes	SEVERE	No	5	No	2

MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Only treatment emergent AEs are displayed.
(1) Outcome: 1 = fatal; 2 = not recovered/not resolved; 3 = recovered/resolved; 4 = recovered/resolved with sequelae; 5 = recovering/resolving; 6 = unknown.
(2) Action taken with study drug: 1 = dose not changed; 2 = drug interrupt; 3 = drug withdrawn; 4 = not applicable; 5 = unknown.
* Study day derived from imputed onset date.
** Duration derived from imputed onset date and/or end date.

表 2.7.4.7-11 データカットオフ日までに試験眼に発現した重篤な有害事象一覧（GR40306試験及び GR40844試験）（続）

Study: GR40844(LUCERNE)
Treatment: Faricimab 6 mg

Center/Patient - Age/Sex/Race Adverse Event MedDRA Preferred Term	Number of Study Drug Administered prior to event	Date of First Study Drug Administration	Study Day of Onset	AE Duration in Days	Serious	Most Extreme Intensity	Caused by Study Drug	Outcome (1)	Treatment for AE	Action Taken with Study Drug (2)
319242/[redacted] - 7[redacted]/M/White										
硝子体炎	7	21OCT2019	265	27	Yes	MODERATE	Yes	3	Yes	2
319364/[redacted]- 5[redacted]/M/Asian										
新生血管加齢黄斑変性	9	25SEP2019	363		Yes	SEVERE	No	5	Yes	3
319534/[redacted] - 7[redacted]/F/White										
白内障	5	04SEP2019	258		Yes	MODERATE	No	2	No	1
319537/[redacted] - 7[redacted]/M/White										
新生血管加齢黄斑変性	2	24JUL2019	29	98	Yes	SEVERE	No	3	No	1
ぶどう膜炎	4	24JUL2019	126		Yes	SEVERE	Yes	2	Yes	3
319667/[redacted] - 5[redacted]/F/White										
ウイルス性ぶどう膜炎	4	11OCT2019	130	79	Yes	MODERATE	No	3	Yes	2
眼圧上昇	4	11OCT2019	137	4	Yes	SEVERE	No	3	Yes	2
脈絡網膜炎	5	11OCT2019	251		Yes	SEVERE	No	5	Yes	2
319912/[redacted] - 6[redacted]/F/White										
硝子体炎	6	23JUL2019	205	37	Yes	MODERATE	Yes	3	Yes	3
320485/[redacted] - 7[redacted]/F/Unknown										
網膜色素上皮裂孔	1	09OCT2019	6		Yes	SEVERE	Yes	2	No	1
323550/[redacted] - 6[redacted]/F/Asian										
網膜色素上皮裂孔	4	10OCT2019	82		Yes	MODERATE	Yes	2	No	3

MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Only treatment emergent AEs are displayed.
(1) Outcome: 1 = fatal; 2 = not recovered/not resolved; 3 = recovered/resolved; 4 = recovered/resolved with sequelae; 5 = recovering/resolving; 6 = unknown.
(2) Action taken with study drug: 1 = dose not changed; 2 = drug interrupt; 3 = drug withdrawn; 4 = not applicable; 5 = unknown.
* Study day derived from imputed onset date.
** Duration derived from imputed onset date and/or end date.

表 2.7.4.7-11 データカットオフ日までに試験眼に発現した重篤な有害事象一覧（GR40306試験及び GR40844試験）（続）

Study: GR40844(LUCERNE)
Treatment: Aflibercept 2 mg

Center/Patient - Age/Sex/Race Adverse Event MedDRA Preferred Term	Number of Study Drug Administered prior to event	Date of First Study Drug Administration	Study Day of Onset	AE Duration in Days	Serious	Most Extreme Intensity	Caused by Study Drug	Outcome (1)	Treatment for AE	Action Taken with Study Drug (2)
319270/[redacted] - 7[redacted]/M/White 角膜浮腫	4	21OCT2019	169	64	Yes	MILD	No	3	No	1
319401/[redacted] - 8[redacted]/F/White 眼内炎	5	28AUG2019	174	31	Yes	MODERATE	No	3	Yes	1
319489/[redacted] - 9[redacted]/M/White ぶどう膜炎	4	05APR2019	123	59	Yes	SEVERE	Yes	3	Yes	3
319489/[redacted] - 8[redacted]/F/White 視力低下	8	20JUN2019	398		Yes	SEVERE	No	2	No	1
319489/[redacted]- 7[redacted]/M/White 硝子体出血	2	31JUL2019	35	29	Yes	MODERATE	No	3	Yes	1
319502/[redacted] - 7[redacted]/F/White 眼のアレルギー	7	10SEP2019	313	32	Yes	MILD	No	3	No	1
319513/[redacted] - 6[redacted]/M/White 非感染性眼内炎	8	24SEP2019	372	50	Yes	MODERATE	Yes	3	Yes	3
319516/[redacted] - 6[redacted]/M/White 皮質白内障 白内障手術合併症	6 8	03OCT2019 03OCT2019	246 365	114 7	Yes Yes	SEVERE SEVERE	No No	3 3	No No	1 2
320030/[redacted] - 7[redacted]/F/White 外傷性白内障	9	05AUG2019	421	32	Yes	SEVERE	No	3	No	1
320032/[redacted] - 8[redacted]/F/White 顔面骨骨折	2	12JUL2019	38	26	Yes	MILD	No	3	Yes	1

MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Only treatment emergent AEs are displayed.
(1) Outcome: 1 = fatal; 2 = not recovered/not resolved; 3 = recovered/resolved; 4 = recovered/resolved with sequelae; 5 = recovering/resolving; 6 = unknown.
(2) Action taken with study drug: 1 = dose not changed; 2 = drug interrupt; 3 = drug withdrawn; 4 = not applicable; 5 = unknown.
* Study day derived from imputed onset date.
** Duration derived from imputed onset date and/or end date.

[5.3.5.3-nAMD-1 l_ae_cod_SOCUL_SER_SE_nAMD_HLS を改変]

表 2.7.4.7-12　データカットオフ日までに試験眼に発現した重篤な有害事象（DME 統合）

Pooled(YOSEMITE and RHINE)
(N=1887)

MedDRA Preferred Term	Faricimab 6 mg Q8W (N=630) Onset after Week 56	Faricimab 6 mg Q8W (N=630) Overall	Faricimab 6 mg PTI (N=632) Onset after Week 56	Faricimab 6 mg PTI (N=632) Overall	Faricimab 6 mg All (N=1262) Onset after Week 56	Faricimab 6 mg All (N=1262) Overall	Aflibercept 2 mg Q8W (N=625) Onset after Week 56	Aflibercept 2 mg Q8W (N=625) Overall
Total number of patients with at least one adverse event	5 (0.8%)	20 (3.2%)	9 (1.4%)	25 (4.0%)	14 (1.1%)	45 (3.6%)	5 (0.8%)	13 (2.1%)
Total number of events	5	25	9	30	14	55	5	13
白内障	2 (0.3%)	4 (0.6%)	2 (0.3%)	2 (0.3%)	4 (0.3%)	6 (0.5%)	1 (0.2%)	3 (0.5%)
糖尿病性網膜浮腫	1 (0.2%)	4 (0.6%)	1 (0.2%)	3 (0.5%)	2 (0.2%)	7 (0.6%)	1 (0.2%)	1 (0.2%)
眼内炎	0	2 (0.3%)	1 (0.2%)	3 (0.5%)	1 (<0.1%)	5 (0.4%)	0	1 (0.2%)
硝子体出血	0	2 (0.3%)	0	1 (0.2%)	0	3 (0.2%)	0	1 (0.2%)
嚢下白内障	1 (0.2%)	1 (0.2%)	0	1 (0.2%)	1 (<0.1%)	2 (0.2%)	1 (0.2%)	1 (0.2%)
網膜裂孔	0	0	1 (0.2%)	3 (0.5%)	1 (<0.1%)	3 (0.2%)	0	0
ぶどう膜炎	0	0	1 (0.2%)	3 (0.5%)	1 (<0.1%)	3 (0.2%)	0	0
一過性視力低下	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	1 (0.2%)
糖尿病網膜症	0	1 (0.2%)	0	0	0	1 (<0.1%)	1 (0.2%)	1 (0.2%)
高眼圧症	0	0	0	2 (0.3%)	0	2 (0.2%)	0	0
視力障害	0	0	1 (0.2%)	2 (0.3%)	1 (<0.1%)	2 (0.2%)	0	0
眼部化学熱傷	0	0	0	0	0	0	0	1 (0.2%)
脈絡網膜炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
医療機器位置異常	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
ドライアイ	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
緑内障	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
インフルエンザ	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
眼圧上昇	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
角膜ぶどう膜炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
黄斑線維症	0	0	0	0	0	0	0	1 (0.2%)
前房狭隅角	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
眼虚血症候群	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
後嚢部混濁	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
網膜動脈閉塞	0	0	0	0	0	0	0	1 (0.2%)
網膜出血	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
網膜血管新生	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
網膜静脈閉塞	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
裂孔原性網膜剥離	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
眼瞼腫脹	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
ぶどう膜炎性緑内障	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
ウイルス性角膜ぶどう膜炎	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.　Page 1 of 1

[5.3.5.3-nAMD-1 t_ae_pt_cod_SOCUL_SER_SE_DME_HLS を改変]

表 2.7.4.7-13 データカットオフ日までに試験眼に発現した重篤な副作用（DME 統合）

	Pooled(YOSEMITE and RHINE) (N=1887)							
	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
MedDRA Preferred Term	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
Total number of patients with at least one adverse event	0	0	3 (0.5%)	7 (1.1%)	3 (0.2%)	7 (0.6%)	0	0
Total number of events	0	0	3	9	3	9	0	0
ぶどう膜炎	0	0	1 (0.2%)	3 (0.5%)	1 (<0.1%)	3 (0.2%)	0	0
白内障	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
脈絡網膜炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
眼内炎	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
角膜ぶどう膜炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
高眼圧症	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

[5.3.5.3-nAMD-1 t_ae_pt_cod_SOCUL_SER_SREL_SE_DME_HLS を改変]

表 2.7.4.7-14　56週時までに試験眼に発現した重篤な有害事象一覧（GR40349試験及び GR40398試験）

Study: GR40349(YOSEMITE)
Treatment: Faricimab 6 mg Q8W

Center/Patient - Age/Sex/Race Adverse Event MedDRA Preferred Term	Treatment Naive Patients	Number of Study Drug Administered prior to event	Date of First Study Drug Administration	Study Day of Onset	AE Duration in Days	Serious	Most Extreme Intensity	Caused by Study Drug	Out come (1)	Treatment for AE	Action Taken with Study Drug (2)
310913/[redacted] - 6[redacted]/M/White											
医療機器位置異常	No	8	15JAN2019	311	5	Yes	MODERATE	No	3	Yes	2
311735/[redacted] - 5[redacted]/M/White											
前房狭隅角	Yes	2	22AUG2019	63	1	Yes	MILD	No	3	Yes	1
312242/[redacted] - 6[redacted]/M/White											
硝子体出血	Yes	8	12AUG2019	277	5	Yes	MILD	No	3	No	1
313212/[redacted] - 4[redacted]/M/White											
裂孔原性網膜剥離	Yes	6	17MAY2019	167	2	Yes	SEVERE	No	3	No	3
314732/[redacted] - 5[redacted]/F/American Indian or Alaska Native											
糖尿病性網膜浮腫	Yes	7	17SEP2019	198	29	Yes	MODERATE	No	3	No	1
ウイルス性角膜ぶどう膜炎	Yes	7	17SEP2019	219		Yes	MILD	No	5	Yes	2
314733/[redacted] - 6[redacted]/M/Unknown											
糖尿病網膜症	Yes	4	15JUL2019	86	133	Yes	MODERATE	No	3	No	1
緑内障	Yes	5	15JUL2019	134	57	Yes	MODERATE	No	3	Yes	2

* Study day derived from imputed onset date.
** Duration derived from imputed onset date and/or end date.
MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W). Investigator text for AEs encoded using MedDRA version 23.1. Only treatment emergent AEs are displayed.(1) Outcome: 1 = fatal; 2 = not recovered/not resolved; 3 = recovered/resolved; 4 = recovered/resolved with sequelae; 5 = recovering/resolving; 6 = unknown.(2) Action taken with study drug: 1 = dose not changed; 2 = drug interrupt; 3 = drug withdrawn; 4 = not applicable; 5 = unknown.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.4.7-14　56週時までに試験眼に発現した重篤な有害事象一覧（GR40349試験及び GR40398試験）（続）

Study: GR40349(YOSEMITE)
Treatment: Faricimab 6 mg PTI

Center/Patient - Age/Sex/Race Adverse Event MedDRA Preferred Term	Treatment Naive Patients	Number of Study Drug Administered prior to event	Date of First Study Drug Administration	Study Day of Onset	AE Duration in Days	Serious	Most Extreme Intensity	Caused by Study Drug	Outcome (1)	Treatment for AE	Action Taken with Study Drug (2)
310914/[redacted] - 5[redacted]/F/Black or African American											
高眼圧症	Yes	4	16AUG2019	85	4	Yes	MODERATE	No	3	Yes	1
ぶどう膜炎性緑内障	Yes	4	16AUG2019	102		Yes	SEVERE	No	2	Yes	2
311571/[redacted] - 6[redacted]/M/White											
角膜ぶどう膜炎	Yes	6	20FEB2019	202	73	Yes	MODERATE	Yes	3	Yes	2
311605/[redacted] - 6[redacted]/M/White											
網膜裂孔	Yes	4	01MAY2019	113	1	Yes	MILD	No	3	No	1
311728/[redacted] - 6[redacted]/F/Black or African American											
ぶどう膜炎	Yes	9	20NOV2018	277		Yes	SEVERE	Yes	5	Yes	3
脈絡網膜炎	Yes	9	20NOV2018	283		Yes	MODERATE	Yes	5	No	4
311763/[redacted] - 6[redacted]/F/White											
糖尿病性網膜浮腫	Yes	8	30JAN2019	315	29	Yes	MODERATE	No	3	No	1
312995/[redacted] - 6[redacted]/F/Black or African American											
眼内炎	Yes	3	03JUL2019	78	146	Yes	MODERATE	No	3	Yes	3
313093/[redacted] - 4[redacted]/M/White											
眼内炎	Yes	5	04JUN2019	143	6	Yes	SEVERE	No	3	Yes	3
314730/[redacted]- 6[redacted]/M/Unknown											
ぶどう膜炎	Yes	7	04JUL2019	334	101	Yes	MODERATE	Yes	4	Yes	2
316928/[redacted] - 6[redacted]/F/Asian											
ぶどう膜炎	Yes	11	08MAY2019	331		Yes	SEVERE	Yes	5	Yes	3

* Study day derived from imputed onset date.
** Duration derived from imputed onset date and/or end date.
MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W). Investigator text for AEs encoded using MedDRA version 23.1. Only treatment emergent AEs are displayed.(1) Outcome: 1 = fatal; 2 = not recovered/not resolved; 3 = recovered/resolved; 4 = recovered/resolved with sequelae; 5 = recovering/resolving; 6 = unknown.(2) Action taken with study drug: 1 = dose not changed; 2 = drug interrupt; 3 = drug withdrawn; 4 = not applicable; 5 = unknown.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.4.7-14　56週時までに試験眼に発現した重篤な有害事象一覧（GR40349試験及び GR40398試験）（続）

Study: GR40349(YOSEMITE)
Treatment: Aflibercept 2 mg Q8W

Center/Patient - Age/Sex/Race Adverse Event MedDRA Preferred Term	Treatment Naive Patients	Number of Study Drug Administered prior to event	Date of First Study Drug Administration	Study Day of Onset	AE Duration in Days	Serious	Most Extreme Intensity	Caused by Study Drug	Out come (1)	Treatment for AE	Action Taken with Study Drug (2)
310321/[redacted] - 5[redacted]/M/American Indian or Alaska Native 網膜動脈閉塞	Yes	6	27MAY2019	211	79	Yes	SEVERE	No	4	Yes	3
316912/[redacted] - 6[redacted]/F/Asian 白内障	Yes	5	03JUN2019	115	35	Yes	MILD	No	3	No	2

* Study day derived from imputed onset date.
** Duration derived from imputed onset date and/or end date.
MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W). Investigator text for AEs encoded using MedDRA version 23.1. Only treatment emergent AEs are displayed.(1) Outcome: 1 = fatal; 2 = not recovered/not resolved; 3 = recovered/resolved; 4 = recovered/resolved with sequelae; 5 = recovering/resolving; 6 = unknown.(2) Action taken with study drug: 1 = dose not changed; 2 = drug interrupt; 3 = drug withdrawn; 4 = not applicable; 5 = unknown.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.4.7-14 56週時までに試験眼に発現した重篤な有害事象一覧（GR40349試験及び GR40398試験）（続）

Study: GR40398(RHINE)
Treatment: Faricimab 6 mg Q8W

Center/Patient - Age/Sex/Race Adverse Event MedDRA Preferred Term	Treatment Naive Patients	Number of Study Drug Administered prior to event	Date of First Study Drug Administration	Study Day of Onset	AE Duration in Days	Serious	Most Extreme Intensity	Caused by Study Drug	Outcome (1)	Treatment for AE	Action Taken with Study Drug (2)
315139/[redacted] - 6[redacted]/F/White											
インフルエンザ	Yes	7	27MAR2019	245	15	Yes	SEVERE	No	3	No	1
315195/[redacted] - 8[redacted]/F/White											
眼内炎	Yes	10	24APR2019	379		Yes	MODERATE	No	5	Yes	2
315200/[redacted] - 4[redacted]/M/White											
糖尿病性網膜浮腫	No	4	21NOV2018	85	22	Yes	MODERATE	No	3	No	1
糖尿病性網膜浮腫	No	6	21NOV2018	141	29	Yes	MODERATE	No	3	No	1
糖尿病性網膜浮腫	No	10	21NOV2018	371	23	Yes	MODERATE	No	3	No	1
315417/[redacted]- 5[redacted]/M/White											
硝子体出血	Yes	1	04APR2019	12		Yes	SEVERE	No	5	No	1
315438/[redacted] - 6[redacted]/F/White											
白内障	Yes	9	27MAR2019	325	151	Yes	SEVERE	No	3	No	1
315438/[redacted] - 6[redacted]/M/Unknown											
白内障	Yes	8	20MAY2019	255		Yes	MODERATE	No	2	No	1
ドライアイ	Yes	8	20MAY2019	255		Yes	SEVERE	No	2	Yes	1
316139/[redacted] - 5[redacted]/M/White											
眼内炎	Yes	7	16APR2019	199	1	Yes	SEVERE	No	3	Yes	1
316515/[redacted] - 6[redacted]/F/White											
一過性視力低下	Yes	2	19JUL2019	36	1	Yes	MODERATE	No	3	No	1
316521/[redacted] - 6[redacted]/F/White											
糖尿病性網膜浮腫	Yes	8	14AUG2019	293	24	Yes	MODERATE	No	3	No	1

* Study day derived from imputed onset date.
** Duration derived from imputed onset date and/or end date.
MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W). Investigator text for AEs encoded using MedDRA version 23.1. Only treatment emergent AEs are displayed.(1) Outcome: 1 = fatal; 2 = not recovered/not resolved; 3 = recovered/resolved; 4 = recovered/resolved with sequelae; 5 = recovering/resolving; 6 = unknown.(2) Action taken with study drug: 1 = dose not changed; 2 = drug interrupt; 3 = drug withdrawn; 4 = not applicable; 5 = unknown.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.4.7-14 56週時までに試験眼に発現した重篤な有害事象一覧（GR40349試験及び GR40398試験）（続）

Study: GR40398(RHINE)
Treatment: Faricimab 6 mg PTI

Center/Patient - Age/Sex/Race Adverse Event MedDRA Preferred Term	Treatment Naive Patients	Number of Study Drug Administered prior to event	Date of First Study Drug Administration	Study Day of Onset	AE Duration in Days	Serious	Most Extreme Intensity	Caused by Study Drug	Out come (1)	Treatment for AE	Action Taken with Study Drug (2)
313216/[redacted] - 7[redacted]/M/White 硝子体出血	Yes	2	03JUL2019	30	304	Yes	MODERATE	No	3	No	2
313947/[redacted] - 6[redacted]/M/White 網膜血管新生	Yes	5	30MAY2019	180	17	Yes	MODERATE	No	3	No	1
313951/[redacted] - 6[redacted]/F/White 糖尿病性網膜浮腫	Yes	4	15MAY2019	141	29	Yes	MODERATE	No	3	No	1
315316/[redacted] - 7[redacted]/M/Asian 網膜裂孔	Yes	6	06MAR2019	232		Yes	MILD	No	2	No	2
315337/[redacted] - 7[redacted]/M/White 一過性視力低下	Yes	6	10APR2019	142	29	Yes	MILD	No	3	No	1
315337/[redacted]- 6[redacted]/M/White 高眼圧症	Yes	9	07MAY2019	394	21	Yes	SEVERE	Yes	3	Yes	3
315372/[redacted] - 6[redacted]/F/White 眼圧上昇	Yes	10	07MAR2019	313	1	Yes	MILD	No	3	No	1
315426/[redacted] - 5[redacted]/F/White 網膜静脈閉塞	Yes	6	17SEP2019	227	48	Yes	SEVERE	No	3	No	1
315437/[redacted]- 6[redacted]/F/White 視力障害	Yes	6	06AUG2019	275	118	Yes	MODERATE	No	3	No	1
316474/[redacted] - 5[redacted]/M/White 嚢下白内障	Yes	11	16APR2019	309	91	Yes	MODERATE	No	3	No	1

* Study day derived from imputed onset date.
** Duration derived from imputed onset date and/or end date.
MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W). Investigator text for AEs encoded using MedDRA version 23.1. Only treatment emergent AEs are displayed.(1) Outcome: 1 = fatal; 2 = not recovered/not resolved; 3 = recovered/resolved; 4 = recovered/resolved with sequelae; 5 = recovering/resolving; 6 = unknown.(2) Action taken with study drug: 1 = dose not changed; 2 = drug interrupt; 3 = drug withdrawn; 4 = not applicable; 5 = unknown.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.4.7-14 56週時までに試験眼に発現した重篤な有害事象一覧（GR40349試験及び GR40398試験）（続）

Study: GR40398(RHINE)
Treatment: Aflibercept 2 mg Q8W

Center/Patient - Age/Sex/Race Adverse Event MedDRA Preferred Term	Treatment Naive Patients	Number of Study Drug Administered prior to event	Date of First Study Drug Administration	Study Day of Onset	AE Duration in Days	Serious	Most Extreme Intensity	Caused by Study Drug	Outcome (1)	Treatment for AE	Action Taken with Study Drug (2)
313958/[redacted] - 7[redacted]/M/Black or African American 硝子体出血	Yes	8	26FEB2019	393	87	Yes	MODERATE	No	3	No	1
313962/[redacted] - 4[redacted]/M/White 白内障	No	6	14JAN2019	267		Yes	MODERATE	No	2	No	1
315339/[redacted]- 6[redacted]/M/White 眼内炎	Yes	9	27AUG2019	340	15	Yes	SEVERE	No	4	Yes	3
315437/[redacted] - 7[redacted]/M/White 眼部化学熱傷	Yes	1	04APR2019	1	4	Yes	MODERATE	No	3	Yes	1
315698/[redacted] - 6[redacted]/M/Asian 黄斑線維症	Yes	5	12AUG2019	120	334	Yes	SEVERE	No	3	Yes	1
316378/[redacted] - 7[redacted]/M/White 一過性視力低下	Yes	4	21AUG2019	85	1	Yes	SEVERE	No	3	No	1

* Study day derived from imputed onset date.
** Duration derived from imputed onset date and/or end date.
MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W). Investigator text for AEs encoded using MedDRA version 23.1. Only treatment emergent AEs are displayed.(1) Outcome: 1 = fatal; 2 = not recovered/not resolved; 3 = recovered/resolved; 4 = recovered/resolved with sequelae; 5 = recovering/resolving; 6 = unknown.(2) Action taken with study drug: 1 = dose not changed; 2 = drug interrupt; 3 = drug withdrawn; 4 = not applicable; 5 = unknown.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

[5.3.5.3-nAMD-1 l_ae_SOCUL_SER_W56_SE_DME_HLS を改変]

表 2.7.4.7-15　48週時までに非試験眼に発現した重篤な有害事象（nAMD 統合，GR40306試験及び GR40844試験）

MedDRA Preferred Term	GR40306(TENAYA) (N=669)		GR40844(LUCERNE) (N=657)		Pooled(TENAYA and LUCERNE) (N=1326)	
	Faricimab 6 mg (N=333)	Aflibercept 2 mg (N=336)	Faricimab 6 mg (N=331)	Aflibercept 2 mg (N=326)	Faricimab 6 mg (N=664)	Aflibercept 2 mg (N=662)
Total number of patients with at least one adverse event	0	5 (1.5%)	7 (2.1%)	2 (0.6%)	7 (1.1%)	7 (1.1%)
Total number of events	0	5	7	2	7	7
新生血管加齢黄斑変性	0	2 (0.6%)	3 (0.9%)	0	3 (0.5%)	2 (0.3%)
裂孔原性網膜剥離	0	2 (0.6%)	0	0	0	2 (0.3%)
閉塞隅角緑内障	0	0	1 (0.3%)	0	1 (0.2%)	0
白内障	0	1 (0.3%)	0	0	0	1 (0.2%)
眼内炎	0	0	0	1 (0.3%)	0	1 (0.2%)
黄斑変性	0	0	1 (0.3%)	0	1 (0.2%)	0
網膜出血	0	0	0	1 (0.3%)	0	1 (0.2%)
網膜静脈閉塞	0	0	1 (0.3%)	0	1 (0.2%)	0
硝子体出血	0	0	1 (0.3%)	0	1 (0.2%)	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).
AE reported as neovascular age-related macular degeneration in the study eye indicates an accelerated worsening of the condition, as judged by the investigator.

[5.3.5.3-nAMD-1 PR11375_t_ae_pt_FOCUL_SER_W48_SE_nAMD_HLS を改変]

表 2.7.4.7-16 データカットオフ日までに非試験眼に発現した重篤な有害事象（nAMD 統合）

	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
MedDRA Preferred Term	Onset after Week 48	Overall	Onset after Week 48	Overall
Total number of patients with at least one adverse event	3 (0.5%)	10 (1.5%)	4 (0.6%)	10 (1.5%)
Total number of events	3	10	4	11
新生血管加齢黄斑変性	0	3 (0.5%)	2 (0.3%)	4 (0.6%)
眼内炎	1 (0.2%)	1 (0.2%)	0	1 (0.2%)
裂孔原性網膜剥離	0	0	1 (0.2%)	2 (0.3%)
閉塞隅角緑内障	0	1 (0.2%)	0	0
白内障	0	0	0	1 (0.2%)
眼圧上昇	0	0	1 (0.2%)	1 (0.2%)
水晶体脱臼	1 (0.2%)	1 (0.2%)	0	0
黄斑変性	0	1 (0.2%)	0	0
網膜出血	0	0	0	1 (0.2%)
網膜静脈閉塞	0	1 (0.2%)	0	0
視力低下	1 (0.2%)	1 (0.2%)	0	0
硝子体出血	0	1 (0.2%)	0	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
AE reported as neovascular age-related macular degeneration in the study eye indicates an accelerated worsening of the condition, as judged by the investigator.

[5.3.5.3-nAMD-1 PR11375_t_ae_pt_cod_FOCUL_SER_SE_nAMD_HLS を改変]

表 2.7.4.7-17　56週時までに非試験眼に発現した重篤な有害事象（DME 統合，GR40349試験及び GR40398試験）

MedDRA Preferred Term	GR40349(YOSEMITE) (N=937) Faricimab 6 mg Q8W (N=313)	GR40349(YOSEMITE) (N=937) Faricimab 6 mg PTI (N=313)	GR40349(YOSEMITE) (N=937) Aflibercept 2 mg Q8W (N=311)	GR40398(RHINE) (N=950) Faricimab 6 mg Q8W (N=317)	GR40398(RHINE) (N=950) Faricimab 6 mg PTI (N=319)	GR40398(RHINE) (N=950) Aflibercept 2 mg Q8W (N=314)
Total number of patients with at least one adverse event	7 (2.2%)	7 (2.2%)	5 (1.6%)	6 (1.9%)	4 (1.3%)	3 (1.0%)
Total number of events	8	8	5	7	4	3
硝子体出血	2 (0.6%)	1 (0.3%)	1 (0.3%)	3 (0.9%)	0	0
糖尿病網膜症	2 (0.6%)	1 (0.3%)	1 (0.3%)	0	1 (0.3%)	0
糖尿病性網膜浮腫	0	0	0	3 (0.9%)	1 (0.3%)	0
視力低下	1 (0.3%)	0	0	0	1 (0.3%)	1 (0.3%)
外傷性白内障	1 (0.3%)	1 (0.3%)	0	0	0	0
角膜擦過傷	1 (0.3%)	0	0	0	0	1 (0.3%)
閉塞隅角緑内障	0	0	1 (0.3%)	0	0	0
白内障	0	1 (0.3%)	0	0	0	0
眼部化学熱傷	0	0	0	0	0	1 (0.3%)
眼内炎	0	1 (0.3%)	0	0	0	0
眼出血	0	0	0	0	1 (0.3%)	0
眼圧上昇	0	0	0	1 (0.3%)	0	0
黄斑線維症	0	0	1 (0.3%)	0	0	0
黄斑浮腫	0	1 (0.3%)	0	0	0	0
前房狭隅角	1 (0.3%)	0	0	0	0	0
網膜出血	0	1 (0.3%)	0	0	0	0
網膜血管新生	0	0	1 (0.3%)	0	0	0
ぶどう膜炎	0	1 (0.3%)	0	0	0	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.4.7-17　56週時までに非試験眼に発現した重篤な有害事象（DME 統合，GR40349試験及び GR40398試験）（続）

MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887) Faricimab 6 mg Q8W (N=630)	Faricimab 6 mg PTI (N=632)	Faricimab 6 mg All (N=1262)	Aflibercept 2 mg Q8W (N=625)
Total number of patients with at least one adverse event	13 (2.1%)	11 (1.7%)	24 (1.9%)	8 (1.3%)
Total number of events	15	12	27	8
硝子体出血	5 (0.8%)	1 (0.2%)	6 (0.5%)	1 (0.2%)
糖尿病網膜症	2 (0.3%)	2 (0.3%)	4 (0.3%)	1 (0.2%)
糖尿病性網膜浮腫	3 (0.5%)	1 (0.2%)	4 (0.3%)	0
視力低下	1 (0.2%)	1 (0.2%)	2 (0.2%)	1 (0.2%)
外傷性白内障	1 (0.2%)	1 (0.2%)	2 (0.2%)	0
角膜擦過傷	1 (0.2%)	0	1 (<0.1%)	1 (0.2%)
閉塞隅角緑内障	0	0	0	1 (0.2%)
白内障	0	1 (0.2%)	1 (<0.1%)	0
眼部化学熱傷	0	0	0	1 (0.2%)
眼内炎	0	1 (0.2%)	1 (<0.1%)	0
眼出血	0	1 (0.2%)	1 (<0.1%)	0
眼圧上昇	1 (0.2%)	0	1 (<0.1%)	0
黄斑線維症	0	0	0	1 (0.2%)
黄斑浮腫	0	1 (0.2%)	1 (<0.1%)	0
前房狭隅角	1 (0.2%)	0	1 (<0.1%)	0
網膜出血	0	1 (0.2%)	1 (<0.1%)	0
網膜血管新生	0	0	0	1 (0.2%)
ぶどう膜炎	0	1 (0.2%)	1 (<0.1%)	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

[5.3.5.3-nAMD-1 PR11375_t_ae_pt_FOCUL_SER_W56_SE_DME_HLS を改変]

表 2.7.4.7-18 データカットオフ日までに非試験眼に発現した重篤な有害事象（DME 統合）

Pooled(YOSEMITE and RHINE)
(N=1887)

MedDRA Preferred Term	Faricimab 6 mg Q8W (N=630) Onset after Week 56	Faricimab 6 mg Q8W (N=630) Overall	Faricimab 6 mg PTI (N=632) Onset after Week 56	Faricimab 6 mg PTI (N=632) Overall	Faricimab 6 mg All (N=1262) Onset after Week 56	Faricimab 6 mg All (N=1262) Overall	Aflibercept 2 mg Q8W (N=625) Onset after Week 56	Aflibercept 2 mg Q8W (N=625) Overall
Total number of patients with at least one adverse event	4 (0.6%)	16 (2.5%)	5 (0.8%)	14 (2.2%)	9 (0.7%)	30 (2.4%)	5 (0.8%)	13 (2.1%)
Total number of events	4	19	6	18	10	37	5	13
硝子体出血	1 (0.2%)	5 (0.8%)	1 (0.2%)	2 (0.3%)	2 (0.2%)	7 (0.6%)	0	1 (0.2%)
糖尿病性網膜浮腫	1 (0.2%)	4 (0.6%)	0	1 (0.2%)	1 (<0.1%)	5 (0.4%)	2 (0.3%)	2 (0.3%)
糖尿病網膜症	0	2 (0.3%)	1 (0.2%)	3 (0.5%)	1 (<0.1%)	5 (0.4%)	1 (0.2%)	2 (0.3%)
視力低下	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	1 (0.2%)
白内障	0	0	0	1 (0.2%)	0	1 (<0.1%)	1 (0.2%)	1 (0.2%)
外傷性白内障	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	0
角膜擦過傷	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	1 (0.2%)
緑内障	1 (0.2%)	1 (0.2%)	1 (0.2%)	1 (0.2%)	2 (0.2%)	2 (0.2%)	0	0
黄斑線維症	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	1 (0.2%)
網膜出血	0	0	1 (0.2%)	2 (0.3%)	1 (<0.1%)	2 (0.2%)	0	0
閉塞隅角緑内障	0	0	0	0	0	0	0	1 (0.2%)
嚢下白内障	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
眼部化学熱傷	0	0	0	0	0	0	0	1 (0.2%)
眼内炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
眼出血	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
眼圧上昇	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
黄斑浮腫	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
前房狭隅角	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
視神経乳頭浮腫	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
網膜血管新生	0	0	0	0	0	0	0	1 (0.2%)
ぶどう膜炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

[5.3.5.3-nAMD-1 PR11375_t_ae_pt_cod_FOCUL_SER_SE_DME_HLS を改変]

表 2.7.4.7-19　データカットオフ日までに眼に発現した治験薬の投与中止に至った有害事象（nAMD 統合）

MedDRA Preferred Term	Pooled(TENAYA and LUCERNE) (N=1326) Faricimab 6 mg (N=664) Onset after Week 48	Faricimab 6 mg (N=664) Overall	Aflibercept 2 mg (N=662) Onset after Week 48	Aflibercept 2 mg (N=662) Overall
Total number of patients with at least one adverse event	2 (0.3%)	8 (1.2%)	2 (0.3%)	3 (0.5%)
Total number of events	2	8	2	3
新生血管加齢黄斑変性	2 (0.3%)	3 (0.5%)	1 (0.2%)	1 (0.2%)
ぶどう膜炎	0	1 (0.2%)	0	1 (0.2%)
虹彩毛様体炎	0	1 (0.2%)	0	0
非感染性眼内炎	0	0	1 (0.2%)	1 (0.2%)
網膜色素上皮裂孔	0	1 (0.2%)	0	0
硝子体剥離	0	1 (0.2%)	0	0
硝子体炎	0	1 (0.2%)	0	0

MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
AE reported as neovascular age-related macular degeneration in the study eye indicates an accelerated worsening of the condition, as judged by the investigator.

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[5.3.5.3-nAMD-1 t_ae_pt_cod_SOCUL_SDSC_SE_nAMD_HLS を改変]

表 2.7.4.7-20　データカットオフ日までに眼に発現した治験中止に至った有害事象（nAMD 統合）

	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
MedDRA Preferred Term	Onset after Week 48	Overall	Onset after Week 48	Overall
Total number of patients with at least one adverse event	2 (0.3%)	2 (0.3%)	1 (0.2%)	1 (0.2%)
Total number of events	2	2	1	1
新生血管加齢黄斑変性	2 (0.3%)	2 (0.3%)	0	0
視力低下	0	0	1 (0.2%)	1 (0.2%)

MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
AE reported as neovascular age-related macular degeneration in the study eye indicates an accelerated worsening of the condition, as judged by the investigator.

[5.3.5.3-nAMD-1 t_ae_pt_cod_SOCUL_DSC_SE_nAMD_HLS を改変]

表 2.7.4.7-21 データカットオフ日までに眼に発現した治験薬の投与中止に至った有害事象（DME 統合）

Pooled(YOSEMITE and RHINE)
(N=1887)

MedDRA Preferred Term	Faricimab 6 mg Q8W (N=630) Onset after Week 56	Faricimab 6 mg Q8W (N=630) Overall	Faricimab 6 mg PTI (N=632) Onset after Week 56	Faricimab 6 mg PTI (N=632) Overall	Faricimab 6 mg All (N=1262) Onset after Week 56	Faricimab 6 mg All (N=1262) Overall	Aflibercept 2 mg Q8W (N=625) Onset after Week 56	Aflibercept 2 mg Q8W (N=625) Overall
Total number of patients with at least one adverse event	0	2 (0.3%)	1 (0.2%)	9 (1.4%)	1 (<0.1%)	11 (0.9%)	0	2 (0.3%)
Total number of events	0	3	1	9	1	12	0	2
眼内炎	0	0	0	2 (0.3%)	0	2 (0.2%)	0	1 (0.2%)
ぶどう膜炎	0	0	1 (0.2%)	3 (0.5%)	1 (<0.1%)	3 (0.2%)	0	0
化学物質アレルギー	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
糖尿病性眼病変	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
眼圧上昇	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
高眼圧症	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
網膜動脈閉塞	0	0	0	0	0	0	0	1 (0.2%)
裂孔原性網膜剥離	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
潰瘍性角膜炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
硝子体炎	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

[5.3.5.3-nAMD-1 t_ae_pt_cod_OCUL_SDSC_SE_DME_HLS を改変]

表 2.7.4.7-22　データカットオフ日までに眼に発現した治験中止に至った有害事象（DME 統合）

Pooled(YOSEMITE and RHINE)
(N=1887)

MedDRA Preferred Term	Faricimab 6 mg Q8W (N=630) Onset after Week 56	Faricimab 6 mg Q8W (N=630) Overall	Faricimab 6 mg PTI (N=632) Onset after Week 56	Faricimab 6 mg PTI (N=632) Overall	Faricimab 6 mg All (N=1262) Onset after Week 56	Faricimab 6 mg All (N=1262) Overall	Aflibercept 2 mg Q8W (N=625) Onset after Week 56	Aflibercept 2 mg Q8W (N=625) Overall
Total number of patients with at least one adverse event	0	2 (0.3%)	0	2 (0.3%)	0	4 (0.3%)	0	1 (0.2%)
Total number of events	0	3	0	2	0	5	0	1
化学物質アレルギー	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
眼内炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
眼圧上昇	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
網膜動脈閉塞	0	0	0	0	0	0	0	1 (0.2%)
裂孔原性網膜剥離	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
硝子体炎	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

[5.3.5.3-nAMD-1 t_ae_pt_cod_OCUL_DSC_SE_DME_HLS を改変]

表 2.7.4.7-23 データカットオフ日までに眼に発現した治験薬の休薬に至った有害事象（nAMD 統合）

Pooled(TENAYA and LUCERNE)
(N=1326)

MedDRA Preferred Term	Faricimab 6 mg (N=664) Onset after Week 48	Faricimab 6 mg (N=664) Overall	Aflibercept 2 mg (N=662) Onset after Week 48	Aflibercept 2 mg (N=662) Overall
Total number of patients with at least one adverse event	4 (0.6%)	15 (2.3%)	1 (0.2%)	9 (1.4%)
Total number of events	4	20	1	9
虹彩毛様体炎	0	3 (0.5%)	0	2 (0.3%)
眼瞼炎	1 (0.2%)	1 (0.2%)	0	2 (0.3%)
眼圧上昇	0	3 (0.5%)	0	0
硝子体炎	1 (0.2%)	2 (0.3%)	0	1 (0.2%)
麦粒腫	0	1 (0.2%)	0	1 (0.2%)
ウイルス性ぶどう膜炎	0	2 (0.3%)	0	0
白内障手術合併症	0	0	1 (0.2%)	1 (0.2%)
脈絡網膜炎	0	1 (0.2%)	0	0
結膜炎	0	0	0	1 (0.2%)
ウイルス性結膜炎	0	1 (0.2%)	0	0
虹彩炎	0	1 (0.2%)	0	0
新生血管加齢黄斑変性	0	0	0	1 (0.2%)
眼部単純ヘルペス	1 (0.2%)	1 (0.2%)	0	0
裂孔原性網膜剥離	1 (0.2%)	1 (0.2%)	0	0
ぶどう膜炎	0	1 (0.2%)	0	0

MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
AE reported as neovascular age-related macular degeneration in the study eye indicates an accelerated worsening of the condition, as judged by the investigator.

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[5.3.5.3-nAMD-1 t_ae_pt_cod_SOCUL_INT_SE_nAMD_HLS を改変]

表 2.7.4.7-24　データカットオフ日までに眼に発現した治験薬の休薬に至った有害事象（DME 統合）

Pooled(YOSEMITE and RHINE)
(N=1887)

MedDRA Preferred Term	Faricimab 6 mg Q8W (N=630) Onset after Week 56	Faricimab 6 mg Q8W (N=630) Overall	Faricimab 6 mg PTI (N=632) Onset after Week 56	Faricimab 6 mg PTI (N=632) Overall	Faricimab 6 mg All (N=1262) Onset after Week 56	Faricimab 6 mg All (N=1262) Overall	Aflibercept 2 mg Q8W (N=625) Onset after Week 56	Aflibercept 2 mg Q8W (N=625) Overall
Total number of patients with at least one adverse event	2 (0.3%)	20 (3.2%)	8 (1.3%)	29 (4.6%)	10 (0.8%)	49 (3.9%)	3 (0.5%)	13 (2.1%)
Total number of events	2	30	8	41	10	71	4	21
結膜炎	0	6 (1.0%)	1 (0.2%)	4 (0.6%)	1 (<0.1%)	10 (0.8%)	0	3 (0.5%)
白内障	1 (0.2%)	1 (0.2%)	2 (0.3%)	5 (0.8%)	3 (0.2%)	6 (0.5%)	1 (0.2%)	3 (0.5%)
眼瞼炎	0	3 (0.5%)	0	2 (0.3%)	0	5 (0.4%)	0	0
眼圧上昇	0	0	0	3 (0.5%)	0	3 (0.2%)	1 (0.2%)	2 (0.3%)
アデノウイルス結膜炎	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	1 (0.2%)
ぶどう膜炎	0	1 (0.2%)	0	2 (0.3%)	0	3 (0.2%)	0	0
霰粒腫	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	1 (0.2%)
緑内障	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	1 (0.2%)
虹彩毛様体炎	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	0
ウイルス性角膜炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	1 (0.2%)
網膜裂孔	0	0	1 (0.2%)	2 (0.3%)	1 (<0.1%)	2 (0.2%)	0	0
硝子体浮遊物	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	0
細菌性結膜炎	0	0	0	0	0	0	0	1 (0.2%)
角膜浮腫	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
後天性涙道狭窄	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
医療機器位置異常	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
複視	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
眼内炎	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-24 データカットオフ日までに眼に発現した治験薬の休薬に至った有害事象（DME 統合）（続）

Pooled(YOSEMITE and RHINE)
(N=1887)

MedDRA Preferred Term	Faricimab 6 mg Q8W (N=630) Onset after Week 56	Faricimab 6 mg Q8W (N=630) Overall	Faricimab 6 mg PTI (N=632) Onset after Week 56	Faricimab 6 mg PTI (N=632) Overall	Faricimab 6 mg All (N=1262) Onset after Week 56	Faricimab 6 mg All (N=1262) Overall	Aflibercept 2 mg Q8W (N=625) Onset after Week 56	Aflibercept 2 mg Q8W (N=625) Overall
麦粒腫	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
虹彩炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
角膜炎	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
細菌性角膜炎	0	0	0	0	0	0	0	1 (0.2%)
角膜ぶどう膜炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
黄斑嚢胞	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
高眼圧症	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
眼虚血症候群	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
処置後炎症	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
製品投与の欠落の問題	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
点状角膜炎	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
網膜動脈閉塞	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
ぶどう膜炎性緑内障	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
ウイルス性角膜ぶどう膜炎	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
硝子体出血	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
硝子体炎	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

[5.3.5.3-nAMD-1 t_ae_pt_cod_OCUL_INT_SE_DME_HLS を改変]

表 2.7.4.7-25　データカットオフ日までに試験眼に発現した眼内炎症（nAMD 統合）

Pooled(TENAYA and LUCERNE)
(N=1326)

MedDRA Preferred Term	Faricimab 6 mg (N=664) Onset after Week 48	Faricimab 6 mg (N=664) Overall	Aflibercept 2 mg (N=662) Onset after Week 48	Aflibercept 2 mg (N=662) Overall
Total number of patients with at least one adverse event	2 (0.3%)	15 (2.3%)	2 (0.3%)	10 (1.5%)
Total number of events	2	18	2	11
虹彩炎	1 (0.2%)	4 (0.6%)	0	2 (0.3%)
虹彩毛様体炎	0	3 (0.5%)	0	2 (0.3%)
硝子体炎	1 (0.2%)	4 (0.6%)	0	1 (0.2%)
ぶどう膜炎	0	2 (0.3%)	0	2 (0.3%)
処置後炎症	0	0	1 (0.2%)	2 (0.3%)
脈絡網膜炎	0	1 (0.2%)	0	0
角膜後面沈着物	0	1 (0.2%)	0	0
非感染性眼内炎	0	0	1 (0.2%)	1 (0.2%)

MedDRA = Medical Dictionary for Regulatory Activities.
Intraocular Inflammation events include Anterior Chamber inflammation, Chorioretinitis, Iridocyclitis, Iritis, Keratic precipitates, Keratouveitis, Non-infectious Endophthalmitis, Post procedural inflammation, Uveitis, Vitritis and Anterior chamber flare. Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

[5.3.5.3-nAMD-1 t_ae_pt_cod_SOCUL_IOI_SE_nAMD_HLS を改変]

表 2.7.4.7-26 データカットオフ日までに試験眼に発現した眼内炎症（DME 統合）

Pooled(YOSEMITE and RHINE)
(N=1887)

MedDRA Preferred Term	Faricimab 6 mg Q8W (N=630) Onset after Week 56	Faricimab 6 mg Q8W (N=630) Overall	Faricimab 6 mg PTI (N=632) Onset after Week 56	Faricimab 6 mg PTI (N=632) Overall	Faricimab 6 mg All (N=1262) Onset after Week 56	Faricimab 6 mg All (N=1262) Overall	Aflibercept 2 mg Q8W (N=625) Onset after Week 56	Aflibercept 2 mg Q8W (N=625) Overall
Total number of patients with at least one adverse event	1 (0.2%)	8 (1.3%)	3 (0.5%)	11 (1.7%)	4 (0.3%)	19 (1.5%)	3 (0.5%)	7 (1.1%)
Total number of events	1	11	3	18	4	29	4	10
虹彩炎	1 (0.2%)	2 (0.3%)	1 (0.2%)	4 (0.6%)	2 (0.2%)	6 (0.5%)	0	2 (0.3%)
ぶどう膜炎	0	2 (0.3%)	2 (0.3%)	5 (0.8%)	2 (0.2%)	7 (0.6%)	0	0
硝子体炎	0	3 (0.5%)	0	1 (0.2%)	0	4 (0.3%)	0	2 (0.3%)
虹彩毛様体炎	0	2 (0.3%)	0	2 (0.3%)	0	4 (0.3%)	1 (0.2%)	1 (0.2%)
処置後炎症	0	0	0	0	0	0	2 (0.3%)	2 (0.3%)
前房の炎症	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
脈絡網膜炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
角膜後面沈着物	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
角膜ぶどう膜炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).Intraocular Inflammation events include Anterior Chamber inflammation, Chorioretinitis, Iridocyclitis, Iritis, Keratic precipitates, Keratouveitis, Non-infectious Endophthalmitis, Post procedural inflammation, Uveitis, and Vitritis. Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately. Includes events with onset up to Day 405 (last day of Week 56 analysis visit window).

[5.3.5.3-nAMD-1 t_ae_pt_cod_SOCUL_IOI_SE_DME_HLS を改変]

表 2.7.4.7-27　データカットオフ日までに眼以外に発現した有害事象（nAMD 統合）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
	Onset after Week 48	Overall	Onset after Week 48	Overall
Total number of patients with at least one adverse event	106 (16.0%)	377 (56.8%)	104 (15.7%)	391 (59.1%)
Overall total number of events	165	1079	171	1095
感染症および寄生虫症				
Total number of patients with at least one adverse event	30 (4.5%)	183 (27.6%)	24 (3.6%)	180 (27.2%)
Total number of events	31	275	25	247
上咽頭炎	2 (0.3%)	43 (6.5%)	1 (0.2%)	45 (6.8%)
尿路感染	10 (1.5%)	34 (5.1%)	8 (1.2%)	28 (4.2%)
上気道感染	1 (0.2%)	15 (2.3%)	0	17 (2.6%)
副鼻腔炎	3 (0.5%)	16 (2.4%)	2 (0.3%)	13 (2.0%)
気管支炎	1 (0.2%)	18 (2.7%)	0	9 (1.4%)
インフルエンザ	0	11 (1.7%)	0	9 (1.4%)
肺炎	0	6 (0.9%)	1 (0.2%)	9 (1.4%)
ＣＯＶＩＤ－１９	2 (0.3%)	7 (1.1%)	0	4 (0.6%)
下気道感染	1 (0.2%)	5 (0.8%)	2 (0.3%)	6 (0.9%)
膀胱炎	0	5 (0.8%)	0	5 (0.8%)
ウイルス性胃腸炎	1 (0.2%)	5 (0.8%)	1 (0.2%)	5 (0.8%)
帯状疱疹	0	6 (0.9%)	1 (0.2%)	4 (0.6%)
歯膿瘍	0	3 (0.5%)	1 (0.2%)	7 (1.1%)
口腔ヘルペス	2 (0.3%)	6 (0.9%)	0	3 (0.5%)
創傷感染	0	2 (0.3%)	1 (0.2%)	5 (0.8%)
蜂巣炎	1 (0.2%)	4 (0.6%)	0	2 (0.3%)
耳感染	0	3 (0.5%)	1 (0.2%)	2 (0.3%)
胃腸炎	0	4 (0.6%)	0	1 (0.2%)
気道感染	1 (0.2%)	3 (0.5%)	1 (0.2%)	2 (0.3%)
鼻炎	0	1 (0.2%)	0	4 (0.6%)
歯肉炎	0	2 (0.3%)	1 (0.2%)	2 (0.3%)
限局性感染	0	3 (0.5%)	0	1 (0.2%)
爪真菌症	0	3 (0.5%)	0	1 (0.2%)
咽頭炎	0	4 (0.6%)	0	0
敗血症	0	0	0	4 (0.6%)

MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
AE reported as neovascular age-related macular degeneration in the study eye indicates an accelerated worsening of the condition, as judged by the investigator.

表 2.7.4.7-27 データカットオフ日までに眼以外に発現した有害事象（nAMD 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
	Onset after Week 48	Overall	Onset after Week 48	Overall
歯感染	1 (0.2%)	2 (0.3%)	0	2 (0.3%)
憩室炎	0	0	0	3 (0.5%)
外耳炎	0	0	0	3 (0.5%)
細菌性肺炎	0	1 (0.2%)	1 (0.2%)	2 (0.3%)
ウイルス性気道感染	0	1 (0.2%)	0	2 (0.3%)
急性副鼻腔炎	0	1 (0.2%)	0	1 (0.2%)
丹毒	1 (0.2%)	2 (0.3%)	0	0
真菌感染	1 (0.2%)	2 (0.3%)	0	0
皮膚真菌感染	0	1 (0.2%)	0	1 (0.2%)
口腔カンジダ症	0	0	0	2 (0.3%)
骨髄炎	0	1 (0.2%)	0	1 (0.2%)
中耳炎	0	2 (0.3%)	0	0
歯周炎	0	2 (0.3%)	0	0
処置後感染	0	0	1 (0.2%)	2 (0.3%)
歯髄炎	0	1 (0.2%)	0	1 (0.2%)
ライノウイルス感染	0	2 (0.3%)	0	0
敗血症性ショック	0	2 (0.3%)	0	0
扁桃炎	0	1 (0.2%)	0	1 (0.2%)
ウイルス性上気道感染	0	0	0	2 (0.3%)
腹部膿瘍	0	0	0	1 (0.2%)
腹部感染	0	1 (0.2%)	0	0
四肢膿瘍	0	0	0	1 (0.2%)
細菌性関節炎	0	1 (0.2%)	0	0
無症候性ＣＯＶＩＤ－１９	0	1 (0.2%)	0	0
胆道性敗血症	0	1 (0.2%)	0	0
感染性水疱	0	1 (0.2%)	0	0
体部白癬	0	1 (0.2%)	0	0
ＣＯＶＩＤ－１９肺炎	0	0	1 (0.2%)	1 (0.2%)
慢性副鼻腔炎	0	0	0	1 (0.2%)
クロストリジウム・ディフィシレ感染	0	0	0	1 (0.2%)
医療機器関連感染	0	1 (0.2%)	0	0
大腸菌性菌血症	1 (0.2%)	1 (0.2%)	0	0

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表 2.7.4.7-27 データカットオフ日までに眼以外に発現した有害事象（nAMD 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
	Onset after Week 48	Overall	Onset after Week 48	Overall
せつ	0	0	0	1 (0.2%)
消化管感染	0	1 (0.2%)	0	0
単純ヘルペス	0	0	1 (0.2%)	1 (0.2%)
ヘルペスウイルス感染	0	1 (0.2%)	0	0
感染性皮膚嚢腫	0	1 (0.2%)	0	0
感染性胸水	0	0	0	1 (0.2%)
感染による慢性閉塞性気道疾患の増悪	0	0	0	1 (0.2%)
椎間板炎	0	1 (0.2%)	0	0
腎感染	0	1 (0.2%)	0	0
迷路炎	0	1 (0.2%)	0	0
肺膿瘍	0	1 (0.2%)	0	0
敗血症性心筋炎	0	1 (0.2%)	0	0
壊死性筋膜炎	0	0	0	1 (0.2%)
食道カンジダ症	0	1 (0.2%)	0	0
急性中耳炎	0	1 (0.2%)	0	0
耳下腺炎	0	0	0	1 (0.2%)
骨盤内炎症性疾患	0	0	0	1 (0.2%)
眼窩周囲蜂巣炎	0	0	0	1 (0.2%)
腎盂炎	1 (0.2%)	1 (0.2%)	0	0
急性腎盂腎炎	0	0	0	1 (0.2%)
皮膚感染	0	0	0	1 (0.2%)
全身性細菌感染	0	0	0	1 (0.2%)
膣感染	0	1 (0.2%)	0	0
筋骨格系および結合組織障害				
Total number of patients with at least one adverse event	18 (2.7%)	88 (13.3%)	16 (2.4%)	81 (12.2%)
Total number of events	19	108	19	101
関節痛	6 (0.9%)	25 (3.8%)	4 (0.6%)	15 (2.3%)
背部痛	4 (0.6%)	16 (2.4%)	4 (0.6%)	15 (2.3%)
変形性関節症	0	7 (1.1%)	1 (0.2%)	8 (1.2%)
関節炎	0	7 (1.1%)	1 (0.2%)	6 (0.9%)
四肢痛	0	2 (0.3%)	3 (0.5%)	9 (1.4%)

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表 2.7.4.7-27 データカットオフ日までに眼以外に発現した有害事象（nAMD 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
	Onset after Week 48	Overall	Onset after Week 48	Overall
筋痙縮	1 (0.2%)	4 (0.6%)	1 (0.2%)	5 (0.8%)
頚部痛	0	7 (1.1%)	0	1 (0.2%)
椎間板突出	1 (0.2%)	2 (0.3%)	2 (0.3%)	4 (0.6%)
肩回旋筋腱板症候群	0	3 (0.5%)	0	3 (0.5%)
脊柱管狭窄症	2 (0.3%)	2 (0.3%)	0	3 (0.5%)
腱炎	1 (0.2%)	1 (0.2%)	0	4 (0.6%)
関節腫脹	0	2 (0.3%)	0	2 (0.3%)
骨粗鬆症	0	2 (0.3%)	0	2 (0.3%)
筋肉痛	1 (0.2%)	2 (0.3%)	0	1 (0.2%)
関節周囲炎	0	3 (0.5%)	0	0
滑液包炎	0	1 (0.2%)	1 (0.2%)	1 (0.2%)
関節滲出液	0	2 (0.3%)	0	0
筋骨格系胸痛	0	1 (0.2%)	0	1 (0.2%)
筋骨格痛	0	1 (0.2%)	0	1 (0.2%)
筋骨格硬直	0	0	0	2 (0.3%)
骨減少症	0	0	0	2 (0.3%)
関節リウマチ	1 (0.2%)	1 (0.2%)	0	1 (0.2%)
変形性脊椎症	0	2 (0.3%)	0	0
外骨腫	1 (0.2%)	1 (0.2%)	0	0
側腹部痛	0	1 (0.2%)	0	0
骨折による偽関節	0	1 (0.2%)	0	0
椎間板変性症	0	0	0	1 (0.2%)
脊柱後弯症	0	0	0	1 (0.2%)
四肢腫瘤	0	1 (0.2%)	0	0
腰部脊柱管狭窄症	0	1 (0.2%)	0	0
筋拘縮	0	0	0	1 (0.2%)
筋緊張	0	1 (0.2%)	0	0
筋力低下	0	0	0	1 (0.2%)
筋骨格障害	0	0	0	1 (0.2%)
骨壊死	0	1 (0.2%)	0	0
閉経後骨粗鬆症	0	0	0	1 (0.2%)
横紋筋融解症	0	0	0	1 (0.2%)

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表 2.7.4.7-27 データカットオフ日までに眼以外に発現した有害事象（nAMD 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
	Onset after Week 48	Overall	Onset after Week 48	Overall
リウマチ性障害	0	0	0	1 (0.2%)
側弯症	0	0	1 (0.2%)	1 (0.2%)
脊椎痛	0	1 (0.2%)	0	0
脊椎すべり症	0	0	0	1 (0.2%)
弾発指	0	0	1 (0.2%)	1 (0.2%)
椎間孔狭窄	0	0	0	1 (0.2%)
傷害、中毒および処置合併症				
Total number of patients with at least one adverse event	19 (2.9%)	62 (9.3%)	19 (2.9%)	71 (10.7%)
Total number of events	27	99	28	107
転倒	11 (1.7%)	22 (3.3%)	11 (1.7%)	28 (4.2%)
挫傷	1 (0.2%)	7 (1.1%)	3 (0.5%)	10 (1.5%)
皮膚裂傷	1 (0.2%)	3 (0.5%)	1 (0.2%)	5 (0.8%)
靱帯捻挫	0	2 (0.3%)	1 (0.2%)	5 (0.8%)
四肢損傷	2 (0.3%)	4 (0.6%)	0	2 (0.3%)
肋骨骨折	0	2 (0.3%)	0	4 (0.6%)
足骨折	0	3 (0.5%)	0	1 (0.2%)
股関節部骨折	0	2 (0.3%)	1 (0.2%)	2 (0.3%)
処置による疼痛	0	1 (0.2%)	0	3 (0.5%)
脊椎圧迫骨折	1 (0.2%)	2 (0.3%)	0	2 (0.3%)
歯牙破折	0	1 (0.2%)	1 (0.2%)	3 (0.5%)
動物咬傷	1 (0.2%)	3 (0.5%)	0	0
節足動物刺傷	2 (0.3%)	3 (0.5%)	0	0
手骨折	0	1 (0.2%)	1 (0.2%)	2 (0.3%)
腰椎骨折	0	0	1 (0.2%)	3 (0.5%)
肉離れ	0	2 (0.3%)	0	1 (0.2%)
交通事故	0	1 (0.2%)	0	2 (0.3%)
漿液腫	0	2 (0.3%)	0	1 (0.2%)
皮膚擦過傷	0	0	1 (0.2%)	3 (0.5%)
上肢骨折	0	2 (0.3%)	0	1 (0.2%)
手首関節骨折	1 (0.2%)	1 (0.2%)	0	2 (0.3%)
節足動物咬傷	0	2 (0.3%)	0	0

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表 2.7.4.7-27 データカットオフ日までに眼以外に発現した有害事象（nAMD 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
	Onset after Week 48	Overall	Onset after Week 48	Overall
骨挫傷	1 (0.2%)	1 (0.2%)	1 (0.2%)	1 (0.2%)
胸部損傷	0	0	1 (0.2%)	2 (0.3%)
脳振盪	1 (0.2%)	2 (0.3%)	0	0
顔面骨骨折	0	1 (0.2%)	0	1 (0.2%)
大腿骨骨折	0	0	0	2 (0.3%)
上腕骨骨折	0	0	0	2 (0.3%)
関節脱臼	0	0	0	2 (0.3%)
骨盤骨折	0	0	1 (0.2%)	2 (0.3%)
皮膚損傷	0	1 (0.2%)	1 (0.2%)	1 (0.2%)
寛骨臼骨折	0	1 (0.2%)	0	0
術後貧血	0	0	0	1 (0.2%)
石綿肺症	0	0	0	1 (0.2%)
粉砕骨折	0	0	1 (0.2%)	1 (0.2%)
圧迫骨折	0	0	0	1 (0.2%)
頭蓋脳損傷	1 (0.2%)	1 (0.2%)	0	0
歯科修復不成功	0	1 (0.2%)	0	0
眼挫傷	0	1 (0.2%)	0	0
顔面損傷	0	1 (0.2%)	0	0
大腿骨頚部骨折	0	0	0	1 (0.2%)
頭部損傷	0	1 (0.2%)	0	0
損傷	0	1 (0.2%)	0	0
半月板損傷	0	1 (0.2%)	0	0
粘膜擦過傷	0	1 (0.2%)	0	0
筋損傷	1 (0.2%)	1 (0.2%)	0	0
神経損傷	0	1 (0.2%)	0	0
人工関節周囲骨折	0	1 (0.2%)	0	0
外傷後頚部症候群	0	1 (0.2%)	0	0
放射線肺臓炎	0	1 (0.2%)	0	0
ストレス骨折	0	0	0	1 (0.2%)
各種物質毒性	0	0	0	1 (0.2%)
外傷性血腫	0	0	0	1 (0.2%)

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表 2.7.4.7-27 データカットオフ日までに眼以外に発現した有害事象（nAMD 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
	Onset after Week 48	Overall	Onset after Week 48	Overall
胃腸障害				
Total number of patients with at least one adverse event	5 (0.8%)	51 (7.7%)	13 (2.0%)	69 (10.4%)
Total number of events	5	62	18	107
下痢	0	6 (0.9%)	0	11 (1.7%)
便秘	1 (0.2%)	8 (1.2%)	1 (0.2%)	8 (1.2%)
悪心	0	2 (0.3%)	1 (0.2%)	8 (1.2%)
齲歯	0	4 (0.6%)	0	5 (0.8%)
上腹部痛	0	3 (0.5%)	0	5 (0.8%)
歯痛	0	3 (0.5%)	1 (0.2%)	5 (0.8%)
鼠径ヘルニア	0	1 (0.2%)	1 (0.2%)	5 (0.8%)
胃炎	0	1 (0.2%)	1 (0.2%)	4 (0.6%)
腹部不快感	0	2 (0.3%)	0	2 (0.3%)
腹痛	0	3 (0.5%)	0	1 (0.2%)
胃腸出血	0	0	1 (0.2%)	4 (0.6%)
憩室	0	1 (0.2%)	0	2 (0.3%)
腸憩室	0	0	1 (0.2%)	3 (0.5%)
胃食道逆流性疾患	0	1 (0.2%)	1 (0.2%)	2 (0.3%)
痔核	0	1 (0.2%)	0	2 (0.3%)
裂孔ヘルニア	0	3 (0.5%)	0	0
大腸ポリープ	0	1 (0.2%)	0	2 (0.3%)
上部消化管出血	0	1 (0.2%)	0	2 (0.3%)
嘔吐	0	0	1 (0.2%)	3 (0.5%)
腹部ヘルニア	0	2 (0.3%)	0	0
慢性胃炎	0	0	1 (0.2%)	2 (0.3%)
鼓腸	1 (0.2%)	1 (0.2%)	0	1 (0.2%)
食中毒	0	2 (0.3%)	0	0
イレウス	0	0	1 (0.2%)	2 (0.3%)
過敏性腸症候群	1 (0.2%)	1 (0.2%)	1 (0.2%)	1 (0.2%)
腹部膨満	0	1 (0.2%)	0	0
下腹部痛	0	0	0	1 (0.2%)
肛門湿疹	0	0	0	1 (0.2%)
腹水	0	0	0	1 (0.2%)

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MedDRA System Organ Class MedDRA Preferred Term	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
	Onset after Week 48	Overall	Onset after Week 48	Overall
バレット食道	0	0	1 (0.2%)	1 (0.2%)
腹腔動脈圧迫症候群	0	1 (0.2%)	0	0
消化不良	0	1 (0.2%)	0	0
糞塊	0	0	0	1 (0.2%)
大腿ヘルニア	0	0	1 (0.2%)	1 (0.2%)
胃粘膜病変	0	0	0	1 (0.2%)
胃腸管血管異形成	0	0	0	1 (0.2%)
胃腸の炎症	0	1 (0.2%)	0	0
消化器痛	0	0	0	1 (0.2%)
胃腸潰瘍	0	1 (0.2%)	0	0
吐血	0	0	1 (0.2%)	1 (0.2%)
血便排泄	1 (0.2%)	1 (0.2%)	0	0
痔出血	0	0	0	1 (0.2%)
嵌頓臍径ヘルニア	0	0	0	1 (0.2%)
腸管虚血	0	1 (0.2%)	0	0
腸閉塞	0	0	0	1 (0.2%)
大腸閉塞	0	0	0	1 (0.2%)
下部消化管出血	0	1 (0.2%)	0	0
機械的イレウス	0	1 (0.2%)	0	0
メレナ	0	0	1 (0.2%)	1 (0.2%)
口腔嚢胞	0	0	1 (0.2%)	1 (0.2%)
口腔内潰瘍形成	0	0	0	1 (0.2%)
非感染性歯肉炎	0	0	0	1 (0.2%)
口腔粘膜血腫	0	1 (0.2%)	0	0
口腔内痛	0	0	0	1 (0.2%)
消化性潰瘍	0	0	1 (0.2%)	1 (0.2%)
口内炎	0	1 (0.2%)	0	0
臍ヘルニア	1 (0.2%)	1 (0.2%)	0	0
食道静脈瘤	0	0	0	1 (0.2%)
神経系障害				
Total number of patients with at least one adverse event	8 (1.2%)	58 (8.7%)	14 (2.1%)	60 (9.1%)

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表 2.7.4.7-27 データカットオフ日までに眼以外に発現した有害事象（nAMD 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
	Onset after Week 48	Overall	Onset after Week 48	Overall
Total number of events	8	73	17	84
頭痛	0	15 (2.3%)	4 (0.6%)	14 (2.1%)
浮動性めまい	2 (0.3%)	13 (2.0%)	3 (0.5%)	10 (1.5%)
坐骨神経痛	1 (0.2%)	4 (0.6%)	0	7 (1.1%)
失神	0	2 (0.3%)	4 (0.6%)	9 (1.4%)
脳血管発作	0	4 (0.6%)	0	4 (0.6%)
一過性脳虚血発作	0	3 (0.5%)	1 (0.2%)	2 (0.3%)
片頭痛	0	0	0	3 (0.5%)
末梢性ニューロパチー	0	2 (0.3%)	0	1 (0.2%)
手根管症候群	0	1 (0.2%)	0	1 (0.2%)
大脳萎縮	0	1 (0.2%)	0	1 (0.2%)
頚髄神経根障害	0	1 (0.2%)	0	1 (0.2%)
認知障害	0	2 (0.3%)	0	0
脳症	0	1 (0.2%)	0	1 (0.2%)
虚血性脳卒中	0	0	0	2 (0.3%)
腰髄神経根障害	0	1 (0.2%)	0	1 (0.2%)
パーキンソン病	0	1 (0.2%)	0	1 (0.2%)
失神寸前の状態	0	2 (0.3%)	0	0
痙攣発作	1 (0.2%)	1 (0.2%)	0	1 (0.2%)
三叉神経痛	0	2 (0.3%)	0	0
健忘	0	1 (0.2%)	0	0
失語症	0	1 (0.2%)	0	0
平衡障害	0	0	0	1 (0.2%)
脳浮腫	0	1 (0.2%)	0	0
頚動脈狭窄	0	0	0	1 (0.2%)
脳動脈硬化症	0	0	1 (0.2%)	1 (0.2%)
脳出血	0	0	0	1 (0.2%)
脳梗塞	0	0	0	1 (0.2%)
アルツハイマー型認知症	0	0	1 (0.2%)	1 (0.2%)
糖尿病性ニューロパチー	1 (0.2%)	1 (0.2%)	0	0
頭蓋内出血	0	1 (0.2%)	0	0
感覚鈍麻	0	1 (0.2%)	0	0

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AE reported as neovascular age-related macular degeneration in the study eye indicates an accelerated worsening of the condition, as judged by the investigator.

表 2.7.4.7-27 データカットオフ日までに眼以外に発現した有害事象（nAMD 統合）（続）

	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
MedDRA System Organ Class MedDRA Preferred Term	Onset after Week 48	Overall	Onset after Week 48	Overall
嗅覚減退	0	0	0	1 (0.2%)
ＩＣＵ関連筋力低下	0	1 (0.2%)	0	0
頭蓋内動脈瘤	0	0	1 (0.2%)	1 (0.2%)
ラクナ脳卒中	0	0	0	1 (0.2%)
記憶障害	1 (0.2%)	1 (0.2%)	0	0
神経圧迫	1 (0.2%)	1 (0.2%)	0	0
神経痛	1 (0.2%)	1 (0.2%)	0	0
周期性四肢運動障害	0	0	0	1 (0.2%)
外傷後頭痛	0	1 (0.2%)	0	0
発作後麻痺	0	1 (0.2%)	0	0
四肢麻痺	0	0	1 (0.2%)	1 (0.2%)
副鼻腔炎に伴う頭痛	0	0	0	1 (0.2%)
傾眠	0	0	0	1 (0.2%)
くも膜下出血	0	1 (0.2%)	0	0
血栓性脳梗塞	0	1 (0.2%)	0	0
血管性認知症	0	0	1 (0.2%)	1 (0.2%)
呼吸器、胸郭および縦隔障害				
Total number of patients with at least one adverse event	12 (1.8%)	51 (7.7%)	4 (0.6%)	49 (7.4%)
Total number of events	13	60	5	60
咳嗽	3 (0.5%)	15 (2.3%)	1 (0.2%)	8 (1.2%)
慢性閉塞性肺疾患	4 (0.6%)	9 (1.4%)	0	3 (0.5%)
喘息	1 (0.2%)	6 (0.9%)	0	4 (0.6%)
呼吸困難	0	1 (0.2%)	1 (0.2%)	9 (1.4%)
口腔咽頭痛	0	3 (0.5%)	0	4 (0.6%)
鼻漏	0	4 (0.6%)	0	3 (0.5%)
肺塞栓症	0	1 (0.2%)	1 (0.2%)	4 (0.6%)
アレルギー性鼻炎	1 (0.2%)	2 (0.3%)	0	1 (0.2%)
無気肺	0	0	0	2 (0.3%)
下気道うっ血	0	1 (0.2%)	0	1 (0.2%)
鼻閉	0	1 (0.2%)	0	1 (0.2%)
誤嚥性肺炎	0	1 (0.2%)	0	1 (0.2%)

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表 2.7.4.7-27 データカットオフ日までに眼以外に発現した有害事象（nAMD 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
	Onset after Week 48	Overall	Onset after Week 48	Overall
呼吸不全	1 (0.2%)	1 (0.2%)	0	1 (0.2%)
急性呼吸不全	1 (0.2%)	1 (0.2%)	0	0
気管支拡張症	0	0	0	1 (0.2%)
慢性気管支炎	0	0	0	1 (0.2%)
咳喘息	0	0	0	1 (0.2%)
労作性呼吸困難	0	1 (0.2%)	0	0
鼻出血	0	1 (0.2%)	0	0
低酸素症	0	0	0	1 (0.2%)
間質性肺疾患	0	0	0	1 (0.2%)
アレルギー性喉頭炎	0	1 (0.2%)	0	0
肺浸潤	0	0	1 (0.2%)	1 (0.2%)
肺穿孔	0	0	0	1 (0.2%)
閉塞性気道障害	0	1 (0.2%)	0	0
副鼻腔分泌過多	0	0	0	1 (0.2%)
胸水	1 (0.2%)	1 (0.2%)	0	0
肺臓炎	0	0	0	1 (0.2%)
肺動脈血栓症	0	0	1 (0.2%)	1 (0.2%)
肺肉芽腫	0	1 (0.2%)	0	0
肺腫瘤	0	1 (0.2%)	0	0
肺水腫	1 (0.2%)	1 (0.2%)	0	0
副鼻腔障害	0	1 (0.2%)	0	0
副鼻腔ポリープ	0	0	0	1 (0.2%)
上気道の炎症	0	0	0	1 (0.2%)
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）				
Total number of patients with at least one adverse event	6 (0.9%)	39 (5.9%)	5 (0.8%)	41 (6.2%)
Total number of events	10	56	5	45
基底細胞癌	3 (0.5%)	12 (1.8%)	0	5 (0.8%)
扁平上皮癌	1 (0.2%)	6 (0.9%)	0	3 (0.5%)
肺の悪性新生物	2 (0.3%)	5 (0.8%)	0	1 (0.2%)
皮膚有棘細胞癌	1 (0.2%)	2 (0.3%)	1 (0.2%)	2 (0.3%)
前立腺癌	0	1 (0.2%)	1 (0.2%)	2 (0.3%)

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表 2.7.4.7-27 データカットオフ日までに眼以外に発現した有害事象（nAMD 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
	Onset after Week 48	Overall	Onset after Week 48	Overall
良性新生物	0	2 (0.3%)	0	0
遠隔転移を伴う肺癌	0	1 (0.2%)	0	1 (0.2%)
メラノサイト性母斑	0	1 (0.2%)	0	1 (0.2%)
髄膜腫	0	0	0	2 (0.3%)
新生物	0	1 (0.2%)	0	1 (0.2%)
膵癌	0	1 (0.2%)	0	1 (0.2%)
皮膚癌	0	2 (0.3%)	0	0
皮膚乳頭腫	0	0	0	2 (0.3%)
アクロコルドン	0	0	0	1 (0.2%)
腺癌	0	1 (0.2%)	0	0
肛門癌	0	0	0	1 (0.2%)
食道の良性新生物	0	1 (0.2%)	0	0
胆管癌	0	0	0	1 (0.2%)
胆道新生物	0	0	0	1 (0.2%)
膀胱新生物	0	0	0	1 (0.2%)
乳癌	0	0	0	1 (0.2%)
乳癌第４期	0	1 (0.2%)	0	0
真珠腫	0	0	0	1 (0.2%)
大腸腺腫	0	0	0	1 (0.2%)
皮膚Ｔ細胞性リンパ腫	0	1 (0.2%)	0	0
本態性血小板血症	0	1 (0.2%)	0	0
節外性辺縁帯Ｂ細胞リンパ腫（ＭＡＬＴ型）	0	0	0	1 (0.2%)
線維性組織球腫	0	0	1 (0.2%)	1 (0.2%)
胃癌	0	1 (0.2%)	0	0
消化器癌	0	0	0	1 (0.2%)
多形性神経膠芽細胞腫	0	0	0	1 (0.2%)
皮膚血管腫	0	0	0	1 (0.2%)
良性毛包腫瘍	0	0	0	1 (0.2%)
浸潤性乳管癌	0	0	0	1 (0.2%)
良性若年性黒色腫	0	1 (0.2%)	0	0
リンパ管腫	0	1 (0.2%)	0	0
悪性黒色腫	0	1 (0.2%)	0	0

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表 2.7.4.7-27 データカットオフ日までに眼以外に発現した有害事象（nAMD 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
	Onset after Week 48	Overall	Onset after Week 48	Overall
肝転移	0	0	0	1 (0.2%)
骨髄異形成症候群	0	0	0	1 (0.2%)
遠隔転移を伴う神経内分泌癌	0	0	0	1 (0.2%)
遠隔転移を伴う卵巣癌	0	1 (0.2%)	0	0
形質細胞性骨髄腫	1 (0.2%)	1 (0.2%)	0	0
直腸癌	0	1 (0.2%)	0	0
腎新生物	0	0	1 (0.2%)	1 (0.2%)
肉腫様癌	0	0	0	1 (0.2%)
肺肉腫様癌	0	0	0	1 (0.2%)
脂漏性角化症	0	1 (0.2%)	0	0
肺扁平上皮癌	0	1 (0.2%)	0	0
舌の悪性新生物、病期不明	0	0	0	1 (0.2%)
腫瘍性閉塞	0	0	1 (0.2%)	1 (0.2%)

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表 2.7.4.7-27 データカットオフ日までに眼以外に発現した有害事象（nAMD 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
	Onset after Week 48	Overall	Onset after Week 48	Overall
血管障害				
Total number of patients with at least one adverse event	7 (1.1%)	38 (5.7%)	5 (0.8%)	38 (5.7%)
Total number of events	7	44	5	42
高血圧	5 (0.8%)	27 (4.1%)	3 (0.5%)	19 (2.9%)
低血圧	0	1 (0.2%)	1 (0.2%)	3 (0.5%)
深部静脈血栓症	1 (0.2%)	1 (0.2%)	0	2 (0.3%)
血腫	0	1 (0.2%)	0	2 (0.3%)
起立性低血圧	0	1 (0.2%)	0	2 (0.3%)
静脈瘤	0	2 (0.3%)	0	1 (0.2%)
大動脈拡張	0	0	0	2 (0.3%)
末梢静脈疾患	0	0	0	2 (0.3%)
血栓性静脈炎	0	2 (0.3%)	0	0
大動脈瘤	0	0	1 (0.2%)	1 (0.2%)
大動脈硬化症	0	0	0	1 (0.2%)
大動脈狭窄	0	1 (0.2%)	0	0
コントロール不良の血圧	0	0	0	1 (0.2%)
本態性高血圧症	0	1 (0.2%)	0	0
高血圧クリーゼ	0	1 (0.2%)	0	0
リンパ浮腫	0	0	0	1 (0.2%)
起立性高血圧	0	0	0	1 (0.2%)
末梢動脈閉塞性疾患	0	0	0	1 (0.2%)
末梢冷感	0	0	0	1 (0.2%)
末梢血管障害	1 (0.2%)	1 (0.2%)	0	0
表在性血栓性静脈炎	0	1 (0.2%)	0	0
血栓症	0	1 (0.2%)	0	0
静脈虚脱	0	0	0	1 (0.2%)
四肢静脈血栓症	0	1 (0.2%)	0	0

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表 2.7.4.7-27 データカットオフ日までに眼以外に発現した有害事象（nAMD 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
	Onset after Week 48	Overall	Onset after Week 48	Overall
一般・全身障害および投与部位の状態				
Total number of patients with at least one adverse event	5 (0.8%)	38 (5.7%)	14 (2.1%)	36 (5.4%)
Total number of events	6	41	15	40
無力症	1 (0.2%)	7 (1.1%)	1 (0.2%)	4 (0.6%)
末梢性浮腫	0	2 (0.3%)	3 (0.5%)	7 (1.1%)
末梢腫脹	1 (0.2%)	5 (0.8%)	3 (0.5%)	3 (0.5%)
疲労	0	5 (0.8%)	0	1 (0.2%)
疼痛	1 (0.2%)	1 (0.2%)	1 (0.2%)	5 (0.8%)
発熱	0	3 (0.5%)	2 (0.3%)	3 (0.5%)
胸痛	0	1 (0.2%)	1 (0.2%)	4 (0.6%)
インフルエンザ様疾患	1 (0.2%)	4 (0.6%)	0	0
倦怠感	1 (0.2%)	2 (0.3%)	0	1 (0.2%)
医薬品副作用	0	1 (0.2%)	0	1 (0.2%)
嚢胞	0	2 (0.3%)	0	0
歩行障害	0	0	0	2 (0.3%)
ヘルニア	0	0	2 (0.3%)	2 (0.3%)
乳房インプラント関連被膜拘縮	0	1 (0.2%)	0	0
カテーテル留置部位血腫	0	0	0	1 (0.2%)
胸部不快感	0	1 (0.2%)	0	0
悪寒	0	1 (0.2%)	0	0
死亡	0	0	0	1 (0.2%)
薬物不耐性	0	1 (0.2%)	0	0
全身健康状態悪化	1 (0.2%)	1 (0.2%)	0	0
不明確な障害	0	1 (0.2%)	0	0
多臓器機能不全症候群	0	1 (0.2%)	0	0
非心臓性胸痛	0	0	0	1 (0.2%)
前癌状態	0	0	1 (0.2%)	1 (0.2%)

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表 2.7.4.7-27 データカットオフ日までに眼以外に発現した有害事象（nAMD 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
	Onset after Week 48	Overall	Onset after Week 48	Overall
代謝および栄養障害				
Total number of patients with at least one adverse event	4 (0.6%)	32 (4.8%)	5 (0.8%)	35 (5.3%)
Total number of events	5	37	5	44
高コレステロール血症	0	6 (0.9%)	1 (0.2%)	4 (0.6%)
糖尿病	2 (0.3%)	4 (0.6%)	1 (0.2%)	3 (0.5%)
低カリウム血症	1 (0.2%)	2 (0.3%)	0	5 (0.8%)
高脂血症	0	2 (0.3%)	0	4 (0.6%)
ビタミンＢ１２欠乏	0	2 (0.3%)	0	4 (0.6%)
脱水	0	1 (0.2%)	1 (0.2%)	4 (0.6%)
痛風	0	2 (0.3%)	0	2 (0.3%)
高血糖	1 (0.2%)	3 (0.5%)	0	1 (0.2%)
２型糖尿病	0	2 (0.3%)	0	2 (0.3%)
ビタミンＤ欠乏	0	1 (0.2%)	1 (0.2%)	3 (0.5%)
低マグネシウム血症	0	1 (0.2%)	0	2 (0.3%)
鉄欠乏	0	1 (0.2%)	1 (0.2%)	2 (0.3%)
脂質異常症	0	1 (0.2%)	0	1 (0.2%)
水分過負荷	0	1 (0.2%)	0	1 (0.2%)
高カリウム血症	0	1 (0.2%)	0	1 (0.2%)
低ナトリウム血症	0	1 (0.2%)	0	1 (0.2%)
ビタミンＢ群欠乏	0	1 (0.2%)	0	1 (0.2%)
異常体重減少	0	1 (0.2%)	0	0
食欲減退	0	0	0	1 (0.2%)
体液貯留	0	1 (0.2%)	0	0
耐糖能障害	0	1 (0.2%)	0	0
高トリグリセリド血症	0	0	0	1 (0.2%)
血液量増加症	1 (0.2%)	1 (0.2%)	0	0
ビタミン欠乏症	0	1 (0.2%)	0	0
乳酸アシドーシス	0	0	0	1 (0.2%)
心臓障害				
Total number of patients with at least one adverse event	6 (0.9%)	31 (4.7%)	3 (0.5%)	34 (5.1%)
Total number of events	6	47	3	50

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表 2.7.4.7-27 データカットオフ日までに眼以外に発現した有害事象（nAMD 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
	Onset after Week 48	Overall	Onset after Week 48	Overall
心房細動	3 (0.5%)	8 (1.2%)	0	8 (1.2%)
うっ血性心不全	1 (0.2%)	5 (0.8%)	0	5 (0.8%)
心不全	0	2 (0.3%)	0	3 (0.5%)
冠動脈疾患	0	3 (0.5%)	0	2 (0.3%)
急性心筋梗塞	0	2 (0.3%)	0	1 (0.2%)
狭心症	0	2 (0.3%)	0	1 (0.2%)
動悸	0	2 (0.3%)	1 (0.2%)	1 (0.2%)
徐脈	0	1 (0.2%)	1 (0.2%)	1 (0.2%)
慢性左室不全	0	0	0	2 (0.3%)
心筋梗塞	1 (0.2%)	1 (0.2%)	0	1 (0.2%)
頻脈	0	1 (0.2%)	0	1 (0.2%)
心室性期外収縮	0	1 (0.2%)	0	1 (0.2%)
急性左室不全	0	1 (0.2%)	0	0
不安定狭心症	0	0	0	1 (0.2%)
大動脈弁閉鎖不全症	0	0	0	1 (0.2%)
不整脈	0	1 (0.2%)	0	0
冠動脈硬化症	0	0	0	1 (0.2%)
心房粗動	1 (0.2%)	1 (0.2%)	0	0
心機能障害	0	0	0	1 (0.2%)
慢性心不全	0	1 (0.2%)	0	0
心タンポナーデ	0	1 (0.2%)	0	0
心拡大	0	0	0	1 (0.2%)
心肺不全	0	0	0	1 (0.2%)
うっ血性心筋症	0	0	0	1 (0.2%)
肺性心	0	1 (0.2%)	0	0
ドレスラー症候群	0	1 (0.2%)	0	0
左室機能不全	0	0	0	1 (0.2%)
左室拡大	0	0	0	1 (0.2%)
僧帽弁閉鎖不全症	0	0	0	1 (0.2%)
僧帽弁逸脱	0	0	0	1 (0.2%)
心筋虚血	0	1 (0.2%)	0	0
発作性房室ブロック	0	0	0	1 (0.2%)

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AE reported as neovascular age-related macular degeneration in the study eye indicates an accelerated worsening of the condition, as judged by the investigator.

表 2.7.4.7-27 データカットオフ日までに眼以外に発現した有害事象（nAMD 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
	Onset after Week 48	Overall	Onset after Week 48	Overall
心嚢液貯留	0	1 (0.2%)	0	0
心膜炎	0	1 (0.2%)	0	0
収縮性心膜炎	0	1 (0.2%)	0	0
洞性徐脈	0	0	1 (0.2%)	1 (0.2%)
洞性頻脈	0	0	0	1 (0.2%)
上室性期外収縮	0	0	0	1 (0.2%)
心室細動	0	1 (0.2%)	0	0

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AE reported as neovascular age-related macular degeneration in the study eye indicates an accelerated worsening of the condition, as judged by the investigator.

表 2.7.4.7-27 データカットオフ日までに眼以外に発現した有害事象（nAMD 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
	Onset after Week 48	Overall	Onset after Week 48	Overall
皮膚および皮下組織障害				
Total number of patients with at least one adverse event	3 (0.5%)	28 (4.2%)	6 (0.9%)	25 (3.8%)
Total number of events	3	36	6	28
発疹	0	6 (0.9%)	0	3 (0.5%)
光線角化症	1 (0.2%)	5 (0.8%)	0	3 (0.5%)
蕁麻疹	1 (0.2%)	5 (0.8%)	1 (0.2%)	2 (0.3%)
湿疹	0	1 (0.2%)	2 (0.3%)	3 (0.5%)
接触皮膚炎	0	1 (0.2%)	1 (0.2%)	2 (0.3%)
皮膚嚢腫	0	1 (0.2%)	0	1 (0.2%)
アレルギー性皮膚炎	0	1 (0.2%)	0	1 (0.2%)
皮膚乾燥	0	1 (0.2%)	0	1 (0.2%)
そう痒症	0	2 (0.3%)	0	0
紅斑性皮疹	0	0	0	2 (0.3%)
脂漏性皮膚炎	1 (0.2%)	2 (0.3%)	0	0
水疱	0	0	1 (0.2%)	1 (0.2%)
褥瘡性潰瘍	0	0	0	1 (0.2%)
皮膚炎	0	0	0	1 (0.2%)
ざ瘡様皮膚炎	0	1 (0.2%)	0	0
乾癬様皮膚炎	0	0	0	1 (0.2%)
貨幣状湿疹	0	0	1 (0.2%)	1 (0.2%)
手皮膚炎	0	1 (0.2%)	0	0
過角化	0	1 (0.2%)	0	0
硬化性苔癬	0	0	0	1 (0.2%)
神経皮膚炎	0	0	0	1 (0.2%)
皮膚病変	0	1 (0.2%)	0	0
皮膚潰瘍	0	0	0	1 (0.2%)
中毒性皮疹	0	1 (0.2%)	0	0
臨床検査				
Total number of patients with at least one adverse event	4 (0.6%)	26 (3.9%)	4 (0.6%)	24 (3.6%)
Total number of events	4	37	5	31
血圧上昇	1 (0.2%)	2 (0.3%)	0	8 (1.2%)

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表 2.7.4.7-27 データカットオフ日までに眼以外に発現した有害事象（nAMD 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
	Onset after Week 48	Overall	Onset after Week 48	Overall
白血球数増加	0	2 (0.3%)	0	2 (0.3%)
好中球数増加	0	2 (0.3%)	0	1 (0.2%)
前立腺特異性抗原増加	0	2 (0.3%)	1 (0.2%)	1 (0.2%)
尿中蛋白陽性	0	2 (0.3%)	0	1 (0.2%)
体重減少	0	1 (0.2%)	0	2 (0.3%)
アラニンアミノトランスフェラーゼ増加	0	1 (0.2%)	0	1 (0.2%)
血中コレステロール増加	0	1 (0.2%)	1 (0.2%)	1 (0.2%)
血中カリウム増加	0	2 (0.3%)	0	0
グリコヘモグロビン増加	0	1 (0.2%)	0	1 (0.2%)
血沈亢進	0	0	0	2 (0.3%)
アスパラギン酸アミノトランスフェラーゼ増加	0	0	0	1 (0.2%)
胸腔吸引	0	1 (0.2%)	0	0
細菌検査陽性	0	0	0	1 (0.2%)
前立腺生検	0	1 (0.2%)	0	0
血中クレアチニン増加	0	1 (0.2%)	0	0
血中ブドウ糖減少	1 (0.2%)	1 (0.2%)	0	0
血中ブドウ糖増加	0	1 (0.2%)	0	0
血中カリウム減少	1 (0.2%)	1 (0.2%)	0	0
血圧低下	0	1 (0.2%)	0	0
収縮期血圧上昇	1 (0.2%)	1 (0.2%)	0	0
血中ナトリウム減少	0	0	1 (0.2%)	1 (0.2%)
血中トリグリセリド増加	0	1 (0.2%)	0	0
血中尿酸増加	0	1 (0.2%)	0	0
尿中血	0	0	0	1 (0.2%)
骨密度減少	0	0	1 (0.2%)	1 (0.2%)
心カテーテル検査	0	1 (0.2%)	0	0
凝固因子増加	0	0	0	1 (0.2%)
結腸内視鏡検査	0	0	1 (0.2%)	1 (0.2%)
尿中結晶陽性	0	0	0	1 (0.2%)
心電図異常	0	1 (0.2%)	0	0
心拍数不整	0	1 (0.2%)	0	0
肝機能検査値上昇	0	1 (0.2%)	0	0

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AE reported as neovascular age-related macular degeneration in the study eye indicates an accelerated worsening of the condition, as judged by the investigator.

表 2.7.4.7-27 データカットオフ日までに眼以外に発現した有害事象（nAMD 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
	Onset after Week 48	Overall	Onset after Week 48	Overall
リンパ球数増加	0	1 (0.2%)	0	0
単球数増加	0	1 (0.2%)	0	0
酸素飽和度低下	0	1 (0.2%)	0	0
尿円柱陽性	0	0	0	1 (0.2%)
尿潜血陽性	0	1 (0.2%)	0	0
ビタミンＢ１２減少	0	0	0	1 (0.2%)
ビタミンＤ減少	0	1 (0.2%)	0	0
尿中白血球陽性	0	1 (0.2%)	0	0
腎および尿路障害				
Total number of patients with at least one adverse event	6 (0.9%)	19 (2.9%)	4 (0.6%)	20 (3.0%)
Total number of events	6	21	4	23
腎結石症	2 (0.3%)	2 (0.3%)	0	5 (0.8%)
急性腎障害	1 (0.2%)	3 (0.5%)	0	3 (0.5%)
血尿	0	2 (0.3%)	1 (0.2%)	3 (0.5%)
尿閉	1 (0.2%)	2 (0.3%)	0	3 (0.5%)
慢性腎臓病	0	2 (0.3%)	1 (0.2%)	2 (0.3%)
腎嚢胞	1 (0.2%)	2 (0.3%)	0	0
腎不全	0	0	1 (0.2%)	2 (0.3%)
尿失禁	0	0	0	2 (0.3%)
膀胱嚢胞	0	1 (0.2%)	0	0
出血性膀胱炎	0	0	0	1 (0.2%)
排尿困難	0	1 (0.2%)	0	0
緊張性膀胱	0	1 (0.2%)	0	0
下部尿路症状	1 (0.2%)	1 (0.2%)	0	0
夜間頻尿	0	1 (0.2%)	0	0
多尿	0	1 (0.2%)	0	0
腎仙痛	0	0	1 (0.2%)	1 (0.2%)
腎損傷	0	1 (0.2%)	0	0
腹圧性尿失禁	0	1 (0.2%)	0	0
尿路閉塞	0	0	0	1 (0.2%)

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表 2.7.4.7-27 データカットオフ日までに眼以外に発現した有害事象（nAMD 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
	Onset after Week 48	Overall	Onset after Week 48	Overall
精神障害				
Total number of patients with at least one adverse event	1 (0.2%)	18 (2.7%)	0	16 (2.4%)
Total number of events	1	18	0	16
うつ病	0	7 (1.1%)	0	2 (0.3%)
不安	0	2 (0.3%)	0	4 (0.6%)
不眠症	0	3 (0.5%)	0	3 (0.5%)
混合性不安抑うつ障害	0	1 (0.2%)	0	1 (0.2%)
アルコール離脱症候群	1 (0.2%)	1 (0.2%)	0	0
不安障害	0	1 (0.2%)	0	0
コミュニケーション障害	0	0	0	1 (0.2%)
錯乱状態	0	0	0	1 (0.2%)
抑うつ気分	0	0	0	1 (0.2%)
遺糞	0	1 (0.2%)	0	0
恐怖	0	1 (0.2%)	0	0
大うつ病	0	0	0	1 (0.2%)
処置に対する不安	0	0	0	1 (0.2%)
ストレス	0	0	0	1 (0.2%)
物質誘発性精神病性障害	0	1 (0.2%)	0	0
耳および迷路障害				
Total number of patients with at least one adverse event	1 (0.2%)	15 (2.3%)	0	14 (2.1%)
Total number of events	1	15	0	15
回転性めまい	1 (0.2%)	7 (1.1%)	0	9 (1.4%)
耳痛	0	3 (0.5%)	0	0
耳鳴	0	2 (0.3%)	0	1 (0.2%)
頭位性回転性めまい	0	1 (0.2%)	0	1 (0.2%)
耳垢栓塞	0	1 (0.2%)	0	0
難聴	0	0	0	1 (0.2%)
両耳難聴	0	1 (0.2%)	0	0
耳管閉塞	0	0	0	1 (0.2%)
外耳の炎症	0	0	0	1 (0.2%)

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表 2.7.4.7-27 データカットオフ日までに眼以外に発現した有害事象（nAMD 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
	Onset after Week 48	Overall	Onset after Week 48	Overall
血液およびリンパ系障害				
Total number of patients with at least one adverse event	1 (0.2%)	9 (1.4%)	2 (0.3%)	15 (2.3%)
Total number of events	1	9	2	17
貧血	1 (0.2%)	5 (0.8%)	1 (0.2%)	5 (0.8%)
鉄欠乏性貧血	0	2 (0.3%)	0	3 (0.5%)
汎血球減少症	0	0	0	3 (0.5%)
血小板減少症	0	1 (0.2%)	0	1 (0.2%)
ビタミンＢ１２欠乏性貧血	0	1 (0.2%)	0	0
失血性貧血	0	0	1 (0.2%)	1 (0.2%)
溶血性貧血	0	0	0	1 (0.2%)
肺門リンパ節腫脹	0	0	0	1 (0.2%)
白血球減少症	0	0	0	1 (0.2%)
血小板増加症	0	0	0	1 (0.2%)
生殖系および乳房障害				
Total number of patients with at least one adverse event	2 (0.3%)	10 (1.5%)	4 (0.6%)	11 (1.7%)
Total number of events	2	11	4	12
良性前立腺肥大症	0	1 (0.2%)	1 (0.2%)	2 (0.3%)
前立腺腫大	0	0	0	3 (0.5%)
萎縮性外陰腟炎	1 (0.2%)	2 (0.3%)	0	0
勃起不全	0	2 (0.3%)	0	0
骨盤痛	0	1 (0.2%)	0	1 (0.2%)
腟出血	0	1 (0.2%)	1 (0.2%)	1 (0.2%)
乳房痛	0	0	1 (0.2%)	1 (0.2%)
膀胱瘤	0	0	0	1 (0.2%)
不正子宮出血	0	1 (0.2%)	0	0
乳頭痛	0	1 (0.2%)	0	0
閉経後出血	1 (0.2%)	1 (0.2%)	0	0
前立腺障害	0	0	1 (0.2%)	1 (0.2%)
子宮脱	0	0	0	1 (0.2%)
腟脱	0	0	0	1 (0.2%)
外陰腟そう痒症	0	1 (0.2%)	0	0

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表 2.7.4.7-27 データカットオフ日までに眼以外に発現した有害事象（nAMD 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
	Onset after Week 48	Overall	Onset after Week 48	Overall
免疫系障害				
Total number of patients with at least one adverse event	1 (0.2%)	12 (1.8%)	0	6 (0.9%)
Total number of events	1	13	0	6
季節性アレルギー	1 (0.2%)	10 (1.5%)	0	3 (0.5%)
節足動物咬傷アレルギー	0	0	0	1 (0.2%)
造影剤アレルギー	0	0	0	1 (0.2%)
薬物過敏症	0	1 (0.2%)	0	0
過敏症	0	1 (0.2%)	0	0
ダニアレルギー	0	1 (0.2%)	0	0
ゴム過敏症	0	0	0	1 (0.2%)
肝胆道系障害				
Total number of patients with at least one adverse event	2 (0.3%)	7 (1.1%)	2 (0.3%)	9 (1.4%)
Total number of events	2	8	2	9
胆石症	0	3 (0.5%)	1 (0.2%)	2 (0.3%)
胆嚢炎	1 (0.2%)	2 (0.3%)	0	1 (0.2%)
胆道仙痛	0	0	1 (0.2%)	1 (0.2%)
胆道閉塞	0	0	0	1 (0.2%)
急性胆嚢炎	0	0	0	1 (0.2%)
肝嚢胞	0	1 (0.2%)	0	0
肝線維症	0	0	0	1 (0.2%)
脂肪肝	0	0	0	1 (0.2%)
肝静脈血栓症	0	0	0	1 (0.2%)
肝炎	1 (0.2%)	1 (0.2%)	0	0
水腫性胆嚢炎	0	1 (0.2%)	0	0

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表 2.7.4.7-27　データカットオフ日までに眼以外に発現した有害事象（nAMD 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
	Onset after Week 48	Overall	Onset after Week 48	Overall
眼障害				
Total number of patients with at least one adverse event	3 (0.5%)	5 (0.8%)	2 (0.3%)	7 (1.1%)
Total number of events	3	5	2	7
ドライアイ	1 (0.2%)	1 (0.2%)	0	1 (0.2%)
新生血管加齢黄斑変性	0	0	0	2 (0.3%)
白内障	1 (0.2%)	1 (0.2%)	0	0
糖尿病網膜症	0	0	0	1 (0.2%)
眼痛	0	0	1 (0.2%)	1 (0.2%)
流涙増加	0	0	0	1 (0.2%)
眼酒さ	0	0	1 (0.2%)	1 (0.2%)
眼窩周囲痛	0	1 (0.2%)	0	0
光視症	0	1 (0.2%)	0	0
視力障害	1 (0.2%)	1 (0.2%)	0	0
内分泌障害				
Total number of patients with at least one adverse event	3 (0.5%)	3 (0.5%)	1 (0.2%)	2 (0.3%)
Total number of events	3	3	1	2
甲状腺機能低下症	3 (0.5%)	3 (0.5%)	0	1 (0.2%)
甲状腺機能亢進症	0	0	1 (0.2%)	1 (0.2%)
外科および内科処置				
Total number of patients with at least one adverse event	1 (0.2%)	1 (0.2%)	0	1 (0.2%)
Total number of events	1	1	0	1
嚢胞切除	1 (0.2%)	1 (0.2%)	0	0
智歯抜歯	0	0	0	1 (0.2%)
製品の問題				
Total number of patients with at least one adverse event	0	0	0	1 (0.2%)
Total number of events	0	0	0	1
医療機器機能不良	0	0	0	1 (0.2%)

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表 2.7.4.7-28 データカットオフ日までに眼以外に発現した有害事象（DME 統合）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887)							
	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
Total number of patients with at least one adverse event	160 (25.4%)	427 (67.8%)	142 (22.5%)	413 (65.3%)	302 (23.9%)	840 (66.6%)	141 (22.6%)	421 (67.4%)
Overall total number of events	358	1710	371	1521	729	3231	318	1486
感染症および寄生虫症								
Total number of patients with at least one adverse event	65 (10.3%)	219 (34.8%)	58 (9.2%)	193 (30.5%)	123 (9.7%)	412 (32.6%)	52 (8.3%)	224 (35.8%)
Total number of events	81	371	74	303	155	674	69	381
上咽頭炎	10 (1.6%)	50 (7.9%)	8 (1.3%)	41 (6.5%)	18 (1.4%)	91 (7.2%)	9 (1.4%)	61 (9.8%)
尿路感染	9 (1.4%)	28 (4.4%)	9 (1.4%)	27 (4.3%)	18 (1.4%)	55 (4.4%)	9 (1.4%)	42 (6.7%)
気管支炎	1 (0.2%)	23 (3.7%)	2 (0.3%)	17 (2.7%)	3 (0.2%)	40 (3.2%)	1 (0.2%)	16 (2.6%)
副鼻腔炎	8 (1.3%)	23 (3.7%)	2 (0.3%)	12 (1.9%)	10 (0.8%)	35 (2.8%)	2 (0.3%)	15 (2.4%)
蜂巣炎	0	17 (2.7%)	5 (0.8%)	13 (2.1%)	5 (0.4%)	30 (2.4%)	4 (0.6%)	19 (3.0%)
肺炎	7 (1.1%)	22 (3.5%)	2 (0.3%)	15 (2.4%)	9 (0.7%)	37 (2.9%)	1 (0.2%)	12 (1.9%)
インフルエンザ	3 (0.5%)	10 (1.6%)	6 (0.9%)	21 (3.3%)	9 (0.7%)	31 (2.5%)	2 (0.3%)	17 (2.7%)
上気道感染	1 (0.2%)	14 (2.2%)	2 (0.3%)	17 (2.7%)	3 (0.2%)	31 (2.5%)	1 (0.2%)	11 (1.8%)
ＣＯＶＩＤ－１９	5 (0.8%)	7 (1.1%)	6 (0.9%)	13 (2.1%)	11 (0.9%)	20 (1.6%)	3 (0.5%)	9 (1.4%)
敗血症	2 (0.3%)	12 (1.9%)	0	2 (0.3%)	2 (0.2%)	14 (1.1%)	1 (0.2%)	8 (1.3%)
限局性感染	3 (0.5%)	5 (0.8%)	3 (0.5%)	7 (1.1%)	6 (0.5%)	12 (1.0%)	4 (0.6%)	9 (1.4%)
帯状疱疹	1 (0.2%)	7 (1.1%)	1 (0.2%)	8 (1.3%)	2 (0.2%)	15 (1.2%)	2 (0.3%)	5 (0.8%)
骨髄炎	0	5 (0.8%)	0	2 (0.3%)	0	7 (0.6%)	1 (0.2%)	8 (1.3%)
耳感染	3 (0.5%)	5 (0.8%)	2 (0.3%)	5 (0.8%)	5 (0.4%)	10 (0.8%)	0	2 (0.3%)
下気道感染	1 (0.2%)	7 (1.1%)	0	1 (0.2%)	1 (<0.1%)	8 (0.6%)	0	3 (0.5%)
ウイルス性胃腸炎	1 (0.2%)	4 (0.6%)	0	1 (0.2%)	1 (<0.1%)	5 (0.4%)	0	5 (0.8%)
歯膿瘍	2 (0.3%)	3 (0.5%)	0	4 (0.6%)	2 (0.2%)	7 (0.6%)	2 (0.3%)	3 (0.5%)
糖尿病性足感染	1 (0.2%)	4 (0.6%)	0	1 (0.2%)	1 (<0.1%)	5 (0.4%)	3 (0.5%)	4 (0.6%)
壊疽	1 (0.2%)	2 (0.3%)	3 (0.5%)	4 (0.6%)	4 (0.3%)	6 (0.5%)	3 (0.5%)	3 (0.5%)
咽頭炎	2 (0.3%)	3 (0.5%)	0	2 (0.3%)	2 (0.2%)	5 (0.4%)	0	4 (0.6%)
歯感染	2 (0.3%)	5 (0.8%)	1 (0.2%)	1 (0.2%)	3 (0.2%)	6 (0.5%)	0	3 (0.5%)
膀胱炎	3 (0.5%)	5 (0.8%)	0	1 (0.2%)	3 (0.2%)	6 (0.5%)	1 (0.2%)	2 (0.3%)
胃腸炎	0	2 (0.3%)	0	3 (0.5%)	0	5 (0.4%)	0	2 (0.3%)
中耳炎	0	0	1 (0.2%)	4 (0.6%)	1 (<0.1%)	4 (0.3%)	0	3 (0.5%)

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-28 データカットオフ日までに眼以外に発現した有害事象（DME 統合）（続）

Pooled(YOSEMITE and RHINE)
(N=1887)

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
鼻炎	0	1 (0.2%)	0	2 (0.3%)	0	3 (0.2%)	0	4 (0.6%)
腎感染	0	2 (0.3%)	3 (0.5%)	4 (0.6%)	3 (0.2%)	6 (0.5%)	0	0
気道感染	0	3 (0.5%)	0	1 (0.2%)	0	4 (0.3%)	0	2 (0.3%)
急性副鼻腔炎	0	0	1 (0.2%)	2 (0.3%)	1 (<0.1%)	2 (0.2%)	1 (0.2%)	3 (0.5%)
コロナウイルス感染	2 (0.3%)	2 (0.3%)	1 (0.2%)	1 (0.2%)	3 (0.2%)	3 (0.2%)	0	2 (0.3%)
腎盂腎炎	0	2 (0.3%)	1 (0.2%)	2 (0.3%)	1 (<0.1%)	4 (0.3%)	1 (0.2%)	1 (0.2%)
ウイルス感染	0	2 (0.3%)	0	2 (0.3%)	0	4 (0.3%)	0	1 (0.2%)
四肢膿瘍	0	0	0	1 (0.2%)	0	1 (<0.1%)	1 (0.2%)	3 (0.5%)
糖尿病性壊疽	1 (0.2%)	2 (0.3%)	0	1 (0.2%)	1 (<0.1%)	3 (0.2%)	0	1 (0.2%)
喉頭炎	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	1 (0.2%)	2 (0.3%)
歯髄炎	1 (0.2%)	2 (0.3%)	0	1 (0.2%)	1 (<0.1%)	3 (0.2%)	0	1 (0.2%)
憩室炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	2 (0.3%)	2 (0.3%)
真菌感染	1 (0.2%)	3 (0.5%)	0	0	1 (<0.1%)	3 (0.2%)	0	0
歯肉炎	1 (0.2%)	2 (0.3%)	0	1 (0.2%)	1 (<0.1%)	3 (0.2%)	0	0
感染性嚢腫	0	0	1 (0.2%)	2 (0.3%)	1 (<0.1%)	2 (0.2%)	0	1 (0.2%)
口腔ヘルペス	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	1 (0.2%)
レンサ球菌性咽頭炎	0	2 (0.3%)	0	0	0	2 (0.2%)	0	1 (0.2%)
ブドウ球菌感染	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	2 (0.3%)
足部白癬	0	0	0	0	0	0	3 (0.5%)	3 (0.5%)
ウイルス性上気道感染	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	2 (0.3%)
外陰腟真菌感染	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	2 (0.3%)
創傷感染	2 (0.3%)	3 (0.5%)	0	0	2 (0.2%)	3 (0.2%)	0	0
顎膿瘍	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	1 (0.2%)
肛門膿瘍	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	1 (0.2%)
菌血症	0	2 (0.3%)	0	0	0	2 (0.2%)	0	0
ウイルス性気管支炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	1 (0.2%)
カンジダ感染	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	1 (0.2%)
壊疽性蜂巣炎	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	1 (0.2%)
クロストリジウム・ディフィシレ大腸炎	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	1 (0.2%)
丹毒	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	0
皮膚真菌感染	1 (0.2%)	1 (0.2%)	0	1 (0.2%)	1 (<0.1%)	2 (0.2%)	0	0
消化管感染	0	0	0	1 (0.2%)	0	1 (<0.1%)	1 (0.2%)	1 (0.2%)
ヘリコバクター感染	1 (0.2%)	2 (0.3%)	0	0	1 (<0.1%)	2 (0.2%)	0	0

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-28　データカットオフ日までに眼以外に発現した有害事象（DME 統合）（続）

Pooled(YOSEMITE and RHINE)
(N=1887)

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
感染性皮膚潰瘍	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	0
迷路炎	0	2 (0.3%)	0	0	0	2 (0.2%)	0	0
ライム病	0	0	1 (0.2%)	2 (0.3%)	1 (<0.1%)	2 (0.2%)	0	0
爪真菌症	0	2 (0.3%)	0	0	0	2 (0.2%)	0	0
爪囲炎	0	0	1 (0.2%)	2 (0.3%)	1 (<0.1%)	2 (0.2%)	0	0
歯周炎	0	1 (0.2%)	1 (0.2%)	1 (0.2%)	1 (<0.1%)	2 (0.2%)	0	0
ウイルス性肺炎	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	1 (0.2%)	1 (0.2%)
敗血症性ショック	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	1 (0.2%)
皮膚感染	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	1 (0.2%)
皮下組織膿瘍	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	1 (0.2%)
扁桃炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	1 (0.2%)
気管炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	1 (0.2%)
腹部膿瘍	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
ダニ皮膚炎	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
歯槽骨炎	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
虫垂炎	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
細菌性関節炎	0	0	0	0	0	0	0	1 (0.2%)
異型肺炎	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
細菌尿	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
ＣＯＶＩＤ－１９肺炎	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
感染性胆嚢炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
合併症を伴う虫垂炎	0	0	0	0	0	0	0	1 (0.2%)
医療機器関連感染	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
感染性下痢	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
心内膜炎	0	0	0	0	0	0	0	1 (0.2%)
大腸菌性敗血症	0	0	0	0	0	0	0	1 (0.2%)
毛包炎	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
真菌性膀胱炎	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
真菌性鼻炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
胆嚢蓄膿	0	0	0	0	0	0	0	1 (0.2%)
胃感染	0	0	0	0	0	0	0	1 (0.2%)
細菌性胃腸炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
ノロウイルス性胃腸炎	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-28 データカットオフ日までに眼以外に発現した有害事象（DME 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887)							
	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
消化管内細菌過剰増殖	0	0	0	0	0	0	0	1 (0.2%)
ウイルス性消化管感染	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
耳帯状疱疹	0	0	0	0	0	0	0	1 (0.2%)
埋込み部位感染	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
咬傷感染	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
感染性皮膚嚢腫	0	0	0	0	0	0	0	1 (0.2%)
伝染性単核症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
感染性血栓症	0	0	0	0	0	0	0	1 (0.2%)
椎間板炎	0	0	0	0	0	0	0	1 (0.2%)
肺膿瘍	0	0	0	0	0	0	0	1 (0.2%)
鼻ヘルペス	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
口腔カンジダ症	0	0	0	0	0	0	0	1 (0.2%)
急性骨髄炎	0	0	0	0	0	0	0	1 (0.2%)
細菌性骨髄炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
慢性骨髄炎	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
外耳炎	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
急性中耳炎	0	0	0	0	0	0	0	1 (0.2%)
腹膜炎	0	0	0	0	0	0	0	1 (0.2%)
細菌性肺炎	0	0	0	0	0	0	0	1 (0.2%)
大腸菌性肺炎	0	0	0	0	0	0	0	1 (0.2%)
マイコプラズマ性肺炎	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
ブドウ球菌性肺炎	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
術後膿瘍	0	0	0	0	0	0	0	1 (0.2%)
シュードモナス性敗血症	0	0	0	0	0	0	0	1 (0.2%)
穿刺部位感染	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
慢性腎盂腎炎	0	0	0	0	0	0	0	1 (0.2%)
ＲＳウイルス気管支炎	0	0	0	0	0	0	0	1 (0.2%)
ウイルス性気道感染	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
ライノウイルス感染	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
陰嚢蜂巣炎	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
敗血症症候群	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
敗血症性凝固異常	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
軟部組織感染	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-28　データカットオフ日までに眼以外に発現した有害事象（DME 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887)							
	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
ＣＯＶＩＤ－１９の疑い	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
尿道炎	0	0	0	0	0	0	0	1 (0.2%)
尿路性敗血症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
外陰部炎	0	0	0	0	0	0	0	1 (0.2%)
代謝および栄養障害								
Total number of patients with at least one adverse event	23 (3.7%)	97 (15.4%)	18 (2.8%)	83 (13.1%)	41 (3.2%)	180 (14.3%)	16 (2.6%)	76 (12.2%)
Total number of events	27	131	26	130	53	261	22	108
高血糖	5 (0.8%)	13 (2.1%)	4 (0.6%)	15 (2.4%)	9 (0.7%)	28 (2.2%)	1 (0.2%)	7 (1.1%)
低血糖	2 (0.3%)	11 (1.7%)	5 (0.8%)	16 (2.5%)	7 (0.6%)	27 (2.1%)	3 (0.5%)	8 (1.3%)
高脂血症	3 (0.5%)	14 (2.2%)	0	10 (1.6%)	3 (0.2%)	24 (1.9%)	1 (0.2%)	10 (1.6%)
糖尿病	3 (0.5%)	14 (2.2%)	2 (0.3%)	10 (1.6%)	5 (0.4%)	24 (1.9%)	2 (0.3%)	4 (0.6%)
高コレステロール血症	0	6 (1.0%)	2 (0.3%)	10 (1.6%)	2 (0.2%)	16 (1.3%)	1 (0.2%)	7 (1.1%)
高カリウム血症	4 (0.6%)	10 (1.6%)	1 (0.2%)	3 (0.5%)	5 (0.4%)	13 (1.0%)	0	5 (0.8%)
脱水	1 (0.2%)	6 (1.0%)	2 (0.3%)	5 (0.8%)	3 (0.2%)	11 (0.9%)	1 (0.2%)	6 (1.0%)
２型糖尿病	0	5 (0.8%)	1 (0.2%)	5 (0.8%)	1 (<0.1%)	10 (0.8%)	0	5 (0.8%)
ビタミンＤ欠乏	0	4 (0.6%)	0	4 (0.6%)	0	8 (0.6%)	2 (0.3%)	7 (1.1%)
コントロール不良の糖尿病	0	7 (1.1%)	0	2 (0.3%)	0	9 (0.7%)	0	5 (0.8%)
痛風	2 (0.3%)	4 (0.6%)	0	4 (0.6%)	2 (0.2%)	8 (0.6%)	2 (0.3%)	5 (0.8%)
体液貯留	0	3 (0.5%)	1 (0.2%)	3 (0.5%)	1 (<0.1%)	6 (0.5%)	1 (0.2%)	5 (0.8%)
低ナトリウム血症	0	3 (0.5%)	1 (0.2%)	3 (0.5%)	1 (<0.1%)	6 (0.5%)	1 (0.2%)	2 (0.3%)
脂質異常症	0	0	0	7 (1.1%)	0	7 (0.6%)	0	0
ビタミンＢ１２欠乏	1 (0.2%)	2 (0.3%)	0	3 (0.5%)	1 (<0.1%)	5 (0.4%)	0	2 (0.3%)
低カリウム血症	0	2 (0.3%)	0	3 (0.5%)	0	5 (0.4%)	0	1 (0.2%)
糖尿病性ケトアシドーシス	0	1 (0.2%)	1 (0.2%)	2 (0.3%)	1 (<0.1%)	3 (0.2%)	1 (0.2%)	2 (0.3%)
糖尿病性代謝代償不全	1 (0.2%)	2 (0.3%)	0	2 (0.3%)	1 (<0.1%)	4 (0.3%)	0	1 (0.2%)
肥満	1 (0.2%)	2 (0.3%)	0	3 (0.5%)	1 (<0.1%)	5 (0.4%)	0	0
高尿酸血症	0	2 (0.3%)	0	0	0	2 (0.2%)	1 (0.2%)	2 (0.3%)
低マグネシウム血症	1 (0.2%)	2 (0.3%)	0	0	1 (<0.1%)	2 (0.2%)	1 (0.2%)	2 (0.3%)
鉄欠乏	0	0	2 (0.3%)	2 (0.3%)	2 (0.2%)	2 (0.2%)	0	2 (0.3%)
アシドーシス	0	2 (0.3%)	0	0	0	2 (0.2%)	0	1 (0.2%)
食欲減退	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	2 (0.3%)

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-28 データカットオフ日までに眼以外に発現した有害事象（DME 統合）（続）

Pooled(YOSEMITE and RHINE)
(N=1887)

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=630) Onset after Week 56	Faricimab 6 mg Q8W (N=630) Overall	Faricimab 6 mg PTI (N=632) Onset after Week 56	Faricimab 6 mg PTI (N=632) Overall	Faricimab 6 mg All (N=1262) Onset after Week 56	Faricimab 6 mg All (N=1262) Overall	Aflibercept 2 mg Q8W (N=625) Onset after Week 56	Aflibercept 2 mg Q8W (N=625) Overall
高トリグリセリド血症	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	1 (0.2%)
マグネシウム欠乏	0	3 (0.5%)	0	0	0	3 (0.2%)	0	0
代謝性アシドーシス	1 (0.2%)	2 (0.3%)	0	1 (0.2%)	1 (<0.1%)	3 (0.2%)	0	0
血液量減少症	0	0	1 (0.2%)	2 (0.3%)	1 (<0.1%)	2 (0.2%)	0	0
乳酸アシドーシス	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	0
栄養障害	0	0	0	1 (0.2%)	0	1 (<0.1%)	1 (0.2%)	1 (0.2%)
代謝性アルカローシス	0	0	0	0	0	0	1 (0.2%)	2 (0.3%)
悪液質	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
カルシウム欠乏	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
糖尿病合併症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
糖尿病性末端器官損傷	0	0	0	0	0	0	0	1 (0.2%)
発育不全	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
葉酸欠乏	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
高血糖性高浸透圧性非ケトン性症候群	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
高浸透圧状態	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
高リン酸塩血症	0	0	0	0	0	0	0	1 (0.2%)
低アルブミン血症	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
低カルシウム血症	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
低クロール血症	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
代謝症候群	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
偽性低ナトリウム血症	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
１型糖尿病	0	0	0	0	0	0	0	1 (0.2%)
ビタミンＢ群欠乏	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
ビタミンＣ欠乏	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
神経系障害								
Total number of patients with at least one adverse event	25 (4.0%)	93 (14.8%)	30 (4.7%)	90 (14.2%)	55 (4.4%)	183 (14.5%)	20 (3.2%)	71 (11.4%)
Total number of events	33	145	34	125	67	270	27	102
頭痛	4 (0.6%)	27 (4.3%)	6 (0.9%)	21 (3.3%)	10 (0.8%)	48 (3.8%)	3 (0.5%)	14 (2.2%)
浮動性めまい	5 (0.8%)	11 (1.7%)	2 (0.3%)	8 (1.3%)	7 (0.6%)	19 (1.5%)	1 (0.2%)	13 (2.1%)
糖尿病性ニューロパチー	2 (0.3%)	9 (1.4%)	1 (0.2%)	5 (0.8%)	3 (0.2%)	14 (1.1%)	2 (0.3%)	7 (1.1%)

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-28 データカットオフ日までに眼以外に発現した有害事象（DME 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887)							
	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
失神	1 (0.2%)	5 (0.8%)	4 (0.6%)	7 (1.1%)	5 (0.4%)	12 (1.0%)	2 (0.3%)	5 (0.8%)
坐骨神経痛	1 (0.2%)	3 (0.5%)	2 (0.3%)	7 (1.1%)	3 (0.2%)	10 (0.8%)	2 (0.3%)	4 (0.6%)
脳血管発作	0	3 (0.5%)	1 (0.2%)	4 (0.6%)	1 (<0.1%)	7 (0.6%)	3 (0.5%)	5 (0.8%)
虚血性脳卒中	2 (0.3%)	5 (0.8%)	2 (0.3%)	2 (0.3%)	4 (0.3%)	7 (0.6%)	2 (0.3%)	3 (0.5%)
片頭痛	2 (0.3%)	6 (1.0%)	0	3 (0.5%)	2 (0.2%)	9 (0.7%)	0	1 (0.2%)
末梢性ニューロパチー	1 (0.2%)	3 (0.5%)	0	3 (0.5%)	1 (<0.1%)	6 (0.5%)	0	4 (0.6%)
感覚鈍麻	2 (0.3%)	3 (0.5%)	1 (0.2%)	3 (0.5%)	3 (0.2%)	6 (0.5%)	0	3 (0.5%)
脳症	0	2 (0.3%)	2 (0.3%)	2 (0.3%)	2 (0.2%)	4 (0.3%)	1 (0.2%)	3 (0.5%)
一過性脳虚血発作	1 (0.2%)	3 (0.5%)	0	2 (0.3%)	1 (<0.1%)	5 (0.4%)	1 (0.2%)	2 (0.3%)
頚動脈硬化症	0	2 (0.3%)	0	3 (0.5%)	0	5 (0.4%)	1 (0.2%)	1 (0.2%)
手根管症候群	0	2 (0.3%)	1 (0.2%)	1 (0.2%)	1 (<0.1%)	3 (0.2%)	1 (0.2%)	2 (0.3%)
代謝性脳症	0	0	2 (0.3%)	3 (0.5%)	2 (0.2%)	3 (0.2%)	0	2 (0.3%)
脳梗塞	1 (0.2%)	3 (0.5%)	0	1 (0.2%)	1 (<0.1%)	4 (0.3%)	0	0
顔面麻痺	0	2 (0.3%)	2 (0.3%)	2 (0.3%)	2 (0.2%)	4 (0.3%)	0	0
神経痛	0	3 (0.5%)	0	0	0	3 (0.2%)	0	1 (0.2%)
平衡障害	0	0	0	1 (0.2%)	0	1 (<0.1%)	2 (0.3%)	2 (0.3%)
頚動脈閉塞	0	1 (0.2%)	1 (0.2%)	1 (0.2%)	1 (<0.1%)	2 (0.2%)	0	1 (0.2%)
頚動脈狭窄	1 (0.2%)	2 (0.3%)	1 (0.2%)	1 (0.2%)	2 (0.2%)	3 (0.2%)	0	0
脳出血	0	2 (0.3%)	1 (0.2%)	1 (0.2%)	1 (<0.1%)	3 (0.2%)	0	0
腰髄神経根障害	0	0	0	2 (0.3%)	0	2 (0.2%)	0	1 (0.2%)
錯感覚	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	1 (0.2%)
失神寸前の状態	0	1 (0.2%)	0	2 (0.3%)	0	3 (0.2%)	0	0
副鼻腔炎に伴う頭痛	0	1 (0.2%)	1 (0.2%)	2 (0.3%)	1 (<0.1%)	3 (0.2%)	0	0
健忘	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	1 (0.2%)
運動失調	1 (0.2%)	2 (0.3%)	0	0	1 (<0.1%)	2 (0.2%)	0	0
脳血管障害	1 (0.2%)	1 (0.2%)	0	1 (0.2%)	1 (<0.1%)	2 (0.2%)	0	0
頚髄神経根障害	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	1 (0.2%)
認知症	1 (0.2%)	2 (0.3%)	0	0	1 (<0.1%)	2 (0.2%)	0	0
アルツハイマー型認知症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	1 (0.2%)
てんかん	0	2 (0.3%)	0	0	0	2 (0.2%)	0	0
不全片麻痺	1 (0.2%)	2 (0.3%)	0	0	1 (<0.1%)	2 (0.2%)	0	0
嗜眠	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	0
意識消失	0	0	0	1 (0.2%)	0	1 (<0.1%)	1 (0.2%)	1 (0.2%)

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-28 データカットオフ日までに眼以外に発現した有害事象（DME 統合）（続）

Pooled(YOSEMITE and RHINE)
(N=1887)

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
パーキンソン病	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	1 (0.2%)
部分発作	1 (0.2%)	1 (0.2%)	0	1 (0.2%)	1 (<0.1%)	2 (0.2%)	0	0
多発ニューロパチー	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	1 (0.2%)
下肢静止不能症候群	0	0	0	2 (0.3%)	0	2 (0.2%)	0	0
痙攣発作	0	0	0	1 (0.2%)	0	1 (<0.1%)	1 (0.2%)	1 (0.2%)
聴神経炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
意識変容状態	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
筋萎縮性側索硬化症	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
無嗅覚	0	0	0	0	0	0	0	1 (0.2%)
失語症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
馬尾症候群	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
脳動脈硬化症	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
大脳動脈狭窄	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
大脳石灰化	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
昏睡	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
ギラン・バレー症候群	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
出血性卒中	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
頭部不快感	0	0	0	0	0	0	0	1 (0.2%)
過眠症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
高血圧性脳症	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
低酸素性虚血性脳症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
ラクナ脳卒中	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
白質脳症	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
記憶障害	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
不全単麻痺	0	0	0	0	0	0	0	1 (0.2%)
多発性硬化症	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
脊髄症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
神経圧迫	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
神経周囲嚢胞	0	0	0	0	0	0	0	1 (0.2%)
末梢性感覚ニューロパチー	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
梨状筋症候群	0	0	0	0	0	0	0	1 (0.2%)
ヘルペス後神経痛	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
脳卒中後てんかん	0	0	0	0	0	0	0	1 (0.2%)

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-28　データカットオフ日までに眼以外に発現した有害事象（DME 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887)							
	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
感覚消失	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
傾眠	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
脊髄圧迫	0	0	0	0	0	0	0	1 (0.2%)
振戦	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
第６脳神経麻痺	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
中枢神経系に起因する回転性めまい	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
声帯不全麻痺	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
筋骨格系および結合組織障害								
Total number of patients with at least one adverse event	36 (5.7%)	105 (16.7%)	23 (3.6%)	70 (11.1%)	59 (4.7%)	175 (13.9%)	20 (3.2%)	70 (11.2%)
Total number of events	43	138	27	96	70	234	22	100
背部痛	10 (1.6%)	26 (4.1%)	4 (0.6%)	13 (2.1%)	14 (1.1%)	39 (3.1%)	3 (0.5%)	12 (1.9%)
関節痛	8 (1.3%)	22 (3.5%)	3 (0.5%)	13 (2.1%)	11 (0.9%)	35 (2.8%)	4 (0.6%)	14 (2.2%)
四肢痛	5 (0.8%)	11 (1.7%)	1 (0.2%)	8 (1.3%)	6 (0.5%)	19 (1.5%)	4 (0.6%)	13 (2.1%)
変形性関節症	3 (0.5%)	7 (1.1%)	4 (0.6%)	9 (1.4%)	7 (0.6%)	16 (1.3%)	2 (0.3%)	8 (1.3%)
筋痙縮	0	4 (0.6%)	1 (0.2%)	3 (0.5%)	1 (<0.1%)	7 (0.6%)	0	6 (1.0%)
関節炎	3 (0.5%)	5 (0.8%)	1 (0.2%)	4 (0.6%)	4 (0.3%)	9 (0.7%)	0	1 (0.2%)
椎間板突出	0	4 (0.6%)	0	1 (0.2%)	0	5 (0.4%)	1 (0.2%)	4 (0.6%)
筋肉痛	1 (0.2%)	7 (1.1%)	0	2 (0.3%)	1 (<0.1%)	9 (0.7%)	0	0
脊椎痛	1 (0.2%)	3 (0.5%)	1 (0.2%)	2 (0.3%)	2 (0.2%)	5 (0.4%)	1 (0.2%)	4 (0.6%)
頚部痛	0	2 (0.3%)	1 (0.2%)	2 (0.3%)	1 (<0.1%)	4 (0.3%)	1 (0.2%)	4 (0.6%)
肩回旋筋腱板症候群	1 (0.2%)	3 (0.5%)	1 (0.2%)	4 (0.6%)	2 (0.2%)	7 (0.6%)	0	1 (0.2%)
神経障害性関節症	0	5 (0.8%)	0	0	0	5 (0.4%)	0	1 (0.2%)
筋力低下	1 (0.2%)	2 (0.3%)	0	1 (0.2%)	1 (<0.1%)	3 (0.2%)	0	2 (0.3%)
骨減少症	0	1 (0.2%)	2 (0.3%)	3 (0.5%)	2 (0.2%)	4 (0.3%)	0	1 (0.2%)
足変形	1 (0.2%)	1 (0.2%)	0	1 (0.2%)	1 (<0.1%)	2 (0.2%)	0	2 (0.3%)
筋骨格硬直	0	3 (0.5%)	0	1 (0.2%)	0	4 (0.3%)	0	0
関節周囲炎	0	1 (0.2%)	1 (0.2%)	1 (0.2%)	1 (<0.1%)	2 (0.2%)	1 (0.2%)	2 (0.3%)
足底筋膜炎	0	1 (0.2%)	1 (0.2%)	2 (0.3%)	1 (<0.1%)	3 (0.2%)	1 (0.2%)	1 (0.2%)
変形性脊椎症	0	1 (0.2%)	1 (0.2%)	2 (0.3%)	1 (<0.1%)	3 (0.2%)	0	1 (0.2%)
滑液包炎	0	2 (0.3%)	0	1 (0.2%)	0	3 (0.2%)	0	0
椎間板変性症	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	2 (0.3%)

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-28 データカットオフ日までに眼以外に発現した有害事象（DME 統合）（続）

Pooled(YOSEMITE and RHINE)
(N=1887)

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
筋骨格痛	2 (0.3%)	3 (0.5%)	0	0	2 (0.2%)	3 (0.2%)	0	0
骨粗鬆症	0	0	1 (0.2%)	2 (0.3%)	1 (<0.1%)	2 (0.2%)	0	1 (0.2%)
側弯症	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	1 (0.2%)
腱炎	1 (0.2%)	2 (0.3%)	0	0	1 (<0.1%)	2 (0.2%)	0	1 (0.2%)
弾発指	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	1 (0.2%)
デュプイトラン拘縮	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	1 (0.2%)
腰部脊柱管狭窄症	0	0	1 (0.2%)	2 (0.3%)	1 (<0.1%)	2 (0.2%)	0	0
筋骨格系胸痛	0	0	0	2 (0.3%)	0	2 (0.2%)	0	0
多発性関節炎	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	0
リウマチ性多発筋痛	0	2 (0.3%)	0	0	0	2 (0.2%)	0	0
関節リウマチ	2 (0.3%)	2 (0.3%)	0	0	2 (0.2%)	2 (0.2%)	0	0
脊椎炎	0	1 (0.2%)	0	0	0	1 (<0.1%)	1 (0.2%)	1 (0.2%)
脊椎すべり症	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	0
関節障害	0	0	0	0	0	0	0	1 (0.2%)
骨代謝障害	0	0	0	0	0	0	0	1 (0.2%)
慢性腎臓病に伴う骨ミネラル代謝異常	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
尾骨痛	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
外骨腫	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
椎間関節症候群	0	0	0	0	0	0	0	1 (0.2%)
関節拘縮	0	0	0	0	0	0	0	1 (0.2%)
関節滲出液	0	0	0	0	0	0	0	1 (0.2%)
関節腫脹	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
四肢不快感	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
四肢腫瘤	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
咀嚼障害	0	0	0	0	0	0	0	1 (0.2%)
中足骨痛	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
運動性低下	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
筋拘縮	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
筋障害	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
ミオパチー	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
骨端症	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
乾癬性関節症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-28 データカットオフ日までに眼以外に発現した有害事象（DME 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887)							
	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
横紋筋融解症	0	0	0	0	0	0	0	1 (0.2%)
交感神経性後頚部症候群	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
滑液嚢腫	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
椎間孔狭窄	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
胃腸障害								
Total number of patients with at least one adverse event	11 (1.7%)	88 (14.0%)	18 (2.8%)	77 (12.2%)	29 (2.3%)	165 (13.1%)	20 (3.2%)	69 (11.0%)
Total number of events	17	132	29	127	46	259	47	134
悪心	1 (0.2%)	17 (2.7%)	3 (0.5%)	14 (2.2%)	4 (0.3%)	31 (2.5%)	7 (1.1%)	22 (3.5%)
嘔吐	2 (0.3%)	20 (3.2%)	2 (0.3%)	7 (1.1%)	4 (0.3%)	27 (2.1%)	4 (0.6%)	13 (2.1%)
下痢	0	10 (1.6%)	3 (0.5%)	10 (1.6%)	3 (0.2%)	20 (1.6%)	2 (0.3%)	10 (1.6%)
便秘	2 (0.3%)	7 (1.1%)	2 (0.3%)	7 (1.1%)	4 (0.3%)	14 (1.1%)	6 (1.0%)	12 (1.9%)
胃食道逆流性疾患	1 (0.2%)	8 (1.3%)	1 (0.2%)	9 (1.4%)	2 (0.2%)	17 (1.3%)	0	8 (1.3%)
上腹部痛	0	6 (1.0%)	0	5 (0.8%)	0	11 (0.9%)	3 (0.5%)	4 (0.6%)
齲歯	0	6 (1.0%)	2 (0.3%)	5 (0.8%)	2 (0.2%)	11 (0.9%)	0	2 (0.3%)
消化不良	0	2 (0.3%)	2 (0.3%)	6 (0.9%)	2 (0.2%)	8 (0.6%)	1 (0.2%)	3 (0.5%)
胃炎	1 (0.2%)	4 (0.6%)	0	5 (0.8%)	1 (<0.1%)	9 (0.7%)	0	2 (0.3%)
腹痛	0	2 (0.3%)	3 (0.5%)	3 (0.5%)	3 (0.2%)	5 (0.4%)	0	4 (0.6%)
嚥下障害	0	1 (0.2%)	0	2 (0.3%)	0	3 (0.2%)	1 (0.2%)	6 (1.0%)
歯痛	0	1 (0.2%)	2 (0.3%)	3 (0.5%)	2 (0.2%)	4 (0.3%)	1 (0.2%)	4 (0.6%)
大腸炎	0	2 (0.3%)	0	2 (0.3%)	0	4 (0.3%)	1 (0.2%)	3 (0.5%)
食中毒	0	2 (0.3%)	0	1 (0.2%)	0	3 (0.2%)	1 (0.2%)	2 (0.3%)
痔核	0	1 (0.2%)	0	2 (0.3%)	0	3 (0.2%)	1 (0.2%)	2 (0.3%)
裂孔ヘルニア	1 (0.2%)	2 (0.3%)	0	1 (0.2%)	1 (<0.1%)	3 (0.2%)	1 (0.2%)	2 (0.3%)
大腸ポリープ	0	1 (0.2%)	0	4 (0.6%)	0	5 (0.4%)	0	0
食道炎	0	0	1 (0.2%)	4 (0.6%)	1 (<0.1%)	4 (0.3%)	0	1 (0.2%)
腸憩室	1 (0.2%)	2 (0.3%)	0	1 (0.2%)	1 (<0.1%)	3 (0.2%)	1 (0.2%)	1 (0.2%)
胃腸出血	1 (0.2%)	2 (0.3%)	0	2 (0.3%)	1 (<0.1%)	4 (0.3%)	0	0
血便排泄	0	2 (0.3%)	0	0	0	2 (0.2%)	1 (0.2%)	2 (0.3%)
腹部不快感	1 (0.2%)	1 (0.2%)	1 (0.2%)	1 (0.2%)	2 (0.2%)	2 (0.2%)	1 (0.2%)	1 (0.2%)
下腹部痛	0	2 (0.3%)	0	1 (0.2%)	0	3 (0.2%)	0	0
腹水	0	1 (0.2%)	2 (0.3%)	2 (0.3%)	2 (0.2%)	3 (0.2%)	0	0

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-28 データカットオフ日までに眼以外に発現した有害事象（DME 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887)							
	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
胃排出不全	0	3 (0.5%)	0	0	0	3 (0.2%)	0	0
膵炎	0	3 (0.5%)	0	0	0	3 (0.2%)	0	0
腹部ヘルニア	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	0
潰瘍性大腸炎	0	1 (0.2%)	1 (0.2%)	1 (0.2%)	1 (<0.1%)	2 (0.2%)	0	0
憩室	0	0	0	1 (0.2%)	0	1 (<0.1%)	1 (0.2%)	1 (0.2%)
十二指腸炎	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	1 (0.2%)
鼓腸	0	1 (0.2%)	1 (0.2%)	1 (0.2%)	1 (<0.1%)	2 (0.2%)	0	0
胃ポリープ	0	0	0	2 (0.3%)	0	2 (0.2%)	0	0
びらん性胃炎	0	1 (0.2%)	0	0	0	1 (<0.1%)	1 (0.2%)	1 (0.2%)
過敏性腸症候群	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	1 (0.2%)
直腸出血	0	0	0	1 (0.2%)	0	1 (<0.1%)	1 (0.2%)	1 (0.2%)
腹部膨満	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
後天性食道ウエッブ	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
裂肛	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
痔瘻	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
肛門失禁	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
肛門直腸静脈瘤	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
慢性胃炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
歯嚢胞	0	0	0	0	0	0	0	1 (0.2%)
糖尿病性胃不全麻痺	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
口内乾燥	0	0	0	0	0	0	0	1 (0.2%)
十二指腸ポリープ	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
十二指腸胃逆流	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
小腸炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
腸炎	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
びらん性食道炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
胃前庭部毛細血管拡張症	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
胃障害	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
胃十二指腸潰瘍	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
胃腸異形成	0	0	0	0	0	0	0	1 (0.2%)
消化管運動過剰	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
消化器痛	0	0	0	0	0	0	0	1 (0.2%)
歯肉嚢胞	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-28 データカットオフ日までに眼以外に発現した有害事象（DME 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887)							
	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
歯肉退縮	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
歯肉腫脹	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
血栓性痔核	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
イレウス	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
腸管虚血	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
腸管ポリープ	0	0	0	0	0	0	0	1 (0.2%)
下部消化管出血	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
非感染性唾液腺炎	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
閉塞性膵炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
食道腫瘤	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
食道静脈瘤出血	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
口腔瘻	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
急性膵炎	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
慢性膵炎	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
逆流性胃炎	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
埋伏歯	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
上部消化管出血	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
口蓋垂炎	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
傷害、中毒および処置合併症								
Total number of patients with at least one adverse event	18 (2.9%)	78 (12.4%)	17 (2.7%)	68 (10.8%)	35 (2.8%)	146 (11.6%)	17 (2.7%)	67 (10.7%)
Total number of events	24	115	22	104	46	219	22	90
転倒	7 (1.1%)	30 (4.8%)	5 (0.8%)	23 (3.6%)	12 (1.0%)	53 (4.2%)	4 (0.6%)	19 (3.0%)
四肢損傷	1 (0.2%)	3 (0.5%)	0	4 (0.6%)	1 (<0.1%)	7 (0.6%)	2 (0.3%)	7 (1.1%)
皮膚裂傷	1 (0.2%)	5 (0.8%)	3 (0.5%)	7 (1.1%)	4 (0.3%)	12 (1.0%)	0	2 (0.3%)
挫傷	2 (0.3%)	4 (0.6%)	2 (0.3%)	5 (0.8%)	4 (0.3%)	9 (0.7%)	1 (0.2%)	4 (0.6%)
足骨折	1 (0.2%)	7 (1.1%)	0	1 (0.2%)	1 (<0.1%)	8 (0.6%)	1 (0.2%)	3 (0.5%)
肋骨骨折	0	3 (0.5%)	1 (0.2%)	3 (0.5%)	1 (<0.1%)	6 (0.5%)	1 (0.2%)	5 (0.8%)
皮膚擦過傷	1 (0.2%)	5 (0.8%)	2 (0.3%)	2 (0.3%)	3 (0.2%)	7 (0.6%)	0	2 (0.3%)
節足動物咬傷	0	1 (0.2%)	1 (0.2%)	4 (0.6%)	1 (<0.1%)	5 (0.4%)	0	3 (0.5%)
頭部損傷	0	2 (0.3%)	0	1 (0.2%)	0	3 (0.2%)	2 (0.3%)	4 (0.6%)
熱傷	2 (0.3%)	4 (0.6%)	0	3 (0.5%)	2 (0.2%)	7 (0.6%)	0	0

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表 2.7.4.7-28 データカットオフ日までに眼以外に発現した有害事象（DME 統合）（続）

	Pooled(YOSEMITE and RHINE) (N=1887)							
	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
MedDRA System Organ Class MedDRA Preferred Term	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
歯牙破折	0	1 (0.2%)	0	2 (0.3%)	0	3 (0.2%)	0	4 (0.6%)
肉離れ	1 (0.2%)	2 (0.3%)	1 (0.2%)	3 (0.5%)	2 (0.2%)	5 (0.4%)	0	1 (0.2%)
処置による疼痛	0	0	1 (0.2%)	4 (0.6%)	1 (<0.1%)	4 (0.3%)	1 (0.2%)	2 (0.3%)
上肢骨折	0	1 (0.2%)	1 (0.2%)	3 (0.5%)	1 (<0.1%)	4 (0.3%)	2 (0.3%)	2 (0.3%)
大腿骨頚部骨折	0	1 (0.2%)	0	2 (0.3%)	0	3 (0.2%)	0	2 (0.3%)
靱帯捻挫	1 (0.2%)	2 (0.3%)	0	2 (0.3%)	1 (<0.1%)	4 (0.3%)	1 (0.2%)	1 (0.2%)
足関節部骨折	1 (0.2%)	2 (0.3%)	0	0	1 (<0.1%)	2 (0.2%)	0	2 (0.3%)
手骨折	1 (0.2%)	2 (0.3%)	0	2 (0.3%)	1 (<0.1%)	4 (0.3%)	0	0
手首関節骨折	0	0	0	2 (0.3%)	0	2 (0.2%)	1 (0.2%)	2 (0.3%)
大腿骨骨折	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	1 (0.2%)
関節損傷	0	2 (0.3%)	0	1 (0.2%)	0	3 (0.2%)	0	0
靱帯断裂	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	2 (0.3%)
投薬過誤	2 (0.3%)	2 (0.3%)	0	1 (0.2%)	2 (0.2%)	3 (0.2%)	0	0
動物咬傷	0	0	0	2 (0.3%)	0	2 (0.2%)	0	0
骨挫傷	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	1 (0.2%)
骨亀裂	0	0	1 (0.2%)	2 (0.3%)	1 (<0.1%)	2 (0.2%)	0	0
脳振盪	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	0
顔面骨骨折	0	0	1 (0.2%)	2 (0.3%)	1 (<0.1%)	2 (0.2%)	0	0
転位骨折	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	1 (0.2%)
上腕骨骨折	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	1 (0.2%)
関節脱臼	0	2 (0.3%)	0	0	0	2 (0.2%)	0	0
四肢骨折	0	2 (0.3%)	0	0	0	2 (0.2%)	0	0
口唇損傷	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	0
半月板損傷	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	1 (0.2%)	1 (0.2%)
鼻部損傷	0	2 (0.3%)	0	0	0	2 (0.2%)	0	0
過量投与	0	0	0	0	0	0	1 (0.2%)	2 (0.3%)
交通事故	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	1 (0.2%)
脊椎圧迫骨折	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	1 (0.2%)
脛骨骨折	1 (0.2%)	2 (0.3%)	0	0	1 (<0.1%)	2 (0.2%)	0	0
創傷	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	1 (0.2%)
事故	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
術後貧血	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
動物による引っかき傷	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0

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表 2.7.4.7-28 データカットオフ日までに眼以外に発現した有害事象（DME 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887)							
	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
動静脈瘻部位合併症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
節足動物刺傷	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
第２度熱傷	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
軟骨損傷	0	0	0	0	0	0	0	1 (0.2%)
胸部損傷	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
禁忌製品使用	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
頭蓋脳損傷	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
耳部損傷	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
上顎炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
顔面損傷	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
体内異物	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
消化管内異物	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
尾骨骨折	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
股関節部骨折	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
腸骨骨折	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
切開部位痛	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
靭帯損傷	0	0	0	0	0	0	0	1 (0.2%)
四肢外傷性切断	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
爪裂離	0	0	0	0	0	0	0	1 (0.2%)
膝蓋骨骨折	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
骨盤骨折	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
処置後炎症	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
術後呼吸不全	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
橈骨骨折	0	0	0	0	0	0	0	1 (0.2%)
鎮静合併症	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
刺創	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
腱断裂	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
歯の脱臼	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
歯牙損傷	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
創離開	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-28 データカットオフ日までに眼以外に発現した有害事象（DME 統合）（続）

Pooled(YOSEMITE and RHINE)
(N=1887)

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
血管障害								
Total number of patients with at least one adverse event	13 (2.1%)	60 (9.5%)	17 (2.7%)	77 (12.2%)	30 (2.4%)	137 (10.9%)	14 (2.2%)	66 (10.6%)
Total number of events	16	80	17	91	33	171	15	81
高血圧	5 (0.8%)	36 (5.7%)	7 (1.1%)	43 (6.8%)	12 (1.0%)	79 (6.3%)	8 (1.3%)	44 (7.0%)
低血圧	3 (0.5%)	7 (1.1%)	1 (0.2%)	7 (1.1%)	4 (0.3%)	14 (1.1%)	0	5 (0.8%)
血圧変動	1 (0.2%)	4 (0.6%)	0	3 (0.5%)	1 (<0.1%)	7 (0.6%)	1 (0.2%)	2 (0.3%)
血腫	0	0	3 (0.5%)	3 (0.5%)	3 (0.2%)	3 (0.2%)	1 (0.2%)	3 (0.5%)
動脈硬化症	1 (0.2%)	3 (0.5%)	0	2 (0.3%)	1 (<0.1%)	5 (0.4%)	0	0
高血圧クリーゼ	1 (0.2%)	1 (0.2%)	0	3 (0.5%)	1 (<0.1%)	4 (0.3%)	0	1 (0.2%)
末梢血管障害	1 (0.2%)	2 (0.3%)	1 (0.2%)	3 (0.5%)	2 (0.2%)	5 (0.4%)	0	0
血管脆弱化	0	2 (0.3%)	0	2 (0.3%)	0	4 (0.3%)	0	1 (0.2%)
末梢動脈閉塞性疾患	1 (0.2%)	2 (0.3%)	0	1 (0.2%)	1 (<0.1%)	3 (0.2%)	1 (0.2%)	1 (0.2%)
大動脈狭窄	0	1 (0.2%)	1 (0.2%)	2 (0.3%)	1 (<0.1%)	3 (0.2%)	0	0
深部静脈血栓症	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	2 (0.3%)
高血圧切迫症	0	0	0	1 (0.2%)	0	1 (<0.1%)	1 (0.2%)	2 (0.3%)
静脈炎	0	0	1 (0.2%)	3 (0.5%)	1 (<0.1%)	3 (0.2%)	0	0
静脈虚脱	0	0	0	2 (0.3%)	0	2 (0.2%)	0	1 (0.2%)
起立性低血圧	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	1 (0.2%)
末梢動脈閉塞	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	1 (0.2%)
末梢動脈狭窄	0	0	0	0	0	0	2 (0.3%)	2 (0.3%)
末梢性虚血	1 (0.2%)	1 (0.2%)	0	1 (0.2%)	1 (<0.1%)	2 (0.2%)	0	0
血栓性静脈炎	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	1 (0.2%)
動脈瘤	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
血管硬化	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
大動脈瘤	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
大動脈硬化症	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
動脈閉塞性疾患	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
コントロール不良の血圧	0	0	0	0	0	0	0	1 (0.2%)
腕頭動脈硬化症	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
塞栓症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
四肢壊死	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
高血圧緊急症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-28 データカットオフ日までに眼以外に発現した有害事象（DME 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887)							
	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
間欠性跛行	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
頚静脈血栓症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
リンパ浮腫	0	0	0	0	0	0	0	1 (0.2%)
末梢動脈血栓症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
末梢冷感	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
末梢静脈疾患	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
末梢循環不良	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
ショック	0	0	0	0	0	0	0	1 (0.2%)
鎖骨下静脈血栓症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
血栓症	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
静脈瘤	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
血管閉塞	0	0	0	0	0	0	0	1 (0.2%)
静脈破裂	0	0	0	0	0	0	0	1 (0.2%)
呼吸器、胸郭および縦隔障害								
Total number of patients with at least one adverse event	12 (1.9%)	67 (10.6%)	18 (2.8%)	65 (10.3%)	30 (2.4%)	132 (10.5%)	12 (1.9%)	46 (7.4%)
Total number of events	20	97	30	111	50	208	15	64
咳嗽	6 (1.0%)	25 (4.0%)	2 (0.3%)	22 (3.5%)	8 (0.6%)	47 (3.7%)	5 (0.8%)	15 (2.4%)
呼吸困難	2 (0.3%)	8 (1.3%)	8 (1.3%)	14 (2.2%)	10 (0.8%)	22 (1.7%)	3 (0.5%)	9 (1.4%)
胸水	1 (0.2%)	5 (0.8%)	0	6 (0.9%)	1 (<0.1%)	11 (0.9%)	1 (0.2%)	4 (0.6%)
急性呼吸不全	1 (0.2%)	3 (0.5%)	2 (0.3%)	4 (0.6%)	3 (0.2%)	7 (0.6%)	3 (0.5%)	7 (1.1%)
鼻漏	1 (0.2%)	6 (1.0%)	1 (0.2%)	7 (1.1%)	2 (0.2%)	13 (1.0%)	0	1 (0.2%)
喘息	1 (0.2%)	4 (0.6%)	1 (0.2%)	4 (0.6%)	2 (0.2%)	8 (0.6%)	0	2 (0.3%)
口腔咽頭痛	2 (0.3%)	6 (1.0%)	1 (0.2%)	1 (0.2%)	3 (0.2%)	7 (0.6%)	0	2 (0.3%)
睡眠時無呼吸症候群	0	3 (0.5%)	1 (0.2%)	2 (0.3%)	1 (<0.1%)	5 (0.4%)	0	1 (0.2%)
慢性閉塞性肺疾患	0	2 (0.3%)	1 (0.2%)	3 (0.5%)	1 (<0.1%)	5 (0.4%)	0	0
低酸素症	1 (0.2%)	1 (0.2%)	1 (0.2%)	2 (0.3%)	2 (0.2%)	3 (0.2%)	0	2 (0.3%)
鼻閉	0	4 (0.6%)	1 (0.2%)	1 (0.2%)	1 (<0.1%)	5 (0.4%)	0	0
肺水腫	1 (0.2%)	3 (0.5%)	0	1 (0.2%)	1 (<0.1%)	4 (0.3%)	0	1 (0.2%)
労作性呼吸困難	0	1 (0.2%)	0	2 (0.3%)	0	3 (0.2%)	0	1 (0.2%)
鼻出血	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	2 (0.3%)
下気道うっ血	0	0	1 (0.2%)	2 (0.3%)	1 (<0.1%)	2 (0.2%)	1 (0.2%)	2 (0.3%)

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-28 データカットオフ日までに眼以外に発現した有害事象（DME 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887)							
	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
呼吸不全	1 (0.2%)	3 (0.5%)	0	1 (0.2%)	1 (<0.1%)	4 (0.3%)	0	0
アレルギー性鼻炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	1 (0.2%)	3 (0.5%)
上気道うっ血	0	0	2 (0.3%)	4 (0.6%)	2 (0.2%)	4 (0.3%)	0	0
湿性咳嗽	1 (0.2%)	1 (0.2%)	0	1 (0.2%)	1 (<0.1%)	2 (0.2%)	0	1 (0.2%)
肺塞栓症	0	2 (0.3%)	0	0	0	2 (0.2%)	0	1 (0.2%)
肺腫瘤	1 (0.2%)	2 (0.3%)	0	0	1 (<0.1%)	2 (0.2%)	0	1 (0.2%)
上気道の炎症	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	2 (0.3%)
無気肺	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	0
気管支痙攣	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	1 (0.2%)
発声障害	0	2 (0.3%)	0	0	0	2 (0.2%)	0	0
肺嚢胞	1 (0.2%)	1 (0.2%)	0	1 (0.2%)	1 (<0.1%)	2 (0.2%)	0	0
胸膜痛	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	1 (0.2%)
肺線維症	0	0	1 (0.2%)	2 (0.3%)	1 (<0.1%)	2 (0.2%)	0	0
呼吸障害	0	2 (0.3%)	0	0	0	2 (0.2%)	0	0
副鼻腔うっ血	0	2 (0.3%)	0	0	0	2 (0.2%)	0	0
頻呼吸	0	0	1 (0.2%)	2 (0.3%)	1 (<0.1%)	2 (0.2%)	0	0
後天性横隔膜性内臓転位	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
無呼吸	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
肺気腫	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
喀血	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
喉頭浮腫	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
肺障害	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
鼻痂皮	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
副鼻腔分泌過多	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
咽頭障害	0	0	0	0	0	0	0	1 (0.2%)
誤嚥性肺炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
肺血管障害	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
呼吸停止	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
呼吸抑制	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
くしゃみ	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
気管の炎症	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-28 データカットオフ日までに眼以外に発現した有害事象（DME 統合）（続）

Pooled(YOSEMITE and RHINE)
(N=1887)

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
心臓障害								
Total number of patients with at least one adverse event	12 (1.9%)	56 (8.9%)	16 (2.5%)	55 (8.7%)	28 (2.2%)	111 (8.8%)	6 (1.0%)	46 (7.4%)
Total number of events	19	91	29	102	48	193	7	60
うっ血性心不全	8 (1.3%)	17 (2.7%)	3 (0.5%)	6 (0.9%)	11 (0.9%)	23 (1.8%)	0	7 (1.1%)
心房細動	0	7 (1.1%)	3 (0.5%)	8 (1.3%)	3 (0.2%)	15 (1.2%)	2 (0.3%)	6 (1.0%)
冠動脈疾患	1 (0.2%)	5 (0.8%)	1 (0.2%)	10 (1.6%)	2 (0.2%)	15 (1.2%)	0	4 (0.6%)
心筋梗塞	0	4 (0.6%)	2 (0.3%)	6 (0.9%)	2 (0.2%)	10 (0.8%)	1 (0.2%)	7 (1.1%)
急性心筋梗塞	2 (0.3%)	4 (0.6%)	0	3 (0.5%)	2 (0.2%)	7 (0.6%)	0	6 (1.0%)
心不全	1 (0.2%)	3 (0.5%)	0	5 (0.8%)	1 (<0.1%)	8 (0.6%)	0	5 (0.8%)
頻脈	1 (0.2%)	2 (0.3%)	1 (0.2%)	5 (0.8%)	2 (0.2%)	7 (0.6%)	1 (0.2%)	3 (0.5%)
狭心症	0	2 (0.3%)	0	4 (0.6%)	0	6 (0.5%)	0	3 (0.5%)
心筋虚血	0	4 (0.6%)	0	1 (0.2%)	0	5 (0.4%)	0	2 (0.3%)
心停止	0	4 (0.6%)	0	1 (0.2%)	0	5 (0.4%)	0	0
心拡大	1 (0.2%)	2 (0.3%)	0	1 (0.2%)	1 (<0.1%)	3 (0.2%)	0	2 (0.3%)
左室肥大	1 (0.2%)	2 (0.3%)	2 (0.3%)	3 (0.5%)	3 (0.2%)	5 (0.4%)	0	0
不整脈	0	0	0	3 (0.5%)	0	3 (0.2%)	1 (0.2%)	1 (0.2%)
冠動脈硬化症	0	0	1 (0.2%)	3 (0.5%)	1 (<0.1%)	3 (0.2%)	0	1 (0.2%)
徐脈	0	1 (0.2%)	0	2 (0.3%)	0	3 (0.2%)	1 (0.2%)	1 (0.2%)
心筋症	0	1 (0.2%)	1 (0.2%)	3 (0.5%)	1 (<0.1%)	4 (0.3%)	0	0
急性左室不全	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	2 (0.3%)
不安定狭心症	0	1 (0.2%)	2 (0.3%)	2 (0.3%)	2 (0.2%)	3 (0.2%)	0	0
慢性心不全	0	1 (0.2%)	0	2 (0.3%)	0	3 (0.2%)	0	0
慢性左室不全	0	2 (0.3%)	1 (0.2%)	1 (0.2%)	1 (<0.1%)	3 (0.2%)	0	0
虚血性心筋症	0	0	0	3 (0.5%)	0	3 (0.2%)	0	0
左室不全	0	1 (0.2%)	1 (0.2%)	2 (0.3%)	1 (<0.1%)	3 (0.2%)	0	0
僧帽弁閉鎖不全症	0	0	2 (0.3%)	3 (0.5%)	2 (0.2%)	3 (0.2%)	0	0
洞結節機能不全	0	0	1 (0.2%)	2 (0.3%)	1 (<0.1%)	2 (0.2%)	0	1 (0.2%)
三尖弁閉鎖不全症	0	0	2 (0.3%)	3 (0.5%)	2 (0.2%)	3 (0.2%)	0	0
大動脈弁閉鎖不全症	0	0	2 (0.3%)	2 (0.3%)	2 (0.2%)	2 (0.2%)	0	0
心房粗動	0	2 (0.3%)	0	0	0	2 (0.2%)	0	0
急性心不全	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	1 (0.2%)
冠動脈狭窄	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	1 (0.2%)

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-28 データカットオフ日までに眼以外に発現した有害事象（DME 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887)							
	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
拡張機能障害	1 (0.2%)	1 (0.2%)	1 (0.2%)	1 (0.2%)	2 (0.2%)	2 (0.2%)	0	0
動悸	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	0
洞性徐脈	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	1 (0.2%)
急性冠動脈症候群	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
大動脈弁狭窄	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
心房頻脈	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
房室ブロック	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
完全房室ブロック	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
脚ブロック	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
右脚ブロック	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
心細動	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
心原性ショック	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
心血管障害	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
心血管不全	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
うっ血性心筋症	0	0	0	0	0	0	0	1 (0.2%)
冠動脈閉塞	0	0	0	0	0	0	0	1 (0.2%)
高血圧性心疾患	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
左房拡張	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
左房拡大	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
左室拡張	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
心筋炎	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
心嚢液貯留	0	0	0	0	0	0	0	1 (0.2%)
心膜炎	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
右房拡張	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
右室不全	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
洞性頻脈	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
心内膜下虚血	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
上室性頻脈	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
心室性頻脈性不整脈	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
腎および尿路障害								
Total number of patients with at least one adverse event	21 (3.3%)	66 (10.5%)	12 (1.9%)	34 (5.4%)	33 (2.6%)	100 (7.9%)	12 (1.9%)	53 (8.5%)

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-28 データカットオフ日までに眼以外に発現した有害事象（DME 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887)							
	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
Total number of events	25	90	14	41	39	131	12	69
慢性腎臓病	9 (1.4%)	24 (3.8%)	1 (0.2%)	5 (0.8%)	10 (0.8%)	29 (2.3%)	1 (0.2%)	12 (1.9%)
急性腎障害	6 (1.0%)	16 (2.5%)	4 (0.6%)	8 (1.3%)	10 (0.8%)	24 (1.9%)	2 (0.3%)	12 (1.9%)
腎不全	3 (0.5%)	10 (1.6%)	0	5 (0.8%)	3 (0.2%)	15 (1.2%)	1 (0.2%)	4 (0.6%)
糖尿病性腎症	0	5 (0.8%)	0	1 (0.2%)	0	6 (0.5%)	0	4 (0.6%)
末期腎疾患	0	6 (1.0%)	0	1 (0.2%)	0	7 (0.6%)	0	2 (0.3%)
腎症	1 (0.2%)	3 (0.5%)	0	0	1 (<0.1%)	3 (0.2%)	2 (0.3%)	6 (1.0%)
腎嚢胞	1 (0.2%)	3 (0.5%)	2 (0.3%)	3 (0.5%)	3 (0.2%)	6 (0.5%)	0	2 (0.3%)
腎機能障害	1 (0.2%)	3 (0.5%)	0	1 (0.2%)	1 (<0.1%)	4 (0.3%)	1 (0.2%)	4 (0.6%)
血尿	1 (0.2%)	2 (0.3%)	3 (0.5%)	3 (0.5%)	4 (0.3%)	5 (0.4%)	1 (0.2%)	2 (0.3%)
腎結石症	0	1 (0.2%)	0	2 (0.3%)	0	3 (0.2%)	1 (0.2%)	3 (0.5%)
蛋白尿	0	2 (0.3%)	1 (0.2%)	1 (0.2%)	1 (<0.1%)	3 (0.2%)	0	2 (0.3%)
頻尿	0	0	0	0	0	0	0	3 (0.5%)
尿路の炎症	0	1 (0.2%)	0	0	0	1 (<0.1%)	1 (0.2%)	2 (0.3%)
尿路結石	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	1 (0.2%)
糖尿	0	1 (0.2%)	1 (0.2%)	1 (0.2%)	1 (<0.1%)	2 (0.2%)	0	0
水腎症	0	1 (0.2%)	1 (0.2%)	1 (0.2%)	1 (<0.1%)	2 (0.2%)	0	0
ミクロアルブミン尿	0	2 (0.3%)	0	0	0	2 (0.2%)	0	0
夜間頻尿	0	0	1 (0.2%)	2 (0.3%)	1 (<0.1%)	2 (0.2%)	0	0
腎仙痛	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	1 (0.2%)
尿失禁	0	0	0	0	0	0	1 (0.2%)	2 (0.3%)
尿閉	0	1 (0.2%)	0	0	0	1 (<0.1%)	1 (0.2%)	1 (0.2%)
高窒素血症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
膀胱嚢胞	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
膀胱壁肥厚	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
緊張性膀胱	0	0	0	0	0	0	0	1 (0.2%)
代謝性腎症	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
神経因性膀胱	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
腎動脈の動脈硬化症	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
腎動脈狭窄症	0	0	0	0	0	0	0	1 (0.2%)
尿細管間質性腎炎	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
尿道狭窄	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
尿生殖器瘻	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-28 データカットオフ日までに眼以外に発現した有害事象（DME 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887)							
	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
一般・全身障害および投与部位の状態								
Total number of patients with at least one adverse event	10 (1.6%)	51 (8.1%)	9 (1.4%)	40 (6.3%)	19 (1.5%)	91 (7.2%)	9 (1.4%)	41 (6.6%)
Total number of events	12	69	14	59	26	128	11	53
末梢性浮腫	2 (0.3%)	9 (1.4%)	2 (0.3%)	10 (1.6%)	4 (0.3%)	19 (1.5%)	1 (0.2%)	6 (1.0%)
発熱	4 (0.6%)	9 (1.4%)	3 (0.5%)	8 (1.3%)	7 (0.6%)	17 (1.3%)	1 (0.2%)	8 (1.3%)
末梢腫脹	0	7 (1.1%)	0	2 (0.3%)	0	9 (0.7%)	1 (0.2%)	8 (1.3%)
無力症	1 (0.2%)	7 (1.1%)	1 (0.2%)	6 (0.9%)	2 (0.2%)	13 (1.0%)	1 (0.2%)	3 (0.5%)
疲労	0	6 (1.0%)	2 (0.3%)	5 (0.8%)	2 (0.2%)	11 (0.9%)	0	5 (0.8%)
胸痛	0	5 (0.8%)	0	4 (0.6%)	0	9 (0.7%)	0	6 (1.0%)
死亡	1 (0.2%)	2 (0.3%)	2 (0.3%)	5 (0.8%)	3 (0.2%)	7 (0.6%)	0	0
疼痛	1 (0.2%)	4 (0.6%)	0	1 (0.2%)	1 (<0.1%)	5 (0.4%)	0	1 (0.2%)
胸部不快感	0	2 (0.3%)	0	1 (0.2%)	0	3 (0.2%)	1 (0.2%)	1 (0.2%)
倦怠感	0	1 (0.2%)	1 (0.2%)	1 (0.2%)	1 (<0.1%)	2 (0.2%)	1 (0.2%)	2 (0.3%)
悪寒	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	2 (0.3%)
歩行障害	0	2 (0.3%)	0	1 (0.2%)	0	3 (0.2%)	0	0
インフルエンザ様疾患	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	1 (0.2%)	1 (0.2%)
不快感	0	0	1 (0.2%)	2 (0.3%)	1 (<0.1%)	2 (0.2%)	0	0
顔面腫脹	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	1 (0.2%)
石灰沈着症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
嚢胞	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
薬物不耐性	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
溢出	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
顔面浮腫	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
体温変動感	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
全身健康状態悪化	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
全身性浮腫	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
異常高熱	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
高体温症	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
不明確な障害	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
疾患	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-28 データカットオフ日までに眼以外に発現した有害事象（DME 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887)							
	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
炎症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
注射部位損傷	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
限局性浮腫	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
多臓器機能不全症候群	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
壊死	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
浮腫	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
軟部組織の炎症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
腫脹	0	0	0	0	0	0	0	1 (0.2%)
治療不成功	0	0	0	0	0	0	0	1 (0.2%)
評価不能の事象	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
臨床検査								
Total number of patients with at least one adverse event	8 (1.3%)	41 (6.5%)	10 (1.6%)	43 (6.8%)	18 (1.4%)	84 (6.7%)	6 (1.0%)	48 (7.7%)
Total number of events	9	51	11	50	20	101	8	64
血中ブドウ糖増加	1 (0.2%)	3 (0.5%)	1 (0.2%)	6 (0.9%)	2 (0.2%)	9 (0.7%)	1 (0.2%)	8 (1.3%)
血圧上昇	0	2 (0.3%)	2 (0.3%)	6 (0.9%)	2 (0.2%)	8 (0.6%)	1 (0.2%)	7 (1.1%)
グリコヘモグロビン増加	1 (0.2%)	6 (1.0%)	0	3 (0.5%)	1 (<0.1%)	9 (0.7%)	0	4 (0.6%)
血中クレアチニン増加	1 (0.2%)	5 (0.8%)	0	0	1 (<0.1%)	5 (0.4%)	0	3 (0.5%)
血中ブドウ糖変動	0	2 (0.3%)	0	3 (0.5%)	0	5 (0.4%)	0	2 (0.3%)
血中カリウム増加	0	1 (0.2%)	1 (0.2%)	5 (0.8%)	1 (<0.1%)	6 (0.5%)	0	1 (0.2%)
血中尿素増加	0	1 (0.2%)	0	3 (0.5%)	0	4 (0.3%)	0	3 (0.5%)
血中コレステロール増加	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	4 (0.6%)
血中尿酸増加	0	2 (0.3%)	0	0	0	2 (0.2%)	0	3 (0.5%)
トロポニン増加	2 (0.3%)	2 (0.3%)	0	0	2 (0.2%)	2 (0.2%)	1 (0.2%)	2 (0.3%)
血中鉄減少	0	1 (0.2%)	0	2 (0.3%)	0	3 (0.2%)	0	0
尿中ブドウ糖陽性	1 (0.2%)	2 (0.3%)	0	0	1 (<0.1%)	2 (0.2%)	0	1 (0.2%)
眼圧上昇	2 (0.3%)	3 (0.5%)	0	0	2 (0.2%)	3 (0.2%)	0	0
前立腺特異性抗原増加	0	2 (0.3%)	0	1 (0.2%)	0	3 (0.2%)	0	0
体重増加	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	2 (0.3%)
アラニンアミノトランスフェラーゼ増加	0	2 (0.3%)	0	0	0	2 (0.2%)	0	0
アスパラギン酸アミノトランスフェラーゼ増加	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	0
駆出率減少	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	1 (0.2%)

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表 2.7.4.7-28 データカットオフ日までに眼以外に発現した有害事象（DME 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887)							
	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
糸球体濾過率減少	1 (0.2%)	2 (0.3%)	0	0	1 (<0.1%)	2 (0.2%)	0	0
ヘモグロビン減少	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	1 (0.2%)
血小板数減少	0	0	1 (0.2%)	2 (0.3%)	1 (<0.1%)	2 (0.2%)	0	0
腎機能検査異常	0	0	2 (0.3%)	2 (0.3%)	2 (0.2%)	2 (0.2%)	0	0
白血球数増加	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	1 (0.2%)
アミラーゼ増加	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
心血管造影	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
胸腔吸引	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
細菌検査陽性	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
血中重炭酸塩減少	0	0	0	0	0	0	0	1 (0.2%)
血中カルシウム減少	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
血中クレアチン増加	0	0	0	0	0	0	0	1 (0.2%)
血中クレアチニン異常	0	0	0	0	0	0	0	1 (0.2%)
血中ブドウ糖減少	0	0	0	0	0	0	0	1 (0.2%)
血中マグネシウム減少	0	0	0	0	0	0	0	1 (0.2%)
血中カリウム減少	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
血圧異常	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
拡張期血圧上昇	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
収縮期血圧上昇	0	0	0	0	0	0	0	1 (0.2%)
血中ナトリウム減少	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
血中テストステロン増加	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
血中甲状腺刺激ホルモン減少	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
血中尿酸異常	0	0	0	0	0	0	0	1 (0.2%)
体温上昇	0	0	0	0	0	0	0	1 (0.2%)
心モニタリング	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
心雑音	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
心臓負荷試験異常	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
胸部Ｘ線異常	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
凝固時間延長	0	0	0	0	0	0	0	1 (0.2%)
コンピュータ断層撮影異常	0	0	0	0	0	0	0	1 (0.2%)
尿中結晶陽性	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
心電図Ｔ波振幅減少	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
フィブリンＤダイマー増加	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-28 データカットオフ日までに眼以外に発現した有害事象（DME 統合）（続）

Pooled(YOSEMITE and RHINE)
(N=1887)

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=630) Onset after Week 56	Faricimab 6 mg Q8W (N=630) Overall	Faricimab 6 mg PTI (N=632) Onset after Week 56	Faricimab 6 mg PTI (N=632) Overall	Faricimab 6 mg All (N=1262) Onset after Week 56	Faricimab 6 mg All (N=1262) Overall	Aflibercept 2 mg Q8W (N=625) Onset after Week 56	Aflibercept 2 mg Q8W (N=625) Overall
心拍数増加	0	0	0	0	0	0	0	1 (0.2%)
ヘリコバクター検査陽性	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
肝酵素上昇	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
Ａ型インフルエンザウイルス検査陽性	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
臨床検査異常	0	0	0	0	0	0	0	1 (0.2%)
脂質増加	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
尿中赤血球	0	0	0	0	0	0	0	1 (0.2%)
ＳＡＲＳ－ＣｏＶ－２検査陽性	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
尿検査異常	0	0	0	0	0	0	0	1 (0.2%)
尿中ウロビリノーゲン増加	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
ビタミンＢ１２増加	0	0	0	0	0	0	0	1 (0.2%)
ビタミンＤ減少	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
体重減少	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
尿中白血球陽性	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
皮膚および皮下組織障害								
Total number of patients with at least one adverse event	6 (1.0%)	43 (6.8%)	9 (1.4%)	38 (6.0%)	15 (1.2%)	81 (6.4%)	6 (1.0%)	30 (4.8%)
Total number of events	6	54	11	44	17	98	6	40
皮膚潰瘍	1 (0.2%)	8 (1.3%)	2 (0.3%)	6 (0.9%)	3 (0.2%)	14 (1.1%)	0	4 (0.6%)
糖尿病性足病変	1 (0.2%)	5 (0.8%)	0	4 (0.6%)	1 (<0.1%)	9 (0.7%)	0	6 (1.0%)
水疱	1 (0.2%)	2 (0.3%)	1 (0.2%)	4 (0.6%)	2 (0.2%)	6 (0.5%)	1 (0.2%)	4 (0.6%)
発疹	0	7 (1.1%)	0	1 (0.2%)	0	8 (0.6%)	1 (0.2%)	2 (0.3%)
接触皮膚炎	1 (0.2%)	1 (0.2%)	0	3 (0.5%)	1 (<0.1%)	4 (0.3%)	1 (0.2%)	4 (0.6%)
そう痒症	0	1 (0.2%)	0	3 (0.5%)	0	4 (0.3%)	0	4 (0.6%)
皮膚炎	0	2 (0.3%)	0	2 (0.3%)	0	4 (0.3%)	0	1 (0.2%)
光線角化症	0	1 (0.2%)	2 (0.3%)	3 (0.5%)	2 (0.2%)	4 (0.3%)	0	0
皮膚嚢腫	0	2 (0.3%)	1 (0.2%)	2 (0.3%)	1 (<0.1%)	4 (0.3%)	0	0
過角化	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	1 (0.2%)
嵌入爪	0	1 (0.2%)	0	0	0	1 (<0.1%)	1 (0.2%)	2 (0.3%)
酒さ	0	1 (0.2%)	0	2 (0.3%)	0	3 (0.2%)	0	0
脱毛症	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	1 (0.2%)
血管浮腫	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	1 (0.2%)

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-28 データカットオフ日までに眼以外に発現した有害事象（DME 統合）（続）

Pooled(YOSEMITE and RHINE)
(N=1887)

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
アトピー性皮膚炎	0	1 (0.2%)	1 (0.2%)	1 (0.2%)	1 (<0.1%)	2 (0.2%)	0	0
皮膚乾燥	0	0	0	1 (0.2%)	0	1 (<0.1%)	1 (0.2%)	1 (0.2%)
斑状出血	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	1 (0.2%)
内方発育毛	0	2 (0.3%)	0	0	0	2 (0.2%)	0	0
点状出血	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	1 (0.2%)
皮膚病変	0	2 (0.3%)	0	0	0	2 (0.2%)	0	0
蕁麻疹	0	0	0	2 (0.3%)	0	2 (0.2%)	0	0
蝶形皮疹	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
褥瘡性潰瘍	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
アレルギー性皮膚炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
糖尿病性水疱	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
糖尿病性手関節症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
糖尿病性皮膚障害	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
糖尿病性潰瘍	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
湿疹	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
手皮膚炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
硬化性苔癬	0	0	0	0	0	0	0	1 (0.2%)
機械性蕁麻疹	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
汗疹	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
爪床の炎症	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
乾癬	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
紫斑	0	0	0	0	0	0	0	1 (0.2%)
紅斑性皮疹	0	0	0	0	0	0	0	1 (0.2%)
皮膚灼熱感	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
皮膚亀裂	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
日光黒子	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
皮下気腫	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
丘疹状蕁麻疹	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-28 データカットオフ日までに眼以外に発現した有害事象（DME 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887)							
	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
血液およびリンパ系障害								
Total number of patients with at least one adverse event	5 (0.8%)	33 (5.2%)	4 (0.6%)	25 (4.0%)	9 (0.7%)	58 (4.6%)	5 (0.8%)	34 (5.4%)
Total number of events	5	36	4	31	9	67	5	40
貧血	3 (0.5%)	23 (3.7%)	4 (0.6%)	18 (2.8%)	7 (0.6%)	41 (3.2%)	4 (0.6%)	23 (3.7%)
血小板減少症	0	5 (0.8%)	0	2 (0.3%)	0	7 (0.6%)	0	1 (0.2%)
鉄欠乏性貧血	0	1 (0.2%)	0	2 (0.3%)	0	3 (0.2%)	0	2 (0.3%)
白血球増加症	0	0	0	2 (0.3%)	0	2 (0.2%)	1 (0.2%)	2 (0.3%)
腎性貧血	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	3 (0.5%)
失血性貧血	1 (0.2%)	2 (0.3%)	0	0	1 (<0.1%)	2 (0.2%)	0	0
小球性貧血	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	1 (0.2%)
巨赤芽球性貧血	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
慢性疾患の貧血	0	0	0	0	0	0	0	1 (0.2%)
溶血性尿毒症症候群	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
リンパ節炎	0	0	0	0	0	0	0	1 (0.2%)
リンパ節症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
微小血管症性溶血性貧血	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
好中球増加症	0	0	0	0	0	0	0	1 (0.2%)
汎血球減少症	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
脾臓障害	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
脾腫	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-28 データカットオフ日までに眼以外に発現した有害事象（DME 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887)							
	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
精神障害								
Total number of patients with at least one adverse event	3 (0.5%)	21 (3.3%)	5 (0.8%)	14 (2.2%)	8 (0.6%)	35 (2.8%)	6 (1.0%)	25 (4.0%)
Total number of events	4	24	5	17	9	41	6	27
不安	2 (0.3%)	4 (0.6%)	2 (0.3%)	5 (0.8%)	4 (0.3%)	9 (0.7%)	2 (0.3%)	7 (1.1%)
うつ病	1 (0.2%)	4 (0.6%)	0	2 (0.3%)	1 (<0.1%)	6 (0.5%)	1 (0.2%)	7 (1.1%)
不眠症	0	5 (0.8%)	1 (0.2%)	3 (0.5%)	1 (<0.1%)	8 (0.6%)	1 (0.2%)	5 (0.8%)
錯乱状態	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	1 (0.2%)	2 (0.3%)
激越	0	2 (0.3%)	0	0	0	2 (0.2%)	0	0
失見当識	0	2 (0.3%)	0	0	0	2 (0.2%)	0	0
精神状態変化	0	2 (0.3%)	0	0	0	2 (0.2%)	0	0
アルコール離脱症候群	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
不安障害	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
自殺既遂	0	0	0	0	0	0	0	1 (0.2%)
譫妄	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
妄想性障害、詳細不明	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
薬物乱用	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
幻視	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
気力低下	0	0	0	0	0	0	0	1 (0.2%)
気分変化	0	0	0	0	0	0	0	1 (0.2%)
パニック発作	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
処置に対する不安	0	0	0	0	0	0	0	1 (0.2%)
精神生理性不眠症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
季節性感情障害	0	0	0	0	0	0	0	1 (0.2%)
睡眠障害	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
ストレス	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
自殺念慮	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）								
Total number of patients with at least one adverse event	3 (0.5%)	16 (2.5%)	6 (0.9%)	23 (3.6%)	9 (0.7%)	39 (3.1%)	4 (0.6%)	17 (2.7%)
Total number of events	3	21	9	29	12	50	4	17

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表 2.7.4.7-28 データカットオフ日までに眼以外に発現した有害事象（DME 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887)							
	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
基底細胞癌	0	2 (0.3%)	0	3 (0.5%)	0	5 (0.4%)	0	0
結腸腺癌	0	0	0	1 (0.2%)	0	1 (<0.1%)	1 (0.2%)	3 (0.5%)
膵癌	0	1 (0.2%)	1 (0.2%)	1 (0.2%)	1 (<0.1%)	2 (0.2%)	0	1 (0.2%)
扁平上皮癌	1 (0.2%)	2 (0.3%)	1 (0.2%)	1 (0.2%)	2 (0.2%)	3 (0.2%)	0	0
子宮平滑筋腫	0	1 (0.2%)	1 (0.2%)	1 (0.2%)	1 (<0.1%)	2 (0.2%)	0	1 (0.2%)
膀胱癌	0	2 (0.3%)	0	0	0	2 (0.2%)	0	0
骨血管腫	0	1 (0.2%)	0	0	0	1 (<0.1%)	1 (0.2%)	1 (0.2%)
平滑筋腫	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	0
新生物	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	1 (0.2%)
遠隔転移を伴う膵癌	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	1 (0.2%)	1 (0.2%)
脂漏性角化症	0	1 (0.2%)	1 (0.2%)	1 (0.2%)	1 (<0.1%)	2 (0.2%)	0	0
腺癌	0	0	0	0	0	0	0	1 (0.2%)
Ｂ細胞性リンパ腫	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
乳房の良性新生物	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
副腎の良性新生物	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
甲状腺の良性新生物	0	0	0	0	0	0	0	1 (0.2%)
腎臓の良性新生物	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
胆管癌	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
膀胱移行上皮癌第２期	0	0	0	0	0	0	0	1 (0.2%)
乳癌	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
慢性リンパ性白血病	0	0	0	0	0	0	0	1 (0.2%)
結腸癌	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
遠隔転移を伴う結腸直腸癌	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
異形成母斑	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
子宮内膜癌第１期	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
ヘアリー細胞白血病	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
肝細胞癌	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
膵管内乳頭粘液性癌	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
白血病	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
脂肪腫	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
肺の悪性新生物	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
メラノサイト性母斑	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0

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表 2.7.4.7-28 データカットオフ日までに眼以外に発現した有害事象（DME 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887)							
	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
骨転移	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
皮膚の新生物	0	0	0	0	0	0	0	1 (0.2%)
リンパ腫性乳頭状嚢胞腺腫	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
形質細胞性骨髄腫	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
前立腺癌	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
腎癌	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
腎新生物	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
腎膨大細胞腫	0	0	0	0	0	0	0	1 (0.2%)
皮膚癌	0	0	0	0	0	0	0	1 (0.2%)
皮膚有棘細胞癌	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
舌の良性新生物	0	0	0	0	0	0	0	1 (0.2%)
移行上皮癌	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
腫瘍浸潤	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
腫瘍性血栓症	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-28 データカットオフ日までに眼以外に発現した有害事象（DME 統合）（続）

Pooled(YOSEMITE and RHINE)
(N=1887)

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
肝胆道系障害								
Total number of patients with at least one adverse event	2 (0.3%)	13 (2.1%)	2 (0.3%)	12 (1.9%)	4 (0.3%)	25 (2.0%)	5 (0.8%)	11 (1.8%)
Total number of events	2	17	2	14	4	31	5	13
胆石症	0	5 (0.8%)	2 (0.3%)	4 (0.6%)	2 (0.2%)	9 (0.7%)	1 (0.2%)	1 (0.2%)
脂肪肝	1 (0.2%)	2 (0.3%)	0	2 (0.3%)	1 (<0.1%)	4 (0.3%)	0	2 (0.3%)
肝硬変	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	2 (0.3%)	3 (0.5%)
胆嚢炎	1 (0.2%)	1 (0.2%)	0	2 (0.3%)	1 (<0.1%)	3 (0.2%)	0	1 (0.2%)
急性胆嚢炎	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	0
慢性胆嚢炎	0	2 (0.3%)	0	0	0	2 (0.2%)	0	0
肝腫大	0	0	0	2 (0.3%)	0	2 (0.2%)	0	0
非アルコール性脂肪性肝炎	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	0
胆管狭窄	0	0	0	0	0	0	0	1 (0.2%)
胆道ジスキネジア	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
慢性肝炎	0	0	0	0	0	0	0	1 (0.2%)
胆嚢障害	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
肝不全	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
高ビリルビン血症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
過形成性胆嚢症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
黄疸	0	0	0	0	0	0	0	1 (0.2%)
肝障害	0	0	0	0	0	0	0	1 (0.2%)
門脈拡張	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-28 データカットオフ日までに眼以外に発現した有害事象（DME 統合）（続）

Pooled(YOSEMITE and RHINE)
(N=1887)

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
生殖系および乳房障害								
Total number of patients with at least one adverse event	2 (0.3%)	10 (1.6%)	1 (0.2%)	10 (1.6%)	3 (0.2%)	20 (1.6%)	4 (0.6%)	13 (2.1%)
Total number of events	2	11	1	10	3	21	4	14
良性前立腺肥大症	1 (0.2%)	4 (0.6%)	0	4 (0.6%)	1 (<0.1%)	8 (0.6%)	1 (0.2%)	5 (0.8%)
勃起不全	0	3 (0.5%)	1 (0.2%)	1 (0.2%)	1 (<0.1%)	4 (0.3%)	0	1 (0.2%)
前立腺腫大	1 (0.2%)	2 (0.3%)	0	1 (0.2%)	1 (<0.1%)	3 (0.2%)	0	1 (0.2%)
卵巣嚢胞	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	1 (0.2%)
腺筋症	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
無月経	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
乳房嚢胞	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
閉経期症状	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
骨盤内嚢胞	0	0	0	0	0	0	0	1 (0.2%)
前立腺炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
陰部そう痒症	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
子宮出血	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
膣出血	0	0	0	0	0	0	0	1 (0.2%)
外陰膣そう痒症	0	0	0	0	0	0	0	1 (0.2%)

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-28 データカットオフ日までに眼以外に発現した有害事象（DME 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887)							
	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
耳および迷路障害								
Total number of patients with at least one adverse event	2 (0.3%)	14 (2.2%)	1 (0.2%)	7 (1.1%)	3 (0.2%)	21 (1.7%)	5 (0.8%)	10 (1.6%)
Total number of events	2	14	2	8	4	22	5	12
回転性めまい	2 (0.3%)	6 (1.0%)	0	1 (0.2%)	2 (0.2%)	7 (0.6%)	4 (0.6%)	4 (0.6%)
聴力低下	0	2 (0.3%)	0	1 (0.2%)	0	3 (0.2%)	0	2 (0.3%)
耳鳴	0	2 (0.3%)	0	1 (0.2%)	0	3 (0.2%)	0	1 (0.2%)
耳閉	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	1 (0.2%)
耳痛	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	0
突発性難聴	0	0	0	1 (0.2%)	0	1 (<0.1%)	1 (0.2%)	1 (0.2%)
伝音難聴	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
片耳難聴	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
耳管機能障害	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
メニエール病	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
乗物酔い	0	0	0	0	0	0	0	1 (0.2%)
前庭障害	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
免疫系障害								
Total number of patients with at least one adverse event	1 (0.2%)	5 (0.8%)	4 (0.6%)	12 (1.9%)	5 (0.4%)	17 (1.3%)	2 (0.3%)	6 (1.0%)
Total number of events	1	7	4	12	5	19	2	6
季節性アレルギー	0	1 (0.2%)	2 (0.3%)	7 (1.1%)	2 (0.2%)	8 (0.6%)	1 (0.2%)	3 (0.5%)
過敏症	1 (0.2%)	3 (0.5%)	1 (0.2%)	2 (0.3%)	2 (0.2%)	5 (0.4%)	0	1 (0.2%)
造影剤アレルギー	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	1 (0.2%)
節足動物咬傷アレルギー	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
アナフィラキシー反応	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
造影剤反応	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
薬物過敏症	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-28 データカットオフ日までに眼以外に発現した有害事象（DME 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887)							
	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
内分泌障害								
Total number of patients with at least one adverse event	2 (0.3%)	6 (1.0%)	1 (0.2%)	8 (1.3%)	3 (0.2%)	14 (1.1%)	1 (0.2%)	6 (1.0%)
Total number of events	2	6	1	9	3	15	1	6
甲状腺機能低下症	2 (0.3%)	4 (0.6%)	0	5 (0.8%)	2 (0.2%)	9 (0.7%)	1 (0.2%)	4 (0.6%)
自己免疫性甲状腺炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
甲状腺腫	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
副甲状腺機能亢進症	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
続発性副甲状腺機能亢進症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
副腎過形成	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
甲状腺機能亢進症	0	0	0	0	0	0	0	1 (0.2%)
性腺機能低下	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
原発性性腺機能低下	0	0	0	0	0	0	0	1 (0.2%)
外科および内科処置								
Total number of patients with at least one adverse event	2 (0.3%)	4 (0.6%)	4 (0.6%)	6 (0.9%)	6 (0.5%)	10 (0.8%)	2 (0.3%)	3 (0.5%)
Total number of events	2	4	4	6	6	10	2	3
関節固定術	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
心臓ペースメーカー挿入	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
手根管除圧	0	0	0	0	0	0	0	1 (0.2%)
胆嚢切除	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
歯内療法	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
中足骨切除	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
色素性母斑切除	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
鼻うっ血除去療法	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
術前ケア	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
外科的脊椎固定	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
ステント留置	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
足指切断	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
抜歯	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-28 データカットオフ日までに眼以外に発現した有害事象（DME 統合）（続）

Pooled(YOSEMITE and RHINE)
(N=1887)

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
眼障害								
Total number of patients with at least one adverse event	1 (0.2%)	3 (0.5%)	1 (0.2%)	2 (0.3%)	2 (0.2%)	5 (0.4%)	0	1 (0.2%)
Total number of events	1	3	1	2	2	5	0	1
白内障	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
複視	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
眼痛	0	0	0	0	0	0	0	1 (0.2%)
羞明	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
閃輝暗点	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
硝子体出血	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
** NOT CODED **								
Total number of patients with at least one adverse event	2 (0.3%)	2 (0.3%)	0	0	2 (0.2%)	2 (0.2%)	0	0
Total number of events	2	2	0	0	2	2	0	0
UNCODED	2 (0.3%)	2 (0.3%)	0	0	2 (0.2%)	2 (0.2%)	0	0
先天性、家族性および遺伝性障害								
Total number of patients with at least one adverse event	0	1 (0.2%)	0	0	0	1 (<0.1%)	1 (0.2%)	1 (0.2%)
Total number of events	0	1	0	0	0	1	1	1
皮様嚢腫	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
包茎	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

[5.3.5.3-nAMD-1 t_ae_cod_NOCUL_SE_DME_HLS を改変]

表 2.7.4.7-29　48週時までに眼以外に発現した重篤な有害事象（nAMD 統合，GR40306試験及び GR40844試験）

MedDRA System Organ Class MedDRA Preferred Term	GR40306(TENAYA) (N=669)		GR40844(LUCERNE) (N=657)		Pooled(TENAYA and LUCERNE) (N=1326)	
	Faricimab 6 mg (N=333)	Aflibercept 2 mg (N=336)	Faricimab 6 mg (N=331)	Aflibercept 2 mg (N=326)	Faricimab 6 mg (N=664)	Aflibercept 2 mg (N=662)
Total number of patients with at least one adverse event	30 (9.0%)	34 (10.1%)	38 (11.5%)	48 (14.7%)	68 (10.2%)	82 (12.4%)
Overall total number of events	42	56	51	113	93	169

MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).

表 2.7.4.7-29　48週時までに眼以外に発現した重篤な有害事象（nAMD 統合，GR40306試験及び GR40844試験）（続）

MedDRA System Organ Class MedDRA Preferred Term	GR40306(TENAYA) (N=669)		GR40844(LUCERNE) (N=657)		Pooled(TENAYA and LUCERNE) (N=1326)	
	Faricimab 6 mg (N=333)	Aflibercept 2 mg (N=336)	Faricimab 6 mg (N=331)	Aflibercept 2 mg (N=326)	Faricimab 6 mg (N=664)	Aflibercept 2 mg (N=662)
心臓障害						
Total number of patients with at least one adverse event	6 (1.8%)	5 (1.5%)	10 (3.0%)	13 (4.0%)	16 (2.4%)	18 (2.7%)
Total number of events	9	6	14	23	23	29
心房細動	3 (0.9%)	3 (0.9%)	1 (0.3%)	2 (0.6%)	4 (0.6%)	5 (0.8%)
うっ血性心不全	1 (0.3%)	1 (0.3%)	2 (0.6%)	4 (1.2%)	3 (0.5%)	5 (0.8%)
心不全	1 (0.3%)	0	1 (0.3%)	3 (0.9%)	2 (0.3%)	3 (0.5%)
急性心筋梗塞	1 (0.3%)	1 (0.3%)	1 (0.3%)	0	2 (0.3%)	1 (0.2%)
狭心症	1 (0.3%)	0	1 (0.3%)	1 (0.3%)	2 (0.3%)	1 (0.2%)
冠動脈疾患	0	0	1 (0.3%)	1 (0.3%)	1 (0.2%)	1 (0.2%)
急性左室不全	1 (0.3%)	0	0	0	1 (0.2%)	0
心肺不全	0	0	0	1 (0.3%)	0	1 (0.2%)
うっ血性心筋症	0	0	0	1 (0.3%)	0	1 (0.2%)
ドレスラー症候群	0	0	1 (0.3%)	0	1 (0.2%)	0
僧帽弁逸脱	0	1 (0.3%)	0	0	0	1 (0.2%)
心筋梗塞	0	0	0	1 (0.3%)	0	1 (0.2%)
心筋虚血	0	0	1 (0.3%)	0	1 (0.2%)	0
動悸	0	0	1 (0.3%)	0	1 (0.2%)	0
発作性房室ブロック	0	0	0	1 (0.3%)	0	1 (0.2%)
心嚢液貯留	0	0	1 (0.3%)	0	1 (0.2%)	0
心膜炎	0	0	1 (0.3%)	0	1 (0.2%)	0
収縮性心膜炎	1 (0.3%)	0	0	0	1 (0.2%)	0
心室性期外収縮	0	0	1 (0.3%)	0	1 (0.2%)	0
心室細動	0	0	1 (0.3%)	0	1 (0.2%)	0

MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).

表 2.7.4.7-29　48週時までに眼以外に発現した重篤な有害事象（nAMD 統合，GR40306試験及び GR40844試験）（続）

MedDRA System Organ Class MedDRA Preferred Term	GR40306(TENAYA) (N=669)		GR40844(LUCERNE) (N=657)		Pooled(TENAYA and LUCERNE) (N=1326)	
	Faricimab 6 mg (N=333)	Aflibercept 2 mg (N=336)	Faricimab 6 mg (N=331)	Aflibercept 2 mg (N=326)	Faricimab 6 mg (N=664)	Aflibercept 2 mg (N=662)
感染症および寄生虫症						
Total number of patients with at least one adverse event	7 (2.1%)	9 (2.7%)	5 (1.5%)	12 (3.7%)	12 (1.8%)	21 (3.2%)
Total number of events	10	9	5	16	15	25
肺炎	1 (0.3%)	3 (0.9%)	1 (0.3%)	2 (0.6%)	2 (0.3%)	5 (0.8%)
ＣＯＶＩＤ－１９	1 (0.3%)	1 (0.3%)	3 (0.9%)	1 (0.3%)	4 (0.6%)	2 (0.3%)
敗血症	0	1 (0.3%)	0	2 (0.6%)	0	3 (0.5%)
気管支炎	1 (0.3%)	0	0	1 (0.3%)	1 (0.2%)	1 (0.2%)
蜂巣炎	0	0	0	2 (0.6%)	0	2 (0.3%)
骨髄炎	0	0	1 (0.3%)	1 (0.3%)	1 (0.2%)	1 (0.2%)
敗血症性ショック	2 (0.6%)	0	0	0	2 (0.3%)	0
尿路感染	1 (0.3%)	1 (0.3%)	0	0	1 (0.2%)	1 (0.2%)
細菌性関節炎	1 (0.3%)	0	0	0	1 (0.2%)	0
胆道性敗血症	1 (0.3%)	0	0	0	1 (0.2%)	0
憩室炎	0	0	0	1 (0.3%)	0	1 (0.2%)
感染性胸水	0	0	0	1 (0.3%)	0	1 (0.2%)
感染による慢性閉塞性気道疾患の増悪	0	0	0	1 (0.3%)	0	1 (0.2%)
インフルエンザ	0	0	0	1 (0.3%)	0	1 (0.2%)
肺膿瘍	1 (0.3%)	0	0	0	1 (0.2%)	0
壊死性筋膜炎	0	0	0	1 (0.3%)	0	1 (0.2%)
細菌性肺炎	1 (0.3%)	0	0	0	1 (0.2%)	0
処置後感染	0	1 (0.3%)	0	0	0	1 (0.2%)
急性腎盂腎炎	0	0	0	1 (0.3%)	0	1 (0.2%)
副鼻腔炎	0	1 (0.3%)	0	0	0	1 (0.2%)
全身性細菌感染	0	1 (0.3%)	0	0	0	1 (0.2%)

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Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).

表 2.7.4.7-29　48週時までに眼以外に発現した重篤な有害事象（nAMD 統合，GR40306試験及び GR40844試験）（続）

MedDRA System Organ Class MedDRA Preferred Term	GR40306(TENAYA) (N=669)		GR40844(LUCERNE) (N=657)		Pooled(TENAYA and LUCERNE) (N=1326)	
	Faricimab 6 mg (N=333)	Aflibercept 2 mg (N=336)	Faricimab 6 mg (N=331)	Aflibercept 2 mg (N=326)	Faricimab 6 mg (N=664)	Aflibercept 2 mg (N=662)
神経系障害						
Total number of patients with at least one adverse event	5 (1.5%)	4 (1.2%)	7 (2.1%)	6 (1.8%)	12 (1.8%)	10 (1.5%)
Total number of events	5	4	8	13	13	17
脳血管発作	2 (0.6%)	1 (0.3%)	1 (0.3%)	3 (0.9%)	3 (0.5%)	4 (0.6%)
失神	1 (0.3%)	1 (0.3%)	1 (0.3%)	2 (0.6%)	2 (0.3%)	3 (0.5%)
虚血性脳卒中	0	0	0	2 (0.6%)	0	2 (0.3%)
一過性脳虚血発作	1 (0.3%)	0	1 (0.3%)	0	2 (0.3%)	0
脳浮腫	0	0	1 (0.3%)	0	1 (0.2%)	0
脳出血	0	0	0	1 (0.3%)	0	1 (0.2%)
浮動性めまい	0	1 (0.3%)	0	0	0	1 (0.2%)
脳症	1 (0.3%)	0	0	0	1 (0.2%)	0
発作後麻痺	0	0	1 (0.3%)	0	1 (0.2%)	0
失神寸前の状態	0	0	1 (0.3%)	0	1 (0.2%)	0
痙攣発作	0	0	0	1 (0.3%)	0	1 (0.2%)
傾眠	0	1 (0.3%)	0	0	0	1 (0.2%)
くも膜下出血	0	0	1 (0.3%)	0	1 (0.2%)	0
血栓性脳梗塞	0	0	1 (0.3%)	0	1 (0.2%)	0

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良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）						
Total number of patients with at least one adverse event	3 (0.9%)	6 (1.8%)	5 (1.5%)	7 (2.1%)	8 (1.2%)	13 (2.0%)
Total number of events	3	6	5	10	8	16
肺の悪性新生物	1 (0.3%)	1 (0.3%)	1 (0.3%)	0	2 (0.3%)	1 (0.2%)
膵癌	0	0	1 (0.3%)	1 (0.3%)	1 (0.2%)	1 (0.2%)
腺癌	0	0	1 (0.3%)	0	1 (0.2%)	0
胆管癌	0	0	0	1 (0.3%)	0	1 (0.2%)
胆道新生物	0	1 (0.3%)	0	0	0	1 (0.2%)
膀胱新生物	0	0	0	1 (0.3%)	0	1 (0.2%)
乳癌第４期	0	0	1 (0.3%)	0	1 (0.2%)	0
大腸腺腫	0	0	0	1 (0.3%)	0	1 (0.2%)
節外性辺縁帯Ｂ細胞リンパ腫（ＭＡＬＴ型）	0	0	0	1 (0.3%)	0	1 (0.2%)
胃癌	1 (0.3%)	0	0	0	1 (0.2%)	0
多形性神経膠芽細胞腫	0	0	0	1 (0.3%)	0	1 (0.2%)
良性毛包腫瘍	0	1 (0.3%)	0	0	0	1 (0.2%)
遠隔転移を伴う肺癌	0	0	0	1 (0.3%)	0	1 (0.2%)
髄膜腫	0	1 (0.3%)	0	0	0	1 (0.2%)
肝転移	0	0	0	1 (0.3%)	0	1 (0.2%)
遠隔転移を伴う神経内分泌癌	0	1 (0.3%)	0	0	0	1 (0.2%)
遠隔転移を伴う卵巣癌	0	0	1 (0.3%)	0	1 (0.2%)	0
直腸癌	1 (0.3%)	0	0	0	1 (0.2%)	0
肉腫様癌	0	0	0	1 (0.3%)	0	1 (0.2%)
肺肉腫様癌	0	0	0	1 (0.3%)	0	1 (0.2%)
舌の悪性新生物、病期不明	0	1 (0.3%)	0	0	0	1 (0.2%)

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胃腸障害						
Total number of patients with at least one adverse event	4 (1.2%)	7 (2.1%)	0	7 (2.1%)	4 (0.6%)	14 (2.1%)
Total number of events	4	8	0	13	4	21
便秘	1 (0.3%)	0	0	3 (0.9%)	1 (0.2%)	3 (0.5%)
胃腸出血	0	2 (0.6%)	0	1 (0.3%)	0	3 (0.5%)
上部消化管出血	1 (0.3%)	1 (0.3%)	0	1 (0.3%)	1 (0.2%)	2 (0.3%)
腹痛	1 (0.3%)	0	0	1 (0.3%)	1 (0.2%)	1 (0.2%)
下痢	0	1 (0.3%)	0	1 (0.3%)	0	2 (0.3%)
腹部不快感	0	1 (0.3%)	0	0	0	1 (0.2%)
腹水	0	0	0	1 (0.3%)	0	1 (0.2%)
腸憩室	0	0	0	1 (0.3%)	0	1 (0.2%)
胃炎	0	0	0	1 (0.3%)	0	1 (0.2%)
裂孔ヘルニア	1 (0.3%)	0	0	0	1 (0.2%)	0
イレウス	0	1 (0.3%)	0	0	0	1 (0.2%)
嵌頓臍径ヘルニア	0	1 (0.3%)	0	0	0	1 (0.2%)
腸閉塞	0	1 (0.3%)	0	0	0	1 (0.2%)

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傷害、中毒および処置合併症						
Total number of patients with at least one adverse event	2 (0.6%)	5 (1.5%)	5 (1.5%)	5 (1.5%)	7 (1.1%)	10 (1.5%)
Total number of events	2	6	6	6	8	12
転倒	0	1 (0.3%)	2 (0.6%)	1 (0.3%)	2 (0.3%)	2 (0.3%)
大腿骨骨折	0	2 (0.6%)	0	0	0	2 (0.3%)
股関節部骨折	0	0	2 (0.6%)	0	2 (0.3%)	0
肋骨骨折	0	0	0	2 (0.6%)	0	2 (0.3%)
術後貧血	0	1 (0.3%)	0	0	0	1 (0.2%)
節足動物咬傷	1 (0.3%)	0	0	0	1 (0.2%)	0
石綿肺症	0	0	0	1 (0.3%)	0	1 (0.2%)
損傷	0	0	1 (0.3%)	0	1 (0.2%)	0
関節脱臼	0	0	0	1 (0.3%)	0	1 (0.2%)
靱帯捻挫	0	1 (0.3%)	0	0	0	1 (0.2%)
腰椎骨折	0	0	0	1 (0.3%)	0	1 (0.2%)
脊椎圧迫骨折	1 (0.3%)	0	0	0	1 (0.2%)	0
各種物質毒性	0	1 (0.3%)	0	0	0	1 (0.2%)
上肢骨折	0	0	1 (0.3%)	0	1 (0.2%)	0

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呼吸器、胸郭および縦隔障害						
Total number of patients with at least one adverse event	2 (0.6%)	3 (0.9%)	1 (0.3%)	8 (2.5%)	3 (0.5%)	11 (1.7%)
Total number of events	2	3	1	10	3	13
慢性閉塞性肺疾患	0	0	1 (0.3%)	2 (0.6%)	1 (0.2%)	2 (0.3%)
呼吸困難	0	1 (0.3%)	0	2 (0.6%)	0	3 (0.5%)
誤嚥性肺炎	1 (0.3%)	1 (0.3%)	0	0	1 (0.2%)	1 (0.2%)
喘息	0	0	0	1 (0.3%)	0	1 (0.2%)
気管支拡張症	0	0	0	1 (0.3%)	0	1 (0.2%)
低酸素症	0	0	0	1 (0.3%)	0	1 (0.2%)
間質性肺疾患	0	0	0	1 (0.3%)	0	1 (0.2%)
肺穿孔	0	0	0	1 (0.3%)	0	1 (0.2%)
胸水	1 (0.3%)	0	0	0	1 (0.2%)	0
肺臓炎	0	0	0	1 (0.3%)	0	1 (0.2%)
肺塞栓症	0	1 (0.3%)	0	0	0	1 (0.2%)

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筋骨格系および結合組織障害						
Total number of patients with at least one adverse event	1 (0.3%)	0	5 (1.5%)	4 (1.2%)	6 (0.9%)	4 (0.6%)
Total number of events	1	0	6	4	7	4
変形性関節症	1 (0.3%)	0	2 (0.6%)	1 (0.3%)	3 (0.5%)	1 (0.2%)
関節炎	0	0	1 (0.3%)	0	1 (0.2%)	0
背部痛	0	0	1 (0.3%)	0	1 (0.2%)	0
骨折による偽関節	0	0	1 (0.3%)	0	1 (0.2%)	0
腰部脊柱管狭窄症	0	0	1 (0.3%)	0	1 (0.2%)	0
筋力低下	0	0	0	1 (0.3%)	0	1 (0.2%)
筋骨格硬直	0	0	0	1 (0.3%)	0	1 (0.2%)
横紋筋融解症	0	0	0	1 (0.3%)	0	1 (0.2%)
一般・全身障害および投与部位の状態						
Total number of patients with at least one adverse event	1 (0.3%)	2 (0.6%)	2 (0.6%)	2 (0.6%)	3 (0.5%)	4 (0.6%)
Total number of events	1	2	2	2	3	4
医薬品副作用	0	0	1 (0.3%)	0	1 (0.2%)	0
無力症	0	1 (0.3%)	0	0	0	1 (0.2%)
死亡	0	0	0	1 (0.3%)	0	1 (0.2%)
歩行障害	0	1 (0.3%)	0	0	0	1 (0.2%)
不明確な障害	0	0	1 (0.3%)	0	1 (0.2%)	0
多臓器機能不全症候群	1 (0.3%)	0	0	0	1 (0.2%)	0
疼痛	0	0	0	1 (0.3%)	0	1 (0.2%)

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血管障害						
Total number of patients with at least one adverse event	1 (0.3%)	2 (0.6%)	1 (0.3%)	2 (0.6%)	2 (0.3%)	4 (0.6%)
Total number of events	1	3	1	2	2	5
高血圧	1 (0.3%)	1 (0.3%)	0	1 (0.3%)	1 (0.2%)	2 (0.3%)
起立性低血圧	0	0	1 (0.3%)	1 (0.3%)	1 (0.2%)	1 (0.2%)
深部静脈血栓症	0	1 (0.3%)	0	0	0	1 (0.2%)
肝胆道系障害						
Total number of patients with at least one adverse event	2 (0.6%)	0	0	3 (0.9%)	2 (0.3%)	3 (0.5%)
Total number of events	2	0	0	3	2	3
胆嚢炎	1 (0.3%)	0	0	1 (0.3%)	1 (0.2%)	1 (0.2%)
胆道閉塞	0	0	0	1 (0.3%)	0	1 (0.2%)
急性胆嚢炎	0	0	0	1 (0.3%)	0	1 (0.2%)
胆石症	1 (0.3%)	0	0	0	1 (0.2%)	0
代謝および栄養障害						
Total number of patients with at least one adverse event	0	2 (0.6%)	0	3 (0.9%)	0	5 (0.8%)
Total number of events	0	2	0	4	0	6
低カリウム血症	0	1 (0.3%)	0	1 (0.3%)	0	2 (0.3%)
脱水	0	1 (0.3%)	0	0	0	1 (0.2%)
水分過負荷	0	0	0	1 (0.3%)	0	1 (0.2%)
高カリウム血症	0	0	0	1 (0.3%)	0	1 (0.2%)
ビタミンＢ１２欠乏	0	0	0	1 (0.3%)	0	1 (0.2%)

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腎および尿路障害						
Total number of patients with at least one adverse event	2 (0.6%)	2 (0.6%)	0	1 (0.3%)	2 (0.3%)	3 (0.5%)
Total number of events	2	4	0	1	2	5
急性腎障害	0	2 (0.6%)	0	0	0	2 (0.3%)
慢性腎臓病	2 (0.6%)	0	0	0	2 (0.3%)	0
出血性膀胱炎	0	0	0	1 (0.3%)	0	1 (0.2%)
血尿	0	1 (0.3%)	0	0	0	1 (0.2%)
尿閉	0	1 (0.3%)	0	0	0	1 (0.2%)
血液およびリンパ系障害						
Total number of patients with at least one adverse event	0	1 (0.3%)	1 (0.3%)	2 (0.6%)	1 (0.2%)	3 (0.5%)
Total number of events	0	1	1	3	1	4
貧血	0	1 (0.3%)	1 (0.3%)	1 (0.3%)	1 (0.2%)	2 (0.3%)
鉄欠乏性貧血	0	0	0	1 (0.3%)	0	1 (0.2%)
汎血球減少症	0	0	0	1 (0.3%)	0	1 (0.2%)
精神障害						
Total number of patients with at least one adverse event	0	1 (0.3%)	1 (0.3%)	0	1 (0.2%)	1 (0.2%)
Total number of events	0	1	1	0	1	1
大うつ病	0	1 (0.3%)	0	0	0	1 (0.2%)
混合性不安抑うつ障害	0	0	1 (0.3%)	0	1 (0.2%)	0

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耳および迷路障害						
Total number of patients with at least one adverse event	0	0	0	1 (0.3%)	0	1 (0.2%)
Total number of events	0	0	0	1	0	1
回転性めまい	0	0	0	1 (0.3%)	0	1 (0.2%)
臨床検査						
Total number of patients with at least one adverse event	0	0	1 (0.3%)	0	1 (0.2%)	0
Total number of events	0	0	1	0	1	0
体重減少	0	0	1 (0.3%)	0	1 (0.2%)	0
製品の問題						
Total number of patients with at least one adverse event	0	0	0	1 (0.3%)	0	1 (0.2%)
Total number of events	0	0	0	1	0	1
医療機器機能不良	0	0	0	1 (0.3%)	0	1 (0.2%)
生殖系および乳房障害						
Total number of patients with at least one adverse event	0	0	0	1 (0.3%)	0	1 (0.2%)
Total number of events	0	0	0	1	0	1
前立腺腫大	0	0	0	1 (0.3%)	0	1 (0.2%)

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).

表 2.7.4.7-29　48週時までに眼以外に発現した重篤な有害事象（nAMD 統合，GR40306試験及び GR40844試験）（続）

MedDRA System Organ Class MedDRA Preferred Term	GR40306(TENAYA) (N=669)		GR40844(LUCERNE) (N=657)		Pooled(TENAYA and LUCERNE) (N=1326)	
	Faricimab 6 mg (N=333)	Aflibercept 2 mg (N=336)	Faricimab 6 mg (N=331)	Aflibercept 2 mg (N=326)	Faricimab 6 mg (N=664)	Aflibercept 2 mg (N=662)
皮膚および皮下組織障害						
Total number of patients with at least one adverse event	0	1 (0.3%)	0	0	0	1 (0.2%)
Total number of events	0	1	0	0	0	1
発疹	0	1 (0.3%)	0	0	0	1 (0.2%)

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).

[5.3.5.3-nAMD-1 t_ae_NOCUL_SER_W48_SE_nAMD_HLS を改変]

表 2.7.4.7-30 データカットオフ日までに眼以外に発現した重篤な有害事象（nAMD 統合）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
	Onset after Week 48	Overall	Onset after Week 48	Overall
Total number of patients with at least one adverse event	14 (2.1%)	76 (11.4%)	18 (2.7%)	96 (14.5%)
Overall total number of events	18	111	26	195
感染症および寄生虫症				
Total number of patients with at least one adverse event	2 (0.3%)	14 (2.1%)	1 (0.2%)	22 (3.3%)
Total number of events	2	17	1	26
肺炎	0	2 (0.3%)	0	5 (0.8%)
ＣＯＶＩＤ－１９	0	4 (0.6%)	0	2 (0.3%)
尿路感染	2 (0.3%)	3 (0.5%)	0	1 (0.2%)
敗血症	0	0	0	3 (0.5%)
気管支炎	0	1 (0.2%)	0	1 (0.2%)
蜂巣炎	0	0	0	2 (0.3%)
骨髄炎	0	1 (0.2%)	0	1 (0.2%)
敗血症性ショック	0	2 (0.3%)	0	0
細菌性関節炎	0	1 (0.2%)	0	0
胆道性敗血症	0	1 (0.2%)	0	0
ＣＯＶＩＤ－１９肺炎	0	0	1 (0.2%)	1 (0.2%)
憩室炎	0	0	0	1 (0.2%)
感染性胸水	0	0	0	1 (0.2%)
感染による慢性閉塞性気道疾患の増悪	0	0	0	1 (0.2%)
インフルエンザ	0	0	0	1 (0.2%)
肺膿瘍	0	1 (0.2%)	0	0
壊死性筋膜炎	0	0	0	1 (0.2%)
細菌性肺炎	0	1 (0.2%)	0	0
処置後感染	0	0	0	1 (0.2%)
急性腎盂腎炎	0	0	0	1 (0.2%)
副鼻腔炎	0	0	0	1 (0.2%)
全身性細菌感染	0	0	0	1 (0.2%)

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-30 データカットオフ日までに眼以外に発現した重篤な有害事象（nAMD 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
	Onset after Week 48	Overall	Onset after Week 48	Overall
心臓障害				
Total number of patients with at least one adverse event	2 (0.3%)	17 (2.6%)	0	18 (2.7%)
Total number of events	2	25	0	29
心房細動	1 (0.2%)	4 (0.6%)	0	5 (0.8%)
うっ血性心不全	0	3 (0.5%)	0	5 (0.8%)
心不全	0	2 (0.3%)	0	3 (0.5%)
急性心筋梗塞	0	2 (0.3%)	0	1 (0.2%)
狭心症	0	2 (0.3%)	0	1 (0.2%)
冠動脈疾患	0	1 (0.2%)	0	1 (0.2%)
心筋梗塞	1 (0.2%)	1 (0.2%)	0	1 (0.2%)
急性左室不全	0	1 (0.2%)	0	0
心肺不全	0	0	0	1 (0.2%)
うっ血性心筋症	0	0	0	1 (0.2%)
ドレスラー症候群	0	1 (0.2%)	0	0
僧帽弁逸脱	0	0	0	1 (0.2%)
心筋虚血	0	1 (0.2%)	0	0
動悸	0	1 (0.2%)	0	0
発作性房室ブロック	0	0	0	1 (0.2%)
心嚢液貯留	0	1 (0.2%)	0	0
心膜炎	0	1 (0.2%)	0	0
収縮性心膜炎	0	1 (0.2%)	0	0
心室性期外収縮	0	1 (0.2%)	0	0
心室細動	0	1 (0.2%)	0	0

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-30 データカットオフ日までに眼以外に発現した重篤な有害事象（nAMD 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
	Onset after Week 48	Overall	Onset after Week 48	Overall
神経系障害				
Total number of patients with at least one adverse event	1 (0.2%)	12 (1.8%)	5 (0.8%)	14 (2.1%)
Total number of events	1	14	8	25
脳血管発作	0	3 (0.5%)	0	4 (0.6%)
失神	0	2 (0.3%)	2 (0.3%)	5 (0.8%)
一過性脳虚血発作	0	2 (0.3%)	1 (0.2%)	1 (0.2%)
浮動性めまい	0	0	1 (0.2%)	2 (0.3%)
虚血性脳卒中	0	0	0	2 (0.3%)
痙攣発作	1 (0.2%)	1 (0.2%)	0	1 (0.2%)
脳浮腫	0	1 (0.2%)	0	0
脳出血	0	0	0	1 (0.2%)
アルツハイマー型認知症	0	0	1 (0.2%)	1 (0.2%)
脳症	0	1 (0.2%)	0	0
頭痛	0	0	1 (0.2%)	1 (0.2%)
発作後麻痺	0	1 (0.2%)	0	0
失神寸前の状態	0	1 (0.2%)	0	0
四肢麻痺	0	0	1 (0.2%)	1 (0.2%)
傾眠	0	0	0	1 (0.2%)
くも膜下出血	0	1 (0.2%)	0	0
血栓性脳梗塞	0	1 (0.2%)	0	0
血管性認知症	0	0	1 (0.2%)	1 (0.2%)

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-30 データカットオフ日までに眼以外に発現した重篤な有害事象（nAMD 統合）（続）

	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
MedDRA System Organ Class MedDRA Preferred Term	Onset after Week 48	Overall	Onset after Week 48	Overall
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）				
Total number of patients with at least one adverse event	2 (0.3%)	10 (1.5%)	1 (0.2%)	14 (2.1%)
Total number of events	2	10	1	17
肺の悪性新生物	2 (0.3%)	4 (0.6%)	0	1 (0.2%)
膵癌	0	1 (0.2%)	0	1 (0.2%)
腺癌	0	1 (0.2%)	0	0
胆管癌	0	0	0	1 (0.2%)
胆道新生物	0	0	0	1 (0.2%)
膀胱新生物	0	0	0	1 (0.2%)
乳癌第４期	0	1 (0.2%)	0	0
大腸腺腫	0	0	0	1 (0.2%)
節外性辺縁帯Ｂ細胞リンパ腫（ＭＡＬＴ型）	0	0	0	1 (0.2%)
胃癌	0	1 (0.2%)	0	0
多形性神経膠芽細胞腫	0	0	0	1 (0.2%)
良性毛包腫瘍	0	0	0	1 (0.2%)
遠隔転移を伴う肺癌	0	0	0	1 (0.2%)
髄膜腫	0	0	0	1 (0.2%)
肝転移	0	0	0	1 (0.2%)
遠隔転移を伴う神経内分泌癌	0	0	0	1 (0.2%)
遠隔転移を伴う卵巣癌	0	1 (0.2%)	0	0
直腸癌	0	1 (0.2%)	0	0
肉腫様癌	0	0	0	1 (0.2%)
肺肉腫様癌	0	0	0	1 (0.2%)
舌の悪性新生物、病期不明	0	0	0	1 (0.2%)
腫瘍性閉塞	0	0	1 (0.2%)	1 (0.2%)

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-30 データカットオフ日までに眼以外に発現した重篤な有害事象（nAMD 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
	Onset after Week 48	Overall	Onset after Week 48	Overall
呼吸器、胸郭および縦隔障害				
Total number of patients with at least one adverse event	5 (0.8%)	7 (1.1%)	2 (0.3%)	13 (2.0%)
Total number of events	6	9	2	15
慢性閉塞性肺疾患	2 (0.3%)	3 (0.5%)	0	2 (0.3%)
呼吸困難	0	0	0	3 (0.5%)
誤嚥性肺炎	0	1 (0.2%)	0	1 (0.2%)
肺塞栓症	0	0	1 (0.2%)	2 (0.3%)
急性呼吸不全	1 (0.2%)	1 (0.2%)	0	0
喘息	0	0	0	1 (0.2%)
気管支拡張症	0	0	0	1 (0.2%)
低酸素症	0	0	0	1 (0.2%)
間質性肺疾患	0	0	0	1 (0.2%)
肺穿孔	0	0	0	1 (0.2%)
胸水	1 (0.2%)	1 (0.2%)	0	0
肺臓炎	0	0	0	1 (0.2%)
肺動脈血栓症	0	0	1 (0.2%)	1 (0.2%)
肺水腫	1 (0.2%)	1 (0.2%)	0	0
呼吸不全	1 (0.2%)	1 (0.2%)	0	0

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-30 データカットオフ日までに眼以外に発現した重篤な有害事象（nAMD 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
	Onset after Week 48	Overall	Onset after Week 48	Overall
胃腸障害				
Total number of patients with at least one adverse event	0	4 (0.6%)	2 (0.3%)	15 (2.3%)
Total number of events	0	4	2	23
便秘	0	1 (0.2%)	0	3 (0.5%)
胃腸出血	0	0	1 (0.2%)	4 (0.6%)
上部消化管出血	0	1 (0.2%)	0	2 (0.3%)
腹痛	0	1 (0.2%)	0	1 (0.2%)
下痢	0	0	0	2 (0.3%)
イレウス	0	0	1 (0.2%)	2 (0.3%)
腹部不快感	0	0	0	1 (0.2%)
腹水	0	0	0	1 (0.2%)
腸憩室	0	0	0	1 (0.2%)
胃炎	0	0	0	1 (0.2%)
裂孔ヘルニア	0	1 (0.2%)	0	0
嵌頓臍径ヘルニア	0	0	0	1 (0.2%)
腸閉塞	0	0	0	1 (0.2%)

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-30 データカットオフ日までに眼以外に発現した重篤な有害事象（nAMD 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
	Onset after Week 48	Overall	Onset after Week 48	Overall
傷害、中毒および処置合併症				
Total number of patients with at least one adverse event	1 (0.2%)	7 (1.1%)	2 (0.3%)	12 (1.8%)
Total number of events	1	9	2	14
転倒	0	2 (0.3%)	0	2 (0.3%)
股関節部骨折	0	2 (0.3%)	1 (0.2%)	1 (0.2%)
大腿骨骨折	0	0	0	2 (0.3%)
肋骨骨折	0	0	0	2 (0.3%)
術後貧血	0	0	0	1 (0.2%)
節足動物咬傷	0	1 (0.2%)	0	0
石綿肺症	0	0	0	1 (0.2%)
粉砕骨折	0	0	1 (0.2%)	1 (0.2%)
損傷	0	1 (0.2%)	0	0
関節脱臼	0	0	0	1 (0.2%)
靱帯捻挫	0	0	0	1 (0.2%)
腰椎骨折	0	0	0	1 (0.2%)
脊椎圧迫骨折	1 (0.2%)	1 (0.2%)	0	0
各種物質毒性	0	0	0	1 (0.2%)
上肢骨折	0	1 (0.2%)	0	0
筋骨格系および結合組織障害				
Total number of patients with at least one adverse event	0	6 (0.9%)	2 (0.3%)	6 (0.9%)
Total number of events	0	7	2	6
変形性関節症	0	3 (0.5%)	1 (0.2%)	2 (0.3%)
関節炎	0	1 (0.2%)	0	0
背部痛	0	1 (0.2%)	0	0
骨折による偽関節	0	1 (0.2%)	0	0
腰部脊柱管狭窄症	0	1 (0.2%)	0	0
筋力低下	0	0	0	1 (0.2%)
筋骨格硬直	0	0	0	1 (0.2%)
横紋筋融解症	0	0	0	1 (0.2%)
側弯症	0	0	1 (0.2%)	1 (0.2%)

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-30 データカットオフ日までに眼以外に発現した重篤な有害事象（nAMD 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
	Onset after Week 48	Overall	Onset after Week 48	Overall
一般・全身障害および投与部位の状態				
Total number of patients with at least one adverse event	1 (0.2%)	4 (0.6%)	2 (0.3%)	6 (0.9%)
Total number of events	1	4	2	6
無力症	1 (0.2%)	1 (0.2%)	1 (0.2%)	2 (0.3%)
医薬品副作用	0	1 (0.2%)	0	0
死亡	0	0	0	1 (0.2%)
歩行障害	0	0	0	1 (0.2%)
ヘルニア	0	0	1 (0.2%)	1 (0.2%)
不明確な障害	0	1 (0.2%)	0	0
多臓器機能不全症候群	0	1 (0.2%)	0	0
疼痛	0	0	0	1 (0.2%)
腎および尿路障害				
Total number of patients with at least one adverse event	1 (0.2%)	3 (0.5%)	2 (0.3%)	5 (0.8%)
Total number of events	1	3	2	7
急性腎障害	1 (0.2%)	1 (0.2%)	0	2 (0.3%)
慢性腎臓病	0	2 (0.3%)	1 (0.2%)	1 (0.2%)
出血性膀胱炎	0	0	0	1 (0.2%)
血尿	0	0	0	1 (0.2%)
腎不全	0	0	1 (0.2%)	1 (0.2%)
尿閉	0	0	0	1 (0.2%)
肝胆道系障害				
Total number of patients with at least one adverse event	1 (0.2%)	3 (0.5%)	1 (0.2%)	4 (0.6%)
Total number of events	1	3	1	4
胆嚢炎	1 (0.2%)	2 (0.3%)	0	1 (0.2%)
胆石症	0	1 (0.2%)	1 (0.2%)	1 (0.2%)
胆道閉塞	0	0	0	1 (0.2%)
急性胆嚢炎	0	0	0	1 (0.2%)

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-30 データカットオフ日までに眼以外に発現した重篤な有害事象（nAMD 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
	Onset after Week 48	Overall	Onset after Week 48	Overall
代謝および栄養障害				
Total number of patients with at least one adverse event	0	0	1 (0.2%)	6 (0.9%)
Total number of events	0	0	1	7
脱水	0	0	1 (0.2%)	2 (0.3%)
低カリウム血症	0	0	0	2 (0.3%)
水分過負荷	0	0	0	1 (0.2%)
高カリウム血症	0	0	0	1 (0.2%)
ビタミンＢ１２欠乏	0	0	0	1 (0.2%)
血管障害				
Total number of patients with at least one adverse event	1 (0.2%)	2 (0.3%)	0	4 (0.6%)
Total number of events	1	3	0	5
高血圧	1 (0.2%)	1 (0.2%)	0	2 (0.3%)
起立性低血圧	0	1 (0.2%)	0	1 (0.2%)
深部静脈血栓症	0	0	0	1 (0.2%)
血液およびリンパ系障害				
Total number of patients with at least one adverse event	0	1 (0.2%)	1 (0.2%)	4 (0.6%)
Total number of events	0	1	1	5
貧血	0	1 (0.2%)	1 (0.2%)	3 (0.5%)
鉄欠乏性貧血	0	0	0	1 (0.2%)
汎血球減少症	0	0	0	1 (0.2%)
精神障害				
Total number of patients with at least one adverse event	0	1 (0.2%)	0	1 (0.2%)
Total number of events	0	1	0	1
大うつ病	0	0	0	1 (0.2%)
混合性不安抑うつ障害	0	1 (0.2%)	0	0
生殖系および乳房障害				
Total number of patients with at least one adverse event	0	0	1 (0.2%)	2 (0.3%)
Total number of events	0	0	1	2
前立腺障害	0	0	1 (0.2%)	1 (0.2%)
前立腺腫大	0	0	0	1 (0.2%)

MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-30 データカットオフ日までに眼以外に発現した重篤な有害事象（nAMD 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
	Onset after Week 48	Overall	Onset after Week 48	Overall
耳および迷路障害				
Total number of patients with at least one adverse event	0	0	0	1 (0.2%)
Total number of events	0	0	0	1
回転性めまい	0	0	0	1 (0.2%)
臨床検査				
Total number of patients with at least one adverse event	0	1 (0.2%)	0	0
Total number of events	0	1	0	0
体重減少	0	1 (0.2%)	0	0
製品の問題				
Total number of patients with at least one adverse event	0	0	0	1 (0.2%)
Total number of events	0	0	0	1
医療機器機能不良	0	0	0	1 (0.2%)
皮膚および皮下組織障害				
Total number of patients with at least one adverse event	0	0	0	1 (0.2%)
Total number of events	0	0	0	1
発疹	0	0	0	1 (0.2%)

MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

[5.3.5.3-nAMD-1 t_ae_cod_NOCUL_SER_SE_nAMD_HLS を改変]

表 2.7.4.7-31　56週時までに眼以外に発現した重篤な有害事象（DME 統合，GR40349試験及び GR40398試験）

MedDRA System Organ Class MedDRA Preferred Term	GR40349(YOSEMITE) (N=937)			GR40398(RHINE) (N=950)		
	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Aflibercept 2 mg Q8W (N=311)	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Aflibercept 2 mg Q8W (N=314)
Total number of patients with at least one adverse event	75 (24.0%)	64 (20.4%)	50 (16.1%)	52 (16.4%)	39 (12.2%)	52 (16.6%)
Overall total number of events	155	95	89	82	65	86
感染症および寄生虫症						
Total number of patients with at least one adverse event	20 (6.4%)	15 (4.8%)	20 (6.4%)	20 (6.3%)	8 (2.5%)	20 (6.4%)
Total number of events	30	16	26	26	10	24
肺炎	4 (1.3%)	3 (1.0%)	5 (1.6%)	5 (1.6%)	4 (1.3%)	3 (1.0%)
蜂巣炎	3 (1.0%)	4 (1.3%)	2 (0.6%)	3 (0.9%)	1 (0.3%)	7 (2.2%)
敗血症	4 (1.3%)	0	6 (1.9%)	5 (1.6%)	0	1 (0.3%)
骨髄炎	3 (1.0%)	1 (0.3%)	3 (1.0%)	2 (0.6%)	1 (0.3%)	3 (1.0%)
糖尿病性足感染	0	1 (0.3%)	0	3 (0.9%)	0	0
尿路感染	2 (0.6%)	0	1 (0.3%)	0	0	1 (0.3%)
ＣＯＶＩＤ－１９	0	3 (1.0%)	0	0	0	0
糖尿病性壊疽	1 (0.3%)	1 (0.3%)	0	0	0	1 (0.3%)
壊疽	0	0	0	1 (0.3%)	2 (0.6%)	0
四肢膿瘍	0	0	1 (0.3%)	0	1 (0.3%)	0
肛門膿瘍	0	0	1 (0.3%)	1 (0.3%)	0	0
壊疽性蜂巣炎	0	0	1 (0.3%)	1 (0.3%)	0	0
腎盂腎炎	1 (0.3%)	0	0	1 (0.3%)	0	0
細菌性関節炎	0	0	0	0	0	1 (0.3%)
菌血症	1 (0.3%)	0	0	0	0	0
気管支炎	1 (0.3%)	0	0	0	0	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.4.7-31　56週時までに眼以外に発現した重篤な有害事象（DME 統合，GR40349試験及び GR40398試験）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887) Faricimab 6 mg Q8W (N=630)	Faricimab 6 mg PTI (N=632)	Faricimab 6 mg All (N=1262)	Aflibercept 2 mg Q8W (N=625)
Total number of patients with at least one adverse event	127 (20.2%)	103 (16.3%)	230 (18.2%)	102 (16.3%)
Overall total number of events	237	160	397	175
感染症および寄生虫症				
Total number of patients with at least one adverse event	40 (6.3%)	23 (3.6%)	63 (5.0%)	40 (6.4%)
Total number of events	56	26	82	50
肺炎	9 (1.4%)	7 (1.1%)	16 (1.3%)	8 (1.3%)
蜂巣炎	6 (1.0%)	5 (0.8%)	11 (0.9%)	9 (1.4%)
敗血症	9 (1.4%)	0	9 (0.7%)	7 (1.1%)
骨髄炎	5 (0.8%)	2 (0.3%)	7 (0.6%)	6 (1.0%)
糖尿病性足感染	3 (0.5%)	1 (0.2%)	4 (0.3%)	0
尿路感染	2 (0.3%)	0	2 (0.2%)	2 (0.3%)
ＣＯＶＩＤ－１９	0	3 (0.5%)	3 (0.2%)	0
糖尿病性壊疽	1 (0.2%)	1 (0.2%)	2 (0.2%)	1 (0.2%)
壊疽	1 (0.2%)	2 (0.3%)	3 (0.2%)	0
四肢膿瘍	0	1 (0.2%)	1 (<0.1%)	1 (0.2%)
肛門膿瘍	1 (0.2%)	0	1 (<0.1%)	1 (0.2%)
壊疽性蜂巣炎	1 (0.2%)	0	1 (<0.1%)	1 (0.2%)
腎盂腎炎	2 (0.3%)	0	2 (0.2%)	0
細菌性関節炎	0	0	0	1 (0.2%)
菌血症	1 (0.2%)	0	1 (<0.1%)	0
気管支炎	1 (0.2%)	0	1 (<0.1%)	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.4.7-31　56週時までに眼以外に発現した重篤な有害事象（DME 統合，GR40349試験及び GR40398試験）（続）

MedDRA System Organ Class MedDRA Preferred Term	GR40349(YOSEMITE) (N=937)			GR40398(RHINE) (N=950)		
	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Aflibercept 2 mg Q8W (N=311)	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Aflibercept 2 mg Q8W (N=314)
ＣＯＶＩＤ－１９肺炎	0	0	0	1 (0.3%)	0	0
感染性胆嚢炎	0	1 (0.3%)	0	0	0	0
クロストリジウム・ディフィシレ大腸炎	0	0	1 (0.3%)	0	0	0
合併症を伴う虫垂炎	0	0	1 (0.3%)	0	0	0
膀胱炎	0	0	0	1 (0.3%)	0	0
憩室炎	0	0	0	0	0	1 (0.3%)
心内膜炎	0	0	0	0	0	1 (0.3%)
丹毒	0	1 (0.3%)	0	0	0	0
大腸菌性敗血症	0	0	0	0	0	1 (0.3%)
真菌感染	1 (0.3%)	0	0	0	0	0
胆嚢蓄膿	0	0	0	0	0	1 (0.3%)
胃腸炎	0	0	0	0	0	1 (0.3%)
ノロウイルス性胃腸炎	1 (0.3%)	0	0	0	0	0
咬傷感染	1 (0.3%)	0	0	0	0	0
腎感染	1 (0.3%)	0	0	0	0	0
限局性感染	0	1 (0.3%)	0	0	0	0
細菌性肺炎	0	0	1 (0.3%)	0	0	0
大腸菌性肺炎	0	0	1 (0.3%)	0	0	0
シュードモナス性敗血症	0	0	1 (0.3%)	0	0	0
気道感染	0	0	0	1 (0.3%)	0	0
敗血症症候群	1 (0.3%)	0	0	0	0	0
副鼻腔炎	1 (0.3%)	0	0	0	0	0
ブドウ球菌感染	1 (0.3%)	0	0	0	0	0
上気道感染	0	0	0	0	1 (0.3%)	0
尿路性敗血症	1 (0.3%)	0	0	0	0	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.4.7-31　56週時までに眼以外に発現した重篤な有害事象（DME 統合，GR40349試験及び GR40398試験）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887) Faricimab 6 mg Q8W (N=630)	Faricimab 6 mg PTI (N=632)	Faricimab 6 mg All (N=1262)	Aflibercept 2 mg Q8W (N=625)
ＣＯＶＩＤ－１９肺炎	1 (0.2%)	0	1 (<0.1%)	0
感染性胆嚢炎	0	1 (0.2%)	1 (<0.1%)	0
クロストリジウム・ディフィシレ大腸炎	0	0	0	1 (0.2%)
合併症を伴う虫垂炎	0	0	0	1 (0.2%)
膀胱炎	1 (0.2%)	0	1 (<0.1%)	0
憩室炎	0	0	0	1 (0.2%)
心内膜炎	0	0	0	1 (0.2%)
丹毒	0	1 (0.2%)	1 (<0.1%)	0
大腸菌性敗血症	0	0	0	1 (0.2%)
真菌感染	1 (0.2%)	0	1 (<0.1%)	0
胆嚢蓄膿	0	0	0	1 (0.2%)
胃腸炎	0	0	0	1 (0.2%)
ノロウイルス性胃腸炎	1 (0.2%)	0	1 (<0.1%)	0
咬傷感染	1 (0.2%)	0	1 (<0.1%)	0
腎感染	1 (0.2%)	0	1 (<0.1%)	0
限局性感染	0	1 (0.2%)	1 (<0.1%)	0
細菌性肺炎	0	0	0	1 (0.2%)
大腸菌性肺炎	0	0	0	1 (0.2%)
シュードモナス性敗血症	0	0	0	1 (0.2%)
気道感染	1 (0.2%)	0	1 (<0.1%)	0
敗血症症候群	1 (0.2%)	0	1 (<0.1%)	0
副鼻腔炎	1 (0.2%)	0	1 (<0.1%)	0
ブドウ球菌感染	1 (0.2%)	0	1 (<0.1%)	0
上気道感染	0	1 (0.2%)	1 (<0.1%)	0
尿路性敗血症	1 (0.2%)	0	1 (<0.1%)	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.4.7-31　56週時までに眼以外に発現した重篤な有害事象（DME 統合，GR40349試験及び GR40398試験）（続）

MedDRA System Organ Class MedDRA Preferred Term	GR40349(YOSEMITE) (N=937)			GR40398(RHINE) (N=950)		
	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Aflibercept 2 mg Q8W (N=311)	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Aflibercept 2 mg Q8W (N=314)
心臓障害						
Total number of patients with at least one adverse event	19 (6.1%)	13 (4.2%)	15 (4.8%)	15 (4.7%)	11 (3.4%)	10 (3.2%)
Total number of events	28	16	19	17	14	13
うっ血性心不全	4 (1.3%)	0	4 (1.3%)	4 (1.3%)	2 (0.6%)	1 (0.3%)
心筋梗塞	1 (0.3%)	3 (1.0%)	4 (1.3%)	3 (0.9%)	1 (0.3%)	2 (0.6%)
急性心筋梗塞	2 (0.6%)	2 (0.6%)	4 (1.3%)	0	1 (0.3%)	2 (0.6%)
冠動脈疾患	2 (0.6%)	4 (1.3%)	2 (0.6%)	1 (0.3%)	1 (0.3%)	1 (0.3%)
心不全	0	2 (0.6%)	1 (0.3%)	1 (0.3%)	1 (0.3%)	3 (1.0%)
心停止	2 (0.6%)	0	0	2 (0.6%)	1 (0.3%)	0
狭心症	1 (0.3%)	0	1 (0.3%)	0	1 (0.3%)	1 (0.3%)
急性左室不全	0	1 (0.3%)	2 (0.6%)	0	0	0
心房細動	1 (0.3%)	0	0	1 (0.3%)	1 (0.3%)	0
心筋虚血	2 (0.6%)	0	0	1 (0.3%)	0	0
不安定狭心症	0	0	0	1 (0.3%)	1 (0.3%)	0
不整脈	0	2 (0.6%)	0	0	0	0
急性心不全	1 (0.3%)	0	0	0	0	1 (0.3%)
急性冠動脈症候群	0	0	0	0	1 (0.3%)	0
大動脈弁狭窄	0	0	0	0	1 (0.3%)	0
冠動脈硬化症	0	0	0	0	0	1 (0.3%)
心房粗動	1 (0.3%)	0	0	0	0	0
完全房室ブロック	0	1 (0.3%)	0	0	0	0
慢性心不全	0	0	0	1 (0.3%)	0	0
心血管障害	0	1 (0.3%)	0	0	0	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.4.7-31　56週時までに眼以外に発現した重篤な有害事象（DME 統合，GR40349試験及び GR40398試験）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887) Faricimab 6 mg Q8W (N=630)	Faricimab 6 mg PTI (N=632)	Faricimab 6 mg All (N=1262)	Aflibercept 2 mg Q8W (N=625)
心臓障害				
Total number of patients with at least one adverse event	34 (5.4%)	24 (3.8%)	58 (4.6%)	25 (4.0%)
Total number of events	45	30	75	32
うっ血性心不全	8 (1.3%)	2 (0.3%)	10 (0.8%)	5 (0.8%)
心筋梗塞	4 (0.6%)	4 (0.6%)	8 (0.6%)	6 (1.0%)
急性心筋梗塞	2 (0.3%)	3 (0.5%)	5 (0.4%)	6 (1.0%)
冠動脈疾患	3 (0.5%)	5 (0.8%)	8 (0.6%)	3 (0.5%)
心不全	1 (0.2%)	3 (0.5%)	4 (0.3%)	4 (0.6%)
心停止	4 (0.6%)	1 (0.2%)	5 (0.4%)	0
狭心症	1 (0.2%)	1 (0.2%)	2 (0.2%)	2 (0.3%)
急性左室不全	0	1 (0.2%)	1 (<0.1%)	2 (0.3%)
心房細動	2 (0.3%)	1 (0.2%)	3 (0.2%)	0
心筋虚血	3 (0.5%)	0	3 (0.2%)	0
不安定狭心症	1 (0.2%)	1 (0.2%)	2 (0.2%)	0
不整脈	0	2 (0.3%)	2 (0.2%)	0
急性心不全	1 (0.2%)	0	1 (<0.1%)	1 (0.2%)
急性冠動脈症候群	0	1 (0.2%)	1 (<0.1%)	0
大動脈弁狭窄	0	1 (0.2%)	1 (<0.1%)	0
冠動脈硬化症	0	0	0	1 (0.2%)
心房粗動	1 (0.2%)	0	1 (<0.1%)	0
完全房室ブロック	0	1 (0.2%)	1 (<0.1%)	0
慢性心不全	1 (0.2%)	0	1 (<0.1%)	0
心血管障害	0	1 (0.2%)	1 (<0.1%)	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.4.7-31　56週時までに眼以外に発現した重篤な有害事象（DME 統合，GR40349試験及び GR40398試験）（続）

MedDRA System Organ Class MedDRA Preferred Term	GR40349(YOSEMITE) (N=937)			GR40398(RHINE) (N=950)		
	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Aflibercept 2 mg Q8W (N=311)	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Aflibercept 2 mg Q8W (N=314)
慢性左室不全	1 (0.3%)	0	0	0	0	0
冠動脈狭窄	1 (0.3%)	0	0	0	0	0
虚血性心筋症	0	0	0	0	1 (0.3%)	0
左房拡張	1 (0.3%)	0	0	0	0	0
左室拡張	1 (0.3%)	0	0	0	0	0
心筋炎	1 (0.3%)	0	0	0	0	0
心膜炎	1 (0.3%)	0	0	0	0	0
右室不全	0	0	0	1 (0.3%)	0	0
心内膜下虚血	0	0	0	1 (0.3%)	0	0
心室性頻脈性不整脈	1 (0.3%)	0	0	0	0	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.4.7-31　56週時までに眼以外に発現した重篤な有害事象（DME 統合，GR40349試験及び GR40398試験）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887) Faricimab 6 mg Q8W (N=630)	Faricimab 6 mg PTI (N=632)	Faricimab 6 mg All (N=1262)	Aflibercept 2 mg Q8W (N=625)
慢性左室不全	1 (0.2%)	0	1 (<0.1%)	0
冠動脈狭窄	1 (0.2%)	0	1 (<0.1%)	0
虚血性心筋症	0	1 (0.2%)	1 (<0.1%)	0
左房拡張	1 (0.2%)	0	1 (<0.1%)	0
左室拡張	1 (0.2%)	0	1 (<0.1%)	0
心筋炎	1 (0.2%)	0	1 (<0.1%)	0
心膜炎	1 (0.2%)	0	1 (<0.1%)	0
右室不全	1 (0.2%)	0	1 (<0.1%)	0
心内膜下虚血	1 (0.2%)	0	1 (<0.1%)	0
心室性頻脈性不整脈	1 (0.2%)	0	1 (<0.1%)	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.4.7-31　56週時までに眼以外に発現した重篤な有害事象（DME 統合，GR40349試験及び GR40398試験）（続）

MedDRA System Organ Class MedDRA Preferred Term	GR40349(YOSEMITE) (N=937)			GR40398(RHINE) (N=950)		
	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Aflibercept 2 mg Q8W (N=311)	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Aflibercept 2 mg Q8W (N=314)
神経系障害						
Total number of patients with at least one adverse event	12 (3.8%)	9 (2.9%)	4 (1.3%)	5 (1.6%)	4 (1.3%)	3 (1.0%)
Total number of events	15	9	5	5	6	4
脳血管発作	2 (0.6%)	3 (1.0%)	1 (0.3%)	1 (0.3%)	1 (0.3%)	1 (0.3%)
虚血性脳卒中	3 (1.0%)	0	1 (0.3%)	0	0	0
失神	2 (0.6%)	1 (0.3%)	0	0	1 (0.3%)	0
脳梗塞	1 (0.3%)	0	0	1 (0.3%)	1 (0.3%)	0
一過性脳虚血発作	1 (0.3%)	1 (0.3%)	0	1 (0.3%)	0	0
脳出血	1 (0.3%)	0	0	1 (0.3%)	0	0
腰髄神経根障害	0	1 (0.3%)	1 (0.3%)	0	0	0
馬尾症候群	0	0	0	1 (0.3%)	0	0
頚髄神経根障害	0	0	0	0	0	1 (0.3%)
昏睡	1 (0.3%)	0	0	0	0	0
浮動性めまい	0	0	1 (0.3%)	0	0	0
てんかん	1 (0.3%)	0	0	0	0	0
ギラン・バレー症候群	0	0	0	0	1 (0.3%)	0
出血性卒中	0	1 (0.3%)	0	0	0	0
高血圧性脳症	0	1 (0.3%)	0	0	0	0
低酸素性虚血性脳症	1 (0.3%)	0	0	0	0	0
ラクナ脳卒中	0	0	0	0	1 (0.3%)	0
代謝性脳症	0	0	0	0	1 (0.3%)	0
失神寸前の状態	1 (0.3%)	0	0	0	0	0
脊髄圧迫	0	0	0	0	0	1 (0.3%)
中枢神経系に起因する回転性めまい	0	1 (0.3%)	0	0	0	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.4.7-31　56週時までに眼以外に発現した重篤な有害事象（DME 統合，GR40349試験及び GR40398試験）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887) Faricimab 6 mg Q8W (N=630)	Faricimab 6 mg PTI (N=632)	Faricimab 6 mg All (N=1262)	Aflibercept 2 mg Q8W (N=625)
神経系障害				
Total number of patients with at least one adverse event	17 (2.7%)	13 (2.1%)	30 (2.4%)	7 (1.1%)
Total number of events	20	15	35	9
脳血管発作	3 (0.5%)	4 (0.6%)	7 (0.6%)	2 (0.3%)
虚血性脳卒中	3 (0.5%)	0	3 (0.2%)	1 (0.2%)
失神	2 (0.3%)	2 (0.3%)	4 (0.3%)	0
脳梗塞	2 (0.3%)	1 (0.2%)	3 (0.2%)	0
一過性脳虚血発作	2 (0.3%)	1 (0.2%)	3 (0.2%)	0
脳出血	2 (0.3%)	0	2 (0.2%)	0
腰髄神経根障害	0	1 (0.2%)	1 (<0.1%)	1 (0.2%)
馬尾症候群	1 (0.2%)	0	1 (<0.1%)	0
頚髄神経根障害	0	0	0	1 (0.2%)
昏睡	1 (0.2%)	0	1 (<0.1%)	0
浮動性めまい	0	0	0	1 (0.2%)
てんかん	1 (0.2%)	0	1 (<0.1%)	0
ギラン・バレー症候群	0	1 (0.2%)	1 (<0.1%)	0
出血性卒中	0	1 (0.2%)	1 (<0.1%)	0
高血圧性脳症	0	1 (0.2%)	1 (<0.1%)	0
低酸素性虚血性脳症	1 (0.2%)	0	1 (<0.1%)	0
ラクナ脳卒中	0	1 (0.2%)	1 (<0.1%)	0
代謝性脳症	0	1 (0.2%)	1 (<0.1%)	0
失神寸前の状態	1 (0.2%)	0	1 (<0.1%)	0
脊髄圧迫	0	0	0	1 (0.2%)
中枢神経系に起因する回転性めまい	0	1 (0.2%)	1 (<0.1%)	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.4.7-31　56週時までに眼以外に発現した重篤な有害事象（DME 統合，GR40349試験及び GR40398試験）（続）

MedDRA System Organ Class MedDRA Preferred Term	GR40349(YOSEMITE) (N=937)			GR40398(RHINE) (N=950)		
	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Aflibercept 2 mg Q8W (N=311)	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Aflibercept 2 mg Q8W (N=314)
腎および尿路障害						
Total number of patients with at least one adverse event	10 (3.2%)	2 (0.6%)	9 (2.9%)	8 (2.5%)	3 (0.9%)	5 (1.6%)
Total number of events	13	2	10	8	3	5
急性腎障害	4 (1.3%)	1 (0.3%)	3 (1.0%)	2 (0.6%)	2 (0.6%)	1 (0.3%)
末期腎疾患	2 (0.6%)	0	2 (0.6%)	2 (0.6%)	1 (0.3%)	0
慢性腎臓病	1 (0.3%)	0	3 (1.0%)	1 (0.3%)	0	1 (0.3%)
腎不全	2 (0.6%)	1 (0.3%)	1 (0.3%)	0	0	1 (0.3%)
腎機能障害	1 (0.3%)	0	1 (0.3%)	0	0	0
高窒素血症	0	0	0	1 (0.3%)	0	0
尿路結石	0	0	0	0	0	1 (0.3%)
糖尿病性腎症	0	0	0	1 (0.3%)	0	0
水腎症	1 (0.3%)	0	0	0	0	0
腎嚢胞	0	0	0	1 (0.3%)	0	0
尿閉	1 (0.3%)	0	0	0	0	0
尿路の炎症	0	0	0	0	0	1 (0.3%)

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.4.7-31　56週時までに眼以外に発現した重篤な有害事象（DME 統合，GR40349試験及び GR40398試験）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887) Faricimab 6 mg Q8W (N=630)	Faricimab 6 mg PTI (N=632)	Faricimab 6 mg All (N=1262)	Aflibercept 2 mg Q8W (N=625)
腎および尿路障害				
Total number of patients with at least one adverse event	18 (2.9%)	5 (0.8%)	23 (1.8%)	14 (2.2%)
Total number of events	21	5	26	15
急性腎障害	6 (1.0%)	3 (0.5%)	9 (0.7%)	4 (0.6%)
末期腎疾患	4 (0.6%)	1 (0.2%)	5 (0.4%)	2 (0.3%)
慢性腎臓病	2 (0.3%)	0	2 (0.2%)	4 (0.6%)
腎不全	2 (0.3%)	1 (0.2%)	3 (0.2%)	2 (0.3%)
腎機能障害	1 (0.2%)	0	1 (<0.1%)	1 (0.2%)
高窒素血症	1 (0.2%)	0	1 (<0.1%)	0
尿路結石	0	0	0	1 (0.2%)
糖尿病性腎症	1 (0.2%)	0	1 (<0.1%)	0
水腎症	1 (0.2%)	0	1 (<0.1%)	0
腎嚢胞	1 (0.2%)	0	1 (<0.1%)	0
尿閉	1 (0.2%)	0	1 (<0.1%)	0
尿路の炎症	0	0	0	1 (0.2%)

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.4.7-31　56週時までに眼以外に発現した重篤な有害事象（DME 統合，GR40349試験及び GR40398試験）（続）

MedDRA System Organ Class MedDRA Preferred Term	GR40349(YOSEMITE) (N=937)			GR40398(RHINE) (N=950)		
	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Aflibercept 2 mg Q8W (N=311)	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Aflibercept 2 mg Q8W (N=314)
一般・全身障害および投与部位の状態						
Total number of patients with at least one adverse event	8 (2.6%)	5 (1.6%)	3 (1.0%)	3 (0.9%)	2 (0.6%)	4 (1.3%)
Total number of events	8	5	3	3	2	5
胸痛	2 (0.6%)	0	3 (1.0%)	0	1 (0.3%)	1 (0.3%)
発熱	1 (0.3%)	1 (0.3%)	0	0	0	3 (1.0%)
死亡	1 (0.3%)	3 (1.0%)	0	0	0	0
疲労	1 (0.3%)	0	0	0	0	0
全身健康状態悪化	1 (0.3%)	0	0	0	0	0
全身性浮腫	1 (0.3%)	0	0	0	0	0
不明確な障害	1 (0.3%)	0	0	0	0	0
炎症	0	0	0	1 (0.3%)	0	0
倦怠感	0	0	0	0	0	1 (0.3%)
多臓器機能不全症候群	0	0	0	0	1 (0.3%)	0
壊死	0	0	0	1 (0.3%)	0	0
末梢性浮腫	0	1 (0.3%)	0	0	0	0
軟部組織の炎症	0	0	0	1 (0.3%)	0	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.4.7-31　56週時までに眼以外に発現した重篤な有害事象（DME 統合，GR40349試験及び GR40398試験）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887) Faricimab 6 mg Q8W (N=630)	Faricimab 6 mg PTI (N=632)	Faricimab 6 mg All (N=1262)	Aflibercept 2 mg Q8W (N=625)
一般・全身障害および投与部位の状態				
Total number of patients with at least one adverse event	11 (1.7%)	7 (1.1%)	18 (1.4%)	7 (1.1%)
Total number of events	11	7	18	8
胸痛	2 (0.3%)	1 (0.2%)	3 (0.2%)	4 (0.6%)
発熱	1 (0.2%)	1 (0.2%)	2 (0.2%)	3 (0.5%)
死亡	1 (0.2%)	3 (0.5%)	4 (0.3%)	0
疲労	1 (0.2%)	0	1 (<0.1%)	0
全身健康状態悪化	1 (0.2%)	0	1 (<0.1%)	0
全身性浮腫	1 (0.2%)	0	1 (<0.1%)	0
不明確な障害	1 (0.2%)	0	1 (<0.1%)	0
炎症	1 (0.2%)	0	1 (<0.1%)	0
倦怠感	0	0	0	1 (0.2%)
多臓器機能不全症候群	0	1 (0.2%)	1 (<0.1%)	0
壊死	1 (0.2%)	0	1 (<0.1%)	0
末梢性浮腫	0	1 (0.2%)	1 (<0.1%)	0
軟部組織の炎症	1 (0.2%)	0	1 (<0.1%)	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.4.7-31　56週時までに眼以外に発現した重篤な有害事象（DME 統合，GR40349試験及び GR40398試験）（続）

MedDRA System Organ Class MedDRA Preferred Term	GR40349(YOSEMITE) (N=937)			GR40398(RHINE) (N=950)		
	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Aflibercept 2 mg Q8W (N=311)	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Aflibercept 2 mg Q8W (N=314)
血管障害						
Total number of patients with at least one adverse event	5 (1.6%)	4 (1.3%)	5 (1.6%)	1 (0.3%)	5 (1.6%)	5 (1.6%)
Total number of events	5	4	6	3	5	6
高血圧	1 (0.3%)	1 (0.3%)	3 (1.0%)	0	0	1 (0.3%)
低血圧	0	0	0	0	2 (0.6%)	1 (0.3%)
大動脈狭窄	1 (0.3%)	1 (0.3%)	0	0	0	0
深部静脈血栓症	0	0	1 (0.3%)	0	0	1 (0.3%)
動脈瘤	1 (0.3%)	0	0	0	0	0
動脈閉塞性疾患	0	0	0	0	1 (0.3%)	0
動脈硬化症	0	1 (0.3%)	0	0	0	0
コントロール不良の血圧	0	0	1 (0.3%)	0	0	0
塞栓症	1 (0.3%)	0	0	0	0	0
四肢壊死	0	0	0	0	1 (0.3%)	0
高血圧クリーゼ	0	0	0	0	1 (0.3%)	0
高血圧切迫症	0	0	0	0	0	1 (0.3%)
起立性低血圧	0	0	0	0	0	1 (0.3%)
末梢動脈閉塞性疾患	0	0	0	1 (0.3%)	0	0
末梢動脈血栓症	1 (0.3%)	0	0	0	0	0
末梢血管障害	0	0	0	1 (0.3%)	0	0
静脈瘤	0	1 (0.3%)	0	0	0	0

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.4.7-31　56週時までに眼以外に発現した重篤な有害事象（DME 統合，GR40349試験及び GR40398試験）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887) Faricimab 6 mg Q8W (N=630)	Faricimab 6 mg PTI (N=632)	Faricimab 6 mg All (N=1262)	Aflibercept 2 mg Q8W (N=625)
血管障害				
Total number of patients with at least one adverse event	6 (1.0%)	9 (1.4%)	15 (1.2%)	10 (1.6%)
Total number of events	8	9	17	12
高血圧	1 (0.2%)	1 (0.2%)	2 (0.2%)	4 (0.6%)
低血圧	0	2 (0.3%)	2 (0.2%)	1 (0.2%)
大動脈狭窄	1 (0.2%)	1 (0.2%)	2 (0.2%)	0
深部静脈血栓症	0	0	0	2 (0.3%)
動脈瘤	1 (0.2%)	0	1 (<0.1%)	0
動脈閉塞性疾患	0	1 (0.2%)	1 (<0.1%)	0
動脈硬化症	0	1 (0.2%)	1 (<0.1%)	0
コントロール不良の血圧	0	0	0	1 (0.2%)
塞栓症	1 (0.2%)	0	1 (<0.1%)	0
四肢壊死	0	1 (0.2%)	1 (<0.1%)	0
高血圧クリーゼ	0	1 (0.2%)	1 (<0.1%)	0
高血圧切迫症	0	0	0	1 (0.2%)
起立性低血圧	0	0	0	1 (0.2%)
末梢動脈閉塞性疾患	1 (0.2%)	0	1 (<0.1%)	0
末梢動脈血栓症	1 (0.2%)	0	1 (<0.1%)	0
末梢血管障害	1 (0.2%)	0	1 (<0.1%)	0
静脈瘤	0	1 (0.2%)	1 (<0.1%)	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.4.7-31　56週時までに眼以外に発現した重篤な有害事象（DME 統合，GR40349試験及び GR40398試験）（続）

MedDRA System Organ Class MedDRA Preferred Term	GR40349(YOSEMITE) (N=937)			GR40398(RHINE) (N=950)		
	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Aflibercept 2 mg Q8W (N=311)	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Aflibercept 2 mg Q8W (N=314)
傷害、中毒および処置合併症						
Total number of patients with at least one adverse event	5 (1.6%)	9 (2.9%)	1 (0.3%)	3 (0.9%)	2 (0.6%)	4 (1.3%)
Total number of events	5	10	1	3	4	5
大腿骨頚部骨折	0	1 (0.3%)	0	1 (0.3%)	1 (0.3%)	2 (0.6%)
転倒	1 (0.3%)	1 (0.3%)	0	0	1 (0.3%)	1 (0.3%)
大腿骨骨折	1 (0.3%)	1 (0.3%)	0	0	0	1 (0.3%)
四肢損傷	0	1 (0.3%)	0	1 (0.3%)	1 (0.3%)	0
転位骨折	0	0	0	1 (0.3%)	0	0
頭部損傷	0	1 (0.3%)	0	0	0	0
股関節部骨折	0	1 (0.3%)	0	0	0	0
腸骨骨折	0	1 (0.3%)	0	0	0	0
爪裂離	0	0	0	0	0	1 (0.3%)
骨盤骨折	0	0	0	0	1 (0.3%)	0
橈骨骨折	0	0	1 (0.3%)	0	0	0
肋骨骨折	0	1 (0.3%)	0	0	0	0
脊椎圧迫骨折	0	1 (0.3%)	0	0	0	0
熱傷	0	1 (0.3%)	0	0	0	0
脛骨骨折	1 (0.3%)	0	0	0	0	0
上肢骨折	1 (0.3%)	0	0	0	0	0
創離開	1 (0.3%)	0	0	0	0	0

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.4.7-31　56週時までに眼以外に発現した重篤な有害事象（DME 統合，GR40349試験及び GR40398試験）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887) Faricimab 6 mg Q8W (N=630)	Faricimab 6 mg PTI (N=632)	Faricimab 6 mg All (N=1262)	Aflibercept 2 mg Q8W (N=625)
傷害、中毒および処置合併症				
Total number of patients with at least one adverse event	8 (1.3%)	11 (1.7%)	19 (1.5%)	5 (0.8%)
Total number of events	8	14	22	6
大腿骨頚部骨折	1 (0.2%)	2 (0.3%)	3 (0.2%)	2 (0.3%)
転倒	1 (0.2%)	2 (0.3%)	3 (0.2%)	1 (0.2%)
大腿骨骨折	1 (0.2%)	1 (0.2%)	2 (0.2%)	1 (0.2%)
四肢損傷	1 (0.2%)	2 (0.3%)	3 (0.2%)	0
転位骨折	1 (0.2%)	0	1 (<0.1%)	0
頭部損傷	0	1 (0.2%)	1 (<0.1%)	0
股関節部骨折	0	1 (0.2%)	1 (<0.1%)	0
腸骨骨折	0	1 (0.2%)	1 (<0.1%)	0
爪裂離	0	0	0	1 (0.2%)
骨盤骨折	0	1 (0.2%)	1 (<0.1%)	0
橈骨骨折	0	0	0	1 (0.2%)
肋骨骨折	0	1 (0.2%)	1 (<0.1%)	0
脊椎圧迫骨折	0	1 (0.2%)	1 (<0.1%)	0
熱傷	0	1 (0.2%)	1 (<0.1%)	0
脛骨骨折	1 (0.2%)	0	1 (<0.1%)	0
上肢骨折	1 (0.2%)	0	1 (<0.1%)	0
創離開	1 (0.2%)	0	1 (<0.1%)	0

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.4.7-31　56週時までに眼以外に発現した重篤な有害事象（DME 統合，GR40349試験及び GR40398試験）（続）

MedDRA System Organ Class MedDRA Preferred Term	GR40349(YOSEMITE) (N=937)			GR40398(RHINE) (N=950)		
	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Aflibercept 2 mg Q8W (N=311)	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Aflibercept 2 mg Q8W (N=314)
代謝および栄養障害						
Total number of patients with at least one adverse event	7 (2.2%)	3 (1.0%)	2 (0.6%)	2 (0.6%)	4 (1.3%)	6 (1.9%)
Total number of events	11	4	2	2	4	12
低血糖	0	2 (0.6%)	0	1 (0.3%)	3 (0.9%)	0
脱水	1 (0.3%)	0	0	1 (0.3%)	0	1 (0.3%)
高血糖	2 (0.6%)	0	1 (0.3%)	0	0	0
高カリウム血症	0	1 (0.3%)	0	0	1 (0.3%)	1 (0.3%)
糖尿病	2 (0.6%)	0	0	0	0	0
糖尿病性ケトアシドーシス	1 (0.3%)	0	0	0	0	1 (0.3%)
糖尿病合併症	1 (0.3%)	0	0	0	0	0
糖尿病性末端器官損傷	0	0	0	0	0	1 (0.3%)
糖尿病性代謝代償不全	0	0	1 (0.3%)	0	0	0
痛風	0	0	0	0	0	1 (0.3%)
低カリウム血症	1 (0.3%)	0	0	0	0	0
低ナトリウム血症	1 (0.3%)	0	0	0	0	0
乳酸アシドーシス	1 (0.3%)	0	0	0	0	0
１型糖尿病	0	0	0	0	0	1 (0.3%)

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.4.7-31　56週時までに眼以外に発現した重篤な有害事象（DME 統合，GR40349試験及び GR40398試験）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887) Faricimab 6 mg Q8W (N=630)	Faricimab 6 mg PTI (N=632)	Faricimab 6 mg All (N=1262)	Aflibercept 2 mg Q8W (N=625)
代謝および栄養障害				
Total number of patients with at least one adverse event	9 (1.4%)	7 (1.1%)	16 (1.3%)	8 (1.3%)
Total number of events	13	8	21	14
低血糖	1 (0.2%)	5 (0.8%)	6 (0.5%)	0
脱水	2 (0.3%)	0	2 (0.2%)	1 (0.2%)
高血糖	2 (0.3%)	0	2 (0.2%)	1 (0.2%)
高カリウム血症	0	2 (0.3%)	2 (0.2%)	1 (0.2%)
糖尿病	2 (0.3%)	0	2 (0.2%)	0
糖尿病性ケトアシドーシス	1 (0.2%)	0	1 (<0.1%)	1 (0.2%)
糖尿病合併症	1 (0.2%)	0	1 (<0.1%)	0
糖尿病性末端器官損傷	0	0	0	1 (0.2%)
糖尿病性代謝代償不全	0	0	0	1 (0.2%)
痛風	0	0	0	1 (0.2%)
低カリウム血症	1 (0.2%)	0	1 (<0.1%)	0
低ナトリウム血症	1 (0.2%)	0	1 (<0.1%)	0
乳酸アシドーシス	1 (0.2%)	0	1 (<0.1%)	0
１型糖尿病	0	0	0	1 (0.2%)

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.4.7-31　56週時までに眼以外に発現した重篤な有害事象（DME 統合，GR40349試験及び GR40398試験）（続）

MedDRA System Organ Class MedDRA Preferred Term	GR40349(YOSEMITE) (N=937)			GR40398(RHINE) (N=950)		
	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Aflibercept 2 mg Q8W (N=311)	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Aflibercept 2 mg Q8W (N=314)
呼吸器、胸郭および縦隔障害						
Total number of patients with at least one adverse event	6 (1.9%)	4 (1.3%)	3 (1.0%)	4 (1.3%)	4 (1.3%)	1 (0.3%)
Total number of events	7	4	4	5	5	1
急性呼吸不全	2 (0.6%)	0	2 (0.6%)	0	1 (0.3%)	1 (0.3%)
呼吸困難	0	0	0	2 (0.6%)	1 (0.3%)	0
胸水	1 (0.3%)	1 (0.3%)	0	0	1 (0.3%)	0
肺塞栓症	2 (0.6%)	0	1 (0.3%)	0	0	0
呼吸不全	1 (0.3%)	0	0	1 (0.3%)	0	0
無呼吸	1 (0.3%)	0	0	0	0	0
慢性閉塞性肺疾患	0	1 (0.3%)	0	0	0	0
労作性呼吸困難	0	1 (0.3%)	0	0	0	0
低酸素症	0	0	1 (0.3%)	0	0	0
肺障害	0	0	0	0	1 (0.3%)	0
誤嚥性肺炎	0	1 (0.3%)	0	0	0	0
肺線維症	0	0	0	0	1 (0.3%)	0
肺水腫	0	0	0	1 (0.3%)	0	0
呼吸停止	0	0	0	1 (0.3%)	0	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.4.7-31　56週時までに眼以外に発現した重篤な有害事象（DME 統合，GR40349試験及び GR40398試験）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887) Faricimab 6 mg Q8W (N=630)	Faricimab 6 mg PTI (N=632)	Faricimab 6 mg All (N=1262)	Aflibercept 2 mg Q8W (N=625)
呼吸器、胸郭および縦隔障害				
Total number of patients with at least one adverse event	10 (1.6%)	8 (1.3%)	18 (1.4%)	4 (0.6%)
Total number of events	12	9	21	5
急性呼吸不全	2 (0.3%)	1 (0.2%)	3 (0.2%)	3 (0.5%)
呼吸困難	2 (0.3%)	1 (0.2%)	3 (0.2%)	0
胸水	1 (0.2%)	2 (0.3%)	3 (0.2%)	0
肺塞栓症	2 (0.3%)	0	2 (0.2%)	1 (0.2%)
呼吸不全	2 (0.3%)	0	2 (0.2%)	0
無呼吸	1 (0.2%)	0	1 (<0.1%)	0
慢性閉塞性肺疾患	0	1 (0.2%)	1 (<0.1%)	0
労作性呼吸困難	0	1 (0.2%)	1 (<0.1%)	0
低酸素症	0	0	0	1 (0.2%)
肺障害	0	1 (0.2%)	1 (<0.1%)	0
誤嚥性肺炎	0	1 (0.2%)	1 (<0.1%)	0
肺線維症	0	1 (0.2%)	1 (<0.1%)	0
肺水腫	1 (0.2%)	0	1 (<0.1%)	0
呼吸停止	1 (0.2%)	0	1 (<0.1%)	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.4.7-31　56週時までに眼以外に発現した重篤な有害事象（DME 統合，GR40349試験及び GR40398試験）（続）

MedDRA System Organ Class MedDRA Preferred Term	GR40349(YOSEMITE) (N=937)			GR40398(RHINE) (N=950)		
	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Aflibercept 2 mg Q8W (N=311)	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Aflibercept 2 mg Q8W (N=314)
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）						
Total number of patients with at least one adverse event	3 (1.0%)	6 (1.9%)	2 (0.6%)	2 (0.6%)	2 (0.6%)	2 (0.6%)
Total number of events	4	6	2	3	2	2
結腸腺癌	0	1 (0.3%)	2 (0.6%)	0	0	0
膀胱癌	1 (0.3%)	0	0	1 (0.3%)	0	0
膵癌	1 (0.3%)	0	0	0	0	1 (0.3%)
腺癌	0	0	0	0	0	1 (0.3%)
胆管癌	1 (0.3%)	0	0	0	0	0
乳癌	1 (0.3%)	0	0	0	0	0
結腸癌	0	0	0	0	1 (0.3%)	0
ヘアリー細胞白血病	0	0	0	0	1 (0.3%)	0
白血病	0	1 (0.3%)	0	0	0	0
肺の悪性新生物	0	0	0	1 (0.3%)	0	0
新生物	0	1 (0.3%)	0	0	0	0
形質細胞性骨髄腫	0	1 (0.3%)	0	0	0	0
腎新生物	0	1 (0.3%)	0	0	0	0
腫瘍浸潤	0	1 (0.3%)	0	0	0	0

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.4.7-31　56週時までに眼以外に発現した重篤な有害事象（DME 統合，GR40349試験及び GR40398試験）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887) Faricimab 6 mg Q8W (N=630)	Faricimab 6 mg PTI (N=632)	Faricimab 6 mg All (N=1262)	Aflibercept 2 mg Q8W (N=625)
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）				
Total number of patients with at least one adverse event	5 (0.8%)	8 (1.3%)	13 (1.0%)	4 (0.6%)
Total number of events	7	8	15	4
結腸腺癌	0	1 (0.2%)	1 (<0.1%)	2 (0.3%)
膀胱癌	2 (0.3%)	0	2 (0.2%)	0
膵癌	1 (0.2%)	0	1 (<0.1%)	1 (0.2%)
腺癌	0	0	0	1 (0.2%)
胆管癌	1 (0.2%)	0	1 (<0.1%)	0
乳癌	1 (0.2%)	0	1 (<0.1%)	0
結腸癌	0	1 (0.2%)	1 (<0.1%)	0
ヘアリー細胞白血病	0	1 (0.2%)	1 (<0.1%)	0
白血病	0	1 (0.2%)	1 (<0.1%)	0
肺の悪性新生物	1 (0.2%)	0	1 (<0.1%)	0
新生物	0	1 (0.2%)	1 (<0.1%)	0
形質細胞性骨髄腫	0	1 (0.2%)	1 (<0.1%)	0
腎新生物	0	1 (0.2%)	1 (<0.1%)	0
腫瘍浸潤	0	1 (0.2%)	1 (<0.1%)	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.4.7-31　56週時までに眼以外に発現した重篤な有害事象（DME 統合，GR40349試験及び GR40398試験）（続）

MedDRA System Organ Class MedDRA Preferred Term	GR40349(YOSEMITE) (N=937)			GR40398(RHINE) (N=950)		
	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Aflibercept 2 mg Q8W (N=311)	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Aflibercept 2 mg Q8W (N=314)
胃腸障害						
Total number of patients with at least one adverse event	6 (1.9%)	3 (1.0%)	1 (0.3%)	1 (0.3%)	3 (0.9%)	2 (0.6%)
Total number of events	9	3	1	1	3	2
大腸炎	1 (0.3%)	0	0	0	0	1 (0.3%)
胃腸出血	1 (0.3%)	0	0	0	1 (0.3%)	0
悪心	1 (0.3%)	0	1 (0.3%)	0	0	0
腹部ヘルニア	1 (0.3%)	0	0	0	0	0
便秘	1 (0.3%)	0	0	0	0	0
糖尿病性胃不全麻痺	0	1 (0.3%)	0	0	0	0
胃腸異形成	0	0	0	0	0	1 (0.3%)
胃食道逆流性疾患	1 (0.3%)	0	0	0	0	0
胃排出不全	0	0	0	1 (0.3%)	0	0
大腸ポリープ	0	1 (0.3%)	0	0	0	0
食道炎	0	1 (0.3%)	0	0	0	0
膵炎	1 (0.3%)	0	0	0	0	0
直腸出血	0	0	0	0	1 (0.3%)	0
上部消化管出血	0	0	0	0	1 (0.3%)	0
嘔吐	1 (0.3%)	0	0	0	0	0

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
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MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887) Faricimab 6 mg Q8W (N=630)	Faricimab 6 mg PTI (N=632)	Faricimab 6 mg All (N=1262)	Aflibercept 2 mg Q8W (N=625)
胃腸障害				
Total number of patients with at least one adverse event	7 (1.1%)	6 (0.9%)	13 (1.0%)	3 (0.5%)
Total number of events	10	6	16	3
大腸炎	1 (0.2%)	0	1 (<0.1%)	1 (0.2%)
胃腸出血	1 (0.2%)	1 (0.2%)	2 (0.2%)	0
悪心	1 (0.2%)	0	1 (<0.1%)	1 (0.2%)
腹部ヘルニア	1 (0.2%)	0	1 (<0.1%)	0
便秘	1 (0.2%)	0	1 (<0.1%)	0
糖尿病性胃不全麻痺	0	1 (0.2%)	1 (<0.1%)	0
胃腸異形成	0	0	0	1 (0.2%)
胃食道逆流性疾患	1 (0.2%)	0	1 (<0.1%)	0
胃排出不全	1 (0.2%)	0	1 (<0.1%)	0
大腸ポリープ	0	1 (0.2%)	1 (<0.1%)	0
食道炎	0	1 (0.2%)	1 (<0.1%)	0
膵炎	1 (0.2%)	0	1 (<0.1%)	0
直腸出血	0	1 (0.2%)	1 (<0.1%)	0
上部消化管出血	0	1 (0.2%)	1 (<0.1%)	0
嘔吐	1 (0.2%)	0	1 (<0.1%)	0

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.4.7-31　56週時までに眼以外に発現した重篤な有害事象（DME 統合，GR40349試験及び GR40398試験）（続）

MedDRA System Organ Class MedDRA Preferred Term	GR40349(YOSEMITE) (N=937)			GR40398(RHINE) (N=950)		
	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Aflibercept 2 mg Q8W (N=311)	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Aflibercept 2 mg Q8W (N=314)
筋骨格系および結合組織障害						
Total number of patients with at least one adverse event	5 (1.6%)	3 (1.0%)	3 (1.0%)	2 (0.6%)	0	0
Total number of events	6	4	3	2	0	0
神経障害性関節症	1 (0.3%)	0	0	1 (0.3%)	0	0
関節痛	1 (0.3%)	0	0	0	0	0
背部痛	0	1 (0.3%)	0	0	0	0
滑液包炎	0	1 (0.3%)	0	0	0	0
椎間板突出	1 (0.3%)	0	0	0	0	0
筋痙縮	1 (0.3%)	0	0	0	0	0
筋力低下	0	0	1 (0.3%)	0	0	0
筋肉痛	1 (0.3%)	0	0	0	0	0
頚部痛	0	0	1 (0.3%)	0	0	0
変形性関節症	0	0	1 (0.3%)	0	0	0
骨端症	0	1 (0.3%)	0	0	0	0
変形性脊椎症	1 (0.3%)	0	0	0	0	0
脊椎炎	0	0	0	1 (0.3%)	0	0

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
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MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887) Faricimab 6 mg Q8W (N=630)	Faricimab 6 mg PTI (N=632)	Faricimab 6 mg All (N=1262)	Aflibercept 2 mg Q8W (N=625)
筋骨格系および結合組織障害				
Total number of patients with at least one adverse event	7 (1.1%)	3 (0.5%)	10 (0.8%)	3 (0.5%)
Total number of events	8	4	12	3
神経障害性関節症	2 (0.3%)	0	2 (0.2%)	0
関節痛	1 (0.2%)	0	1 (<0.1%)	0
背部痛	0	1 (0.2%)	1 (<0.1%)	0
滑液包炎	0	1 (0.2%)	1 (<0.1%)	0
椎間板突出	1 (0.2%)	0	1 (<0.1%)	0
筋痙縮	1 (0.2%)	0	1 (<0.1%)	0
筋力低下	0	0	0	1 (0.2%)
筋肉痛	1 (0.2%)	0	1 (<0.1%)	0
頚部痛	0	0	0	1 (0.2%)
変形性関節症	0	0	0	1 (0.2%)
骨端症	0	1 (0.2%)	1 (<0.1%)	0
変形性脊椎症	1 (0.2%)	0	1 (<0.1%)	0
脊椎炎	1 (0.2%)	0	1 (<0.1%)	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.4.7-31　56週時までに眼以外に発現した重篤な有害事象（DME 統合，GR40349試験及び GR40398試験）（続）

MedDRA System Organ Class MedDRA Preferred Term	GR40349(YOSEMITE) (N=937)			GR40398(RHINE) (N=950)		
	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Aflibercept 2 mg Q8W (N=311)	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Aflibercept 2 mg Q8W (N=314)
肝胆道系障害						
Total number of patients with at least one adverse event	4 (1.3%)	1 (0.3%)	2 (0.6%)	0	2 (0.6%)	2 (0.6%)
Total number of events	7	1	2	0	2	2
胆嚢炎	0	0	0	0	1 (0.3%)	1 (0.3%)
急性胆嚢炎	1 (0.3%)	1 (0.3%)	0	0	0	0
胆石症	1 (0.3%)	0	0	0	1 (0.3%)	0
肝硬変	1 (0.3%)	0	1 (0.3%)	0	0	0
胆管狭窄	0	0	0	0	0	1 (0.3%)
胆道ジスキネジア	1 (0.3%)	0	0	0	0	0
慢性胆嚢炎	1 (0.3%)	0	0	0	0	0
慢性肝炎	0	0	1 (0.3%)	0	0	0
非アルコール性脂肪性肝炎	1 (0.3%)	0	0	0	0	0
血液およびリンパ系障害						
Total number of patients with at least one adverse event	1 (0.3%)	2 (0.6%)	0	1 (0.3%)	1 (0.3%)	3 (1.0%)
Total number of events	1	5	0	1	1	3
貧血	0	2 (0.6%)	0	1 (0.3%)	1 (0.3%)	2 (0.6%)
小球性貧血	0	0	0	0	0	1 (0.3%)
血小板減少症	1 (0.3%)	0	0	0	0	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.4.7-31　56週時までに眼以外に発現した重篤な有害事象（DME 統合，GR40349試験及び GR40398試験）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887) Faricimab 6 mg Q8W (N=630)	Faricimab 6 mg PTI (N=632)	Faricimab 6 mg All (N=1262)	Aflibercept 2 mg Q8W (N=625)
肝胆道系障害				
Total number of patients with at least one adverse event	4 (0.6%)	3 (0.5%)	7 (0.6%)	4 (0.6%)
Total number of events	7	3	10	4
胆嚢炎	0	1 (0.2%)	1 (<0.1%)	1 (0.2%)
急性胆嚢炎	1 (0.2%)	1 (0.2%)	2 (0.2%)	0
胆石症	1 (0.2%)	1 (0.2%)	2 (0.2%)	0
肝硬変	1 (0.2%)	0	1 (<0.1%)	1 (0.2%)
胆管狭窄	0	0	0	1 (0.2%)
胆道ジスキネジア	1 (0.2%)	0	1 (<0.1%)	0
慢性胆嚢炎	1 (0.2%)	0	1 (<0.1%)	0
慢性肝炎	0	0	0	1 (0.2%)
非アルコール性脂肪性肝炎	1 (0.2%)	0	1 (<0.1%)	0
血液およびリンパ系障害				
Total number of patients with at least one adverse event	2 (0.3%)	3 (0.5%)	5 (0.4%)	3 (0.5%)
Total number of events	2	6	8	3
貧血	1 (0.2%)	3 (0.5%)	4 (0.3%)	2 (0.3%)
小球性貧血	0	0	0	1 (0.2%)
血小板減少症	1 (0.2%)	0	1 (<0.1%)	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.4.7-31　56週時までに眼以外に発現した重篤な有害事象（DME 統合，GR40349試験及び GR40398試験）（続）

MedDRA System Organ Class MedDRA Preferred Term	GR40349(YOSEMITE) (N=937)			GR40398(RHINE) (N=950)		
	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Aflibercept 2 mg Q8W (N=311)	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Aflibercept 2 mg Q8W (N=314)
精神障害						
Total number of patients with at least one adverse event	3 (1.0%)	0	2 (0.6%)	1 (0.3%)	1 (0.3%)	0
Total number of events	3	0	2	1	1	0
うつ病	0	0	1 (0.3%)	1 (0.3%)	0	0
自殺既遂	0	0	1 (0.3%)	0	0	0
譫妄	0	0	0	0	1 (0.3%)	0
妄想性障害、詳細不明	1 (0.3%)	0	0	0	0	0
失見当識	1 (0.3%)	0	0	0	0	0
精神状態変化	1 (0.3%)	0	0	0	0	0
皮膚および皮下組織障害						
Total number of patients with at least one adverse event	0	1 (0.3%)	3 (1.0%)	0	2 (0.6%)	1 (0.3%)
Total number of events	0	1	3	0	2	1
糖尿病性足病変	0	1 (0.3%)	3 (1.0%)	0	2 (0.6%)	1 (0.3%)

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.4.7-31　56週時までに眼以外に発現した重篤な有害事象（DME 統合，GR40349試験及び GR40398試験）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887) Faricimab 6 mg Q8W (N=630)	Faricimab 6 mg PTI (N=632)	Faricimab 6 mg All (N=1262)	Aflibercept 2 mg Q8W (N=625)
精神障害				
Total number of patients with at least one adverse event	4 (0.6%)	1 (0.2%)	5 (0.4%)	2 (0.3%)
Total number of events	4	1	5	2
うつ病	1 (0.2%)	0	1 (<0.1%)	1 (0.2%)
自殺既遂	0	0	0	1 (0.2%)
譫妄	0	1 (0.2%)	1 (<0.1%)	0
妄想性障害、詳細不明	1 (0.2%)	0	1 (<0.1%)	0
失見当識	1 (0.2%)	0	1 (<0.1%)	0
精神状態変化	1 (0.2%)	0	1 (<0.1%)	0
皮膚および皮下組織障害				
Total number of patients with at least one adverse event	0	3 (0.5%)	3 (0.2%)	4 (0.6%)
Total number of events	0	3	3	4
糖尿病性足病変	0	3 (0.5%)	3 (0.2%)	4 (0.6%)

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.4.7-31　56週時までに眼以外に発現した重篤な有害事象（DME 統合，GR40349試験及び GR40398試験）（続）

MedDRA System Organ Class MedDRA Preferred Term	GR40349(YOSEMITE) (N=937)			GR40398(RHINE) (N=950)		
	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Aflibercept 2 mg Q8W (N=311)	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Aflibercept 2 mg Q8W (N=314)
臨床検査						
Total number of patients with at least one adverse event	2 (0.6%)	2 (0.6%)	0	1 (0.3%)	0	0
Total number of events	2	2	0	1	0	0
血中クレアチニン増加	1 (0.3%)	0	0	0	0	0
血中ブドウ糖変動	0	0	0	1 (0.3%)	0	0
血中カリウム増加	0	1 (0.3%)	0	0	0	0
血中テストステロン増加	0	1 (0.3%)	0	0	0	0
Ａ型インフルエンザウイルス検査陽性	1 (0.3%)	0	0	0	0	0
耳および迷路障害						
Total number of patients with at least one adverse event	0	2 (0.6%)	0	1 (0.3%)	0	0
Total number of events	0	2	0	1	0	0
突発性難聴	0	1 (0.3%)	0	0	0	0
耳鳴	0	0	0	1 (0.3%)	0	0
前庭障害	0	1 (0.3%)	0	0	0	0
免疫系障害						
Total number of patients with at least one adverse event	0	0	0	0	1 (0.3%)	1 (0.3%)
Total number of events	0	0	0	0	1	1
アナフィラキシー反応	0	0	0	0	1 (0.3%)	0
過敏症	0	0	0	0	0	1 (0.3%)

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.4.7-31　56週時までに眼以外に発現した重篤な有害事象（DME 統合，GR40349試験及び GR40398試験）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887) Faricimab 6 mg Q8W (N=630)	Faricimab 6 mg PTI (N=632)	Faricimab 6 mg All (N=1262)	Aflibercept 2 mg Q8W (N=625)
臨床検査				
Total number of patients with at least one adverse event	3 (0.5%)	2 (0.3%)	5 (0.4%)	0
Total number of events	3	2	5	0
血中クレアチニン増加	1 (0.2%)	0	1 (<0.1%)	0
血中ブドウ糖変動	1 (0.2%)	0	1 (<0.1%)	0
血中カリウム増加	0	1 (0.2%)	1 (<0.1%)	0
血中テストステロン増加	0	1 (0.2%)	1 (<0.1%)	0
Ａ型インフルエンザウイルス検査陽性	1 (0.2%)	0	1 (<0.1%)	0
耳および迷路障害				
Total number of patients with at least one adverse event	1 (0.2%)	2 (0.3%)	3 (0.2%)	0
Total number of events	1	2	3	0
突発性難聴	0	1 (0.2%)	1 (<0.1%)	0
耳鳴	1 (0.2%)	0	1 (<0.1%)	0
前庭障害	0	1 (0.2%)	1 (<0.1%)	0
免疫系障害				
Total number of patients with at least one adverse event	0	1 (0.2%)	1 (<0.1%)	1 (0.2%)
Total number of events	0	1	1	1
アナフィラキシー反応	0	1 (0.2%)	1 (<0.1%)	0
過敏症	0	0	0	1 (0.2%)

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.4.7-31　56週時までに眼以外に発現した重篤な有害事象（DME 統合，GR40349試験及び GR40398試験）（続）

MedDRA System Organ Class MedDRA Preferred Term	GR40349(YOSEMITE) (N=937)			GR40398(RHINE) (N=950)		
	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Aflibercept 2 mg Q8W (N=311)	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Aflibercept 2 mg Q8W (N=314)
生殖系および乳房障害						
Total number of patients with at least one adverse event	0	1 (0.3%)	0	0	0	0
Total number of events	0	1	0	0	0	0
卵巣嚢胞	0	1 (0.3%)	0	0	0	0
外科および内科処置						
Total number of patients with at least one adverse event	1 (0.3%)	0	0	0	0	0
Total number of events	1	0	0	0	0	0
胆嚢切除	1 (0.3%)	0	0	0	0	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.4.7-31　56週時までに眼以外に発現した重篤な有害事象（DME 統合，GR40349試験及び GR40398試験）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887) Faricimab 6 mg Q8W (N=630)	Faricimab 6 mg PTI (N=632)	Faricimab 6 mg All (N=1262)	Aflibercept 2 mg Q8W (N=625)
生殖系および乳房障害				
Total number of patients with at least one adverse event	0	1 (0.2%)	1 (<0.1%)	0
Total number of events	0	1	1	0
卵巣嚢胞	0	1 (0.2%)	1 (<0.1%)	0
外科および内科処置				
Total number of patients with at least one adverse event	1 (0.2%)	0	1 (<0.1%)	0
Total number of events	1	0	1	0
胆嚢切除	1 (0.2%)	0	1 (<0.1%)	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

[5.3.5.3-nAMD-1 t_ae_NOCUL_SER_W56_SE_DME_HLS を改変]

表 2.7.4.7-32 データカットオフ日までに眼以外に発現した重篤な有害事象（DME 統合）

Pooled(YOSEMITE and RHINE)
(N=1887)

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
Total number of patients with at least one adverse event	33 (5.2%)	150 (23.8%)	35 (5.5%)	126 (19.9%)	68 (5.4%)	276 (21.9%)	40 (6.4%)	132 (21.1%)
Overall total number of events	52	289	56	216	108	505	55	230
感染症および寄生虫症								
Total number of patients with at least one adverse event	13 (2.1%)	52 (8.3%)	12 (1.9%)	32 (5.1%)	25 (2.0%)	84 (6.7%)	14 (2.2%)	51 (8.2%)
Total number of events	16	72	14	40	30	112	18	68
肺炎	4 (0.6%)	13 (2.1%)	1 (0.2%)	8 (1.3%)	5 (0.4%)	21 (1.7%)	1 (0.2%)	8 (1.3%)
蜂巣炎	0	6 (1.0%)	1 (0.2%)	6 (0.9%)	1 (<0.1%)	12 (1.0%)	1 (0.2%)	10 (1.6%)
敗血症	2 (0.3%)	11 (1.7%)	0	0	2 (0.2%)	11 (0.9%)	1 (0.2%)	8 (1.3%)
骨髄炎	0	5 (0.8%)	0	2 (0.3%)	0	7 (0.6%)	1 (0.2%)	7 (1.1%)
ＣＯＶＩＤ－１９	1 (0.2%)	1 (0.2%)	4 (0.6%)	7 (1.1%)	5 (0.4%)	8 (0.6%)	2 (0.3%)	2 (0.3%)
壊疽	1 (0.2%)	2 (0.3%)	3 (0.5%)	4 (0.6%)	4 (0.3%)	6 (0.5%)	3 (0.5%)	3 (0.5%)
尿路感染	1 (0.2%)	3 (0.5%)	2 (0.3%)	2 (0.3%)	3 (0.2%)	5 (0.4%)	2 (0.3%)	4 (0.6%)
糖尿病性足感染	1 (0.2%)	4 (0.6%)	0	1 (0.2%)	1 (<0.1%)	5 (0.4%)	2 (0.3%)	2 (0.3%)
糖尿病性壊疽	1 (0.2%)	2 (0.3%)	0	1 (0.2%)	1 (<0.1%)	3 (0.2%)	0	1 (0.2%)
限局性感染	1 (0.2%)	1 (0.2%)	0	1 (0.2%)	1 (<0.1%)	2 (0.2%)	1 (0.2%)	1 (0.2%)
四肢膿瘍	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	1 (0.2%)
肛門膿瘍	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	1 (0.2%)
壊疽性蜂巣炎	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	1 (0.2%)
腎感染	0	1 (0.2%)	1 (0.2%)	1 (0.2%)	1 (<0.1%)	2 (0.2%)	0	0
腎盂腎炎	0	2 (0.3%)	0	0	0	2 (0.2%)	0	0
細菌性関節炎	0	0	0	0	0	0	0	1 (0.2%)
菌血症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
気管支炎	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
ＣＯＶＩＤ－１９肺炎	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
感染性胆嚢炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
クロストリジウム・ディフィシレ大腸炎	0	0	0	0	0	0	0	1 (0.2%)
合併症を伴う虫垂炎	0	0	0	0	0	0	0	1 (0.2%)
コロナウイルス感染	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
膀胱炎	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-32 データカットオフ日までに眼以外に発現した重篤な有害事象（DME 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887)							
	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
医療機器関連感染	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
憩室炎	0	0	0	0	0	0	0	1 (0.2%)
心内膜炎	0	0	0	0	0	0	0	1 (0.2%)
丹毒	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
大腸菌性敗血症	0	0	0	0	0	0	0	1 (0.2%)
真菌感染	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
胆嚢蓄膿	0	0	0	0	0	0	0	1 (0.2%)
胃腸炎	0	0	0	0	0	0	0	1 (0.2%)
ノロウイルス性胃腸炎	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
咬傷感染	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
ライム病	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
上咽頭炎	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
慢性骨髄炎	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
咽頭炎	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
細菌性肺炎	0	0	0	0	0	0	0	1 (0.2%)
大腸菌性肺炎	0	0	0	0	0	0	0	1 (0.2%)
ウイルス性肺炎	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
シュードモナス性敗血症	0	0	0	0	0	0	0	1 (0.2%)
気道感染	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
敗血症症候群	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
副鼻腔炎	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
ブドウ球菌感染	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
上気道感染	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
尿路性敗血症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
心臓障害								
Total number of patients with at least one adverse event	11 (1.7%)	42 (6.7%)	6 (0.9%)	27 (4.3%)	17 (1.3%)	69 (5.5%)	2 (0.3%)	27 (4.3%)
Total number of events	12	57	6	36	18	93	2	34
うっ血性心不全	8 (1.3%)	14 (2.2%)	2 (0.3%)	4 (0.6%)	10 (0.8%)	18 (1.4%)	0	5 (0.8%)
心筋梗塞	0	4 (0.6%)	1 (0.2%)	5 (0.8%)	1 (<0.1%)	9 (0.7%)	1 (0.2%)	7 (1.1%)
急性心筋梗塞	2 (0.3%)	4 (0.6%)	0	3 (0.5%)	2 (0.2%)	7 (0.6%)	0	6 (1.0%)
冠動脈疾患	0	3 (0.5%)	0	5 (0.8%)	0	8 (0.6%)	0	3 (0.5%)

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-32 データカットオフ日までに眼以外に発現した重篤な有害事象（DME 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887)							
	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
心不全	1 (0.2%)	2 (0.3%)	0	3 (0.5%)	1 (<0.1%)	5 (0.4%)	0	4 (0.6%)
心停止	0	4 (0.6%)	0	1 (0.2%)	0	5 (0.4%)	0	0
狭心症	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	2 (0.3%)
急性左室不全	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	2 (0.3%)
不安定狭心症	0	1 (0.2%)	2 (0.3%)	2 (0.3%)	2 (0.2%)	3 (0.2%)	0	0
心房細動	0	2 (0.3%)	0	1 (0.2%)	0	3 (0.2%)	0	0
心筋虚血	0	3 (0.5%)	0	0	0	3 (0.2%)	0	0
不整脈	0	0	0	2 (0.3%)	0	2 (0.2%)	0	0
急性心不全	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	1 (0.2%)
慢性左室不全	0	1 (0.2%)	1 (0.2%)	1 (0.2%)	1 (<0.1%)	2 (0.2%)	0	0
急性冠動脈症候群	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
大動脈弁狭窄	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
冠動脈硬化症	0	0	0	0	0	0	0	1 (0.2%)
心房粗動	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
房室ブロック	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
完全房室ブロック	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
慢性心不全	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
心原性ショック	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
心血管障害	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
冠動脈狭窄	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
虚血性心筋症	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
左房拡張	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
左室拡張	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
心筋炎	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
心膜炎	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
右室不全	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
心内膜下虚血	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
心室性頻脈性不整脈	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-32 データカットオフ日までに眼以外に発現した重篤な有害事象（DME 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887)							
	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
神経系障害								
Total number of patients with at least one adverse event	7 (1.1%)	24 (3.8%)	7 (1.1%)	19 (3.0%)	14 (1.1%)	43 (3.4%)	9 (1.4%)	16 (2.6%)
Total number of events	7	27	8	23	15	50	9	18
脳血管発作	0	3 (0.5%)	1 (0.2%)	4 (0.6%)	1 (<0.1%)	7 (0.6%)	3 (0.5%)	5 (0.8%)
虚血性脳卒中	2 (0.3%)	5 (0.8%)	2 (0.3%)	2 (0.3%)	4 (0.3%)	7 (0.6%)	2 (0.3%)	3 (0.5%)
失神	0	2 (0.3%)	0	2 (0.3%)	0	4 (0.3%)	2 (0.3%)	2 (0.3%)
一過性脳虚血発作	1 (0.2%)	3 (0.5%)	0	1 (0.2%)	1 (<0.1%)	4 (0.3%)	1 (0.2%)	1 (0.2%)
脳梗塞	1 (0.2%)	3 (0.5%)	0	1 (0.2%)	1 (<0.1%)	4 (0.3%)	0	0
脳出血	0	2 (0.3%)	1 (0.2%)	1 (0.2%)	1 (<0.1%)	3 (0.2%)	0	0
代謝性脳症	0	0	2 (0.3%)	3 (0.5%)	2 (0.2%)	3 (0.2%)	0	0
浮動性めまい	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	1 (0.2%)
脳症	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	1 (0.2%)	1 (0.2%)
腰髄神経根障害	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	1 (0.2%)
馬尾症候群	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
脳血管障害	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
頚髄神経根障害	0	0	0	0	0	0	0	1 (0.2%)
昏睡	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
てんかん	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
ギラン・バレー症候群	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
出血性卒中	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
高血圧性脳症	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
低酸素性虚血性脳症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
ラクナ脳卒中	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
白質脳症	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
失神寸前の状態	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
脊髄圧迫	0	0	0	0	0	0	0	1 (0.2%)
中枢神経系に起因する回転性めまい	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-32 データカットオフ日までに眼以外に発現した重篤な有害事象（DME 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887)							
	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
腎および尿路障害								
Total number of patients with at least one adverse event	5 (0.8%)	22 (3.5%)	3 (0.5%)	8 (1.3%)	8 (0.6%)	30 (2.4%)	1 (0.2%)	15 (2.4%)
Total number of events	6	27	3	8	9	35	1	16
急性腎障害	2 (0.3%)	8 (1.3%)	2 (0.3%)	5 (0.8%)	4 (0.3%)	13 (1.0%)	1 (0.2%)	5 (0.8%)
慢性腎臓病	2 (0.3%)	4 (0.6%)	0	0	2 (0.2%)	4 (0.3%)	0	4 (0.6%)
末期腎疾患	0	4 (0.6%)	0	1 (0.2%)	0	5 (0.4%)	0	2 (0.3%)
腎不全	2 (0.3%)	4 (0.6%)	0	1 (0.2%)	2 (0.2%)	5 (0.4%)	0	2 (0.3%)
腎機能障害	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	1 (0.2%)
高窒素血症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
尿路結石	0	0	0	0	0	0	0	1 (0.2%)
糖尿病性腎症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
血尿	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
水腎症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
腎嚢胞	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
尿閉	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
尿路の炎症	0	0	0	0	0	0	0	1 (0.2%)

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-32 データカットオフ日までに眼以外に発現した重篤な有害事象（DME 統合）（続）

Pooled(YOSEMITE and RHINE)
(N=1887)

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
代謝および栄養障害								
Total number of patients with at least one adverse event	2 (0.3%)	11 (1.7%)	3 (0.5%)	10 (1.6%)	5 (0.4%)	21 (1.7%)	3 (0.5%)	11 (1.8%)
Total number of events	3	16	5	13	8	29	3	17
低血糖	0	1 (0.2%)	2 (0.3%)	7 (1.1%)	2 (0.2%)	8 (0.6%)	1 (0.2%)	1 (0.2%)
高血糖	1 (0.2%)	3 (0.5%)	1 (0.2%)	1 (0.2%)	2 (0.2%)	4 (0.3%)	0	1 (0.2%)
糖尿病性ケトアシドーシス	0	1 (0.2%)	1 (0.2%)	1 (0.2%)	1 (<0.1%)	2 (0.2%)	1 (0.2%)	2 (0.3%)
高カリウム血症	1 (0.2%)	1 (0.2%)	0	2 (0.3%)	1 (<0.1%)	3 (0.2%)	0	1 (0.2%)
脱水	0	2 (0.3%)	0	0	0	2 (0.2%)	0	1 (0.2%)
糖尿病	0	2 (0.3%)	0	0	0	2 (0.2%)	0	0
糖尿病性代謝代償不全	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	1 (0.2%)
糖尿病合併症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
糖尿病性末端器官損傷	0	0	0	0	0	0	0	1 (0.2%)
発育不全	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
痛風	0	0	0	0	0	0	0	1 (0.2%)
高浸透圧状態	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
低カリウム血症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
低ナトリウム血症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
乳酸アシドーシス	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
１型糖尿病	0	0	0	0	0	0	0	1 (0.2%)

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-32 データカットオフ日までに眼以外に発現した重篤な有害事象（DME 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887)							
	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
一般・全身障害および投与部位の状態								
Total number of patients with at least one adverse event	1 (0.2%)	12 (1.9%)	3 (0.5%)	10 (1.6%)	4 (0.3%)	22 (1.7%)	1 (0.2%)	8 (1.3%)
Total number of events	1	12	3	10	4	22	1	9
胸痛	0	2 (0.3%)	0	1 (0.2%)	0	3 (0.2%)	0	4 (0.6%)
死亡	1 (0.2%)	2 (0.3%)	2 (0.3%)	5 (0.8%)	3 (0.2%)	7 (0.6%)	0	0
発熱	0	1 (0.2%)	1 (0.2%)	2 (0.3%)	1 (<0.1%)	3 (0.2%)	0	3 (0.5%)
末梢性浮腫	0	0	0	1 (0.2%)	0	1 (<0.1%)	1 (0.2%)	1 (0.2%)
疲労	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
全身健康状態悪化	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
全身性浮腫	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
不明確な障害	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
炎症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
倦怠感	0	0	0	0	0	0	0	1 (0.2%)
多臓器機能不全症候群	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
壊死	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
軟部組織の炎症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-32 データカットオフ日までに眼以外に発現した重篤な有害事象（DME 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887)							
	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
呼吸器、胸郭および縦隔障害								
Total number of patients with at least one adverse event	1 (0.2%)	11 (1.7%)	5 (0.8%)	13 (2.1%)	6 (0.5%)	24 (1.9%)	1 (0.2%)	5 (0.8%)
Total number of events	1	13	7	16	8	29	1	6
急性呼吸不全	0	2 (0.3%)	2 (0.3%)	3 (0.5%)	2 (0.2%)	5 (0.4%)	1 (0.2%)	4 (0.6%)
呼吸困難	0	2 (0.3%)	2 (0.3%)	3 (0.5%)	2 (0.2%)	5 (0.4%)	0	0
胸水	0	1 (0.2%)	0	2 (0.3%)	0	3 (0.2%)	0	0
肺塞栓症	0	2 (0.3%)	0	0	0	2 (0.2%)	0	1 (0.2%)
呼吸不全	1 (0.2%)	3 (0.5%)	0	0	1 (<0.1%)	3 (0.2%)	0	0
肺線維症	0	0	1 (0.2%)	2 (0.3%)	1 (<0.1%)	2 (0.2%)	0	0
無呼吸	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
慢性閉塞性肺疾患	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
労作性呼吸困難	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
低酸素症	0	0	0	0	0	0	0	1 (0.2%)
肺障害	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
胸膜痛	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
誤嚥性肺炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
肺水腫	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
呼吸停止	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
呼吸抑制	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-32 データカットオフ日までに眼以外に発現した重篤な有害事象（DME 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887)							
	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
血管障害								
Total number of patients with at least one adverse event	1 (0.2%)	7 (1.1%)	1 (0.2%)	10 (1.6%)	2 (0.2%)	17 (1.3%)	2 (0.3%)	12 (1.9%)
Total number of events	2	10	1	10	3	20	2	14
高血圧	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	4 (0.6%)
低血圧	1 (0.2%)	1 (0.2%)	0	2 (0.3%)	1 (<0.1%)	3 (0.2%)	0	1 (0.2%)
大動脈狭窄	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	0
深部静脈血栓症	0	0	0	0	0	0	0	2 (0.3%)
血腫	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	1 (0.2%)	1 (0.2%)
末梢血管障害	1 (0.2%)	2 (0.3%)	0	0	1 (<0.1%)	2 (0.2%)	0	0
動脈瘤	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
動脈閉塞性疾患	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
動脈硬化症	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
コントロール不良の血圧	0	0	0	0	0	0	0	1 (0.2%)
塞栓症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
四肢壊死	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
高血圧クリーゼ	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
高血圧切迫症	0	0	0	0	0	0	0	1 (0.2%)
起立性低血圧	0	0	0	0	0	0	0	1 (0.2%)
末梢動脈閉塞性疾患	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
末梢動脈狭窄	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
末梢動脈血栓症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
静脈瘤	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-32 データカットオフ日までに眼以外に発現した重篤な有害事象（DME 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887)							
	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
傷害、中毒および処置合併症								
Total number of patients with at least one adverse event	1 (0.2%)	9 (1.4%)	0	11 (1.7%)	1 (<0.1%)	20 (1.6%)	2 (0.3%)	7 (1.1%)
Total number of events	1	9	0	14	1	23	2	8
大腿骨頚部骨折	0	1 (0.2%)	0	2 (0.3%)	0	3 (0.2%)	0	2 (0.3%)
転倒	0	1 (0.2%)	0	2 (0.3%)	0	3 (0.2%)	0	1 (0.2%)
大腿骨骨折	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	1 (0.2%)
四肢損傷	0	1 (0.2%)	0	2 (0.3%)	0	3 (0.2%)	0	0
脛骨骨折	1 (0.2%)	2 (0.3%)	0	0	1 (<0.1%)	2 (0.2%)	0	0
上肢骨折	0	1 (0.2%)	0	0	0	1 (<0.1%)	1 (0.2%)	1 (0.2%)
転位骨折	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
頭部損傷	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
股関節部骨折	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
腸骨骨折	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
爪裂離	0	0	0	0	0	0	0	1 (0.2%)
過量投与	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
骨盤骨折	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
橈骨骨折	0	0	0	0	0	0	0	1 (0.2%)
肋骨骨折	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
脊椎圧迫骨折	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
熱傷	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
創離開	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-32 データカットオフ日までに眼以外に発現した重篤な有害事象（DME 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887)							
	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）								
Total number of patients with at least one adverse event	1 (0.2%)	6 (1.0%)	3 (0.5%)	10 (1.6%)	4 (0.3%)	16 (1.3%)	3 (0.5%)	7 (1.1%)
Total number of events	1	8	4	12	5	20	3	7
結腸腺癌	0	0	0	1 (0.2%)	0	1 (<0.1%)	1 (0.2%)	3 (0.5%)
膵癌	0	1 (0.2%)	1 (0.2%)	1 (0.2%)	1 (<0.1%)	2 (0.2%)	0	1 (0.2%)
膀胱癌	0	2 (0.3%)	0	0	0	2 (0.2%)	0	0
遠隔転移を伴う膵癌	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	1 (0.2%)	1 (0.2%)
腺癌	0	0	0	0	0	0	0	1 (0.2%)
胆管癌	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
乳癌	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
結腸癌	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
遠隔転移を伴う結腸直腸癌	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
ヘアリー細胞白血病	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
肝細胞癌	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
白血病	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
肺の悪性新生物	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
骨転移	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
新生物	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
形質細胞性骨髄腫	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
腎癌	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
腎新生物	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
腫瘍浸潤	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-32 データカットオフ日までに眼以外に発現した重篤な有害事象（DME 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887)							
	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
胃腸障害								
Total number of patients with at least one adverse event	1 (0.2%)	8 (1.3%)	1 (0.2%)	7 (1.1%)	2 (0.2%)	15 (1.2%)	3 (0.5%)	6 (1.0%)
Total number of events	1	11	1	7	2	18	4	7
胃腸出血	1 (0.2%)	2 (0.3%)	0	1 (0.2%)	1 (<0.1%)	3 (0.2%)	0	0
大腸炎	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	1 (0.2%)
悪心	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	1 (0.2%)
腹部ヘルニア	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
肛門直腸静脈瘤	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
潰瘍性大腸炎	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
便秘	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
糖尿病性胃不全麻痺	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
胃腸異形成	0	0	0	0	0	0	0	1 (0.2%)
胃食道逆流性疾患	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
胃排出不全	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
腸管虚血	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
大腸ポリープ	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
食道静脈瘤出血	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
食道炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
膵炎	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
急性膵炎	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
直腸出血	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
上部消化管出血	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
嘔吐	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-32 データカットオフ日までに眼以外に発現した重篤な有害事象（DME 統合）（続）

Pooled(YOSEMITE and RHINE)
(N=1887)

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
筋骨格系および結合組織障害								
Total number of patients with at least one adverse event	0	7 (1.1%)	1 (0.2%)	4 (0.6%)	1 (<0.1%)	11 (0.9%)	1 (0.2%)	4 (0.6%)
Total number of events	0	8	1	5	1	13	1	4
神経障害性関節症	0	2 (0.3%)	0	0	0	2 (0.2%)	0	0
関節痛	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
背部痛	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
滑液包炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
椎間板突出	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
筋痙縮	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
筋力低下	0	0	0	0	0	0	0	1 (0.2%)
筋肉痛	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
頚部痛	0	0	0	0	0	0	0	1 (0.2%)
変形性関節症	0	0	0	0	0	0	0	1 (0.2%)
骨端症	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
四肢痛	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
肩回旋筋腱板症候群	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
変形性脊椎症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
脊椎炎	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
肝胆道系障害								
Total number of patients with at least one adverse event	0	4 (0.6%)	0	3 (0.5%)	0	7 (0.6%)	1 (0.2%)	5 (0.8%)
Total number of events	0	7	0	3	0	10	1	5
胆石症	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	1 (0.2%)	1 (0.2%)
胆嚢炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	1 (0.2%)
急性胆嚢炎	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	0
肝硬変	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	1 (0.2%)
胆管狭窄	0	0	0	0	0	0	0	1 (0.2%)
胆道ジスキネジア	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
慢性胆嚢炎	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
慢性肝炎	0	0	0	0	0	0	0	1 (0.2%)
非アルコール性脂肪性肝炎	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-32 データカットオフ日までに眼以外に発現した重篤な有害事象（DME 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887)							
	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
血液およびリンパ系障害								
Total number of patients with at least one adverse event	0	2 (0.3%)	0	3 (0.5%)	0	5 (0.4%)	2 (0.3%)	5 (0.8%)
Total number of events	0	2	0	6	0	8	2	5
貧血	0	1 (0.2%)	0	3 (0.5%)	0	4 (0.3%)	2 (0.3%)	4 (0.6%)
小球性貧血	0	0	0	0	0	0	0	1 (0.2%)
血小板減少症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
精神障害								
Total number of patients with at least one adverse event	0	4 (0.6%)	0	1 (0.2%)	0	5 (0.4%)	3 (0.5%)	5 (0.8%)
Total number of events	0	4	0	1	0	5	3	5
うつ病	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	1 (0.2%)
不安	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
自殺既遂	0	0	0	0	0	0	0	1 (0.2%)
錯乱状態	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
譫妄	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
妄想性障害、詳細不明	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
失見当識	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
薬物乱用	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
精神状態変化	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
皮膚および皮下組織障害								
Total number of patients with at least one adverse event	1 (0.2%)	1 (0.2%)	1 (0.2%)	4 (0.6%)	2 (0.2%)	5 (0.4%)	0	4 (0.6%)
Total number of events	1	1	1	4	2	5	0	4
糖尿病性足病変	1 (0.2%)	1 (0.2%)	0	3 (0.5%)	1 (<0.1%)	4 (0.3%)	0	4 (0.6%)
血管浮腫	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-32 データカットオフ日までに眼以外に発現した重篤な有害事象（DME 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887)							
	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
臨床検査								
Total number of patients with at least one adverse event	0	3 (0.5%)	1 (0.2%)	3 (0.5%)	1 (<0.1%)	6 (0.5%)	0	0
Total number of events	0	3	1	3	1	6	0	0
血中クレアチニン増加	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
血中ブドウ糖変動	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
血中カリウム増加	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
血中テストステロン増加	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
Ａ型インフルエンザウイルス検査陽性	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
ＳＡＲＳ－ＣｏＶ－２検査陽性	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
耳および迷路障害								
Total number of patients with at least one adverse event	0	1 (0.2%)	0	2 (0.3%)	0	3 (0.2%)	0	0
Total number of events	0	1	0	2	0	3	0	0
突発性難聴	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
耳鳴	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
前庭障害	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
免疫系障害								
Total number of patients with at least one adverse event	0	0	1 (0.2%)	2 (0.3%)	1 (<0.1%)	2 (0.2%)	0	1 (0.2%)
Total number of events	0	0	1	2	1	2	0	1
アナフィラキシー反応	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
薬物過敏症	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
過敏症	0	0	0	0	0	0	0	1 (0.2%)

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-32　データカットオフ日までに眼以外に発現した重篤な有害事象（DME 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887)							
	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
外科および内科処置								
Total number of patients with at least one adverse event	0	1 (0.2%)	0	0	0	1 (<0.1%)	2 (0.3%)	2 (0.3%)
Total number of events	0	1	0	0	0	1	2	2
胆嚢切除	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
ステント留置	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
足指切断	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
生殖系および乳房障害								
Total number of patients with at least one adverse event	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
Total number of events	0	0	0	1	0	1	0	0
卵巣嚢胞	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

[5.3.5.3-nAMD-1 t_ae_cod_NOCUL_SER_SE_DME_HLS を改変]

表 2.7.4.7-33　データカットオフ日までに眼以外に発現した治験薬の投与中止に至った有害事象（nAMD 統合）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
	Onset after Week 48	Overall	Onset after Week 48	Overall
Total number of patients with at least one adverse event	1 (0.2%)	6 (0.9%)	1 (0.2%)	4 (0.6%)
Overall total number of events	1	6	3	6
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）				
Total number of patients with at least one adverse event	1 (0.2%)	1 (0.2%)	0	3 (0.5%)
Total number of events	1	1	0	3
肺の悪性新生物	1 (0.2%)	1 (0.2%)	0	1 (0.2%)
遠隔転移を伴う神経内分泌癌	0	0	0	1 (0.2%)
舌の悪性新生物、病期不明	0	0	0	1 (0.2%)
神経系障害				
Total number of patients with at least one adverse event	0	3 (0.5%)	1 (0.2%)	1 (0.2%)
Total number of events	0	3	3	3
認知障害	0	2 (0.3%)	0	0
アルツハイマー型認知症	0	0	1 (0.2%)	1 (0.2%)
血栓性脳梗塞	0	1 (0.2%)	0	0
一過性脳虚血発作	0	0	1 (0.2%)	1 (0.2%)
血管性認知症	0	0	1 (0.2%)	1 (0.2%)
心臓障害				
Total number of patients with at least one adverse event	0	1 (0.2%)	0	0
Total number of events	0	1	0	0
心不全	0	1 (0.2%)	0	0
筋骨格系および結合組織障害				
Total number of patients with at least one adverse event	0	1 (0.2%)	0	0
Total number of events	0	1	0	0
変形性脊椎症	0	1 (0.2%)	0	0

MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

[5.3.5.3-nAMD-1 t_ae_cod_NOCUL_SDSC_SE_nAMD_HLS を改変]

表 2.7.4.7-34　データカットオフ日までに眼以外に発現した治験中止に至った有害事象（nAMD 統合）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
	Onset after Week 48	Overall	Onset after Week 48	Overall
Total number of patients with at least one adverse event	2 (0.3%)	10 (1.5%)	2 (0.3%)	12 (1.8%)
Overall total number of events	2	11	4	15
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）				
Total number of patients with at least one adverse event	1 (0.2%)	1 (0.2%)	0	4 (0.6%)
Total number of events	1	1	0	4
肺の悪性新生物	1 (0.2%)	1 (0.2%)	0	1 (0.2%)
胆管癌	0	0	0	1 (0.2%)
遠隔転移を伴う神経内分泌癌	0	0	0	1 (0.2%)
舌の悪性新生物、病期不明	0	0	0	1 (0.2%)
神経系障害				
Total number of patients with at least one adverse event	0	4 (0.6%)	1 (0.2%)	1 (0.2%)
Total number of events	0	5	3	3
認知障害	0	2 (0.3%)	0	0
脳浮腫	0	1 (0.2%)	0	0
アルツハイマー型認知症	0	0	1 (0.2%)	1 (0.2%)
くも膜下出血	0	1 (0.2%)	0	0
血栓性脳梗塞	0	1 (0.2%)	0	0
一過性脳虚血発作	0	0	1 (0.2%)	1 (0.2%)
血管性認知症	0	0	1 (0.2%)	1 (0.2%)
心臓障害				
Total number of patients with at least one adverse event	0	1 (0.2%)	0	3 (0.5%)
Total number of events	0	1	0	3
心不全	0	1 (0.2%)	0	2 (0.3%)
心肺不全	0	0	0	1 (0.2%)

MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-34 データカットオフ日までに眼以外に発現した治験中止に至った有害事象（nAMD 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(TENAYA and LUCERNE) (N=1326)			
	Faricimab 6 mg (N=664)		Aflibercept 2 mg (N=662)	
	Onset after Week 48	Overall	Onset after Week 48	Overall
一般・全身障害および投与部位の状態				
Total number of patients with at least one adverse event	0	2 (0.3%)	0	1 (0.2%)
Total number of events	0	2	0	1
死亡	0	0	0	1 (0.2%)
不明確な障害	0	1 (0.2%)	0	0
多臓器機能不全症候群	0	1 (0.2%)	0	0
呼吸器、胸郭および縦隔障害				
Total number of patients with at least one adverse event	1 (0.2%)	1 (0.2%)	1 (0.2%)	2 (0.3%)
Total number of events	1	1	1	2
肺穿孔	0	0	0	1 (0.2%)
肺塞栓症	0	0	1 (0.2%)	1 (0.2%)
呼吸不全	1 (0.2%)	1 (0.2%)	0	0
感染症および寄生虫症				
Total number of patients with at least one adverse event	0	1 (0.2%)	0	0
Total number of events	0	1	0	0
肺炎	0	1 (0.2%)	0	0
傷害、中毒および処置合併症				
Total number of patients with at least one adverse event	0	0	0	1 (0.2%)
Total number of events	0	0	0	1
転倒	0	0	0	1 (0.2%)
腎および尿路障害				
Total number of patients with at least one adverse event	0	0	0	1 (0.2%)
Total number of events	0	0	0	1
急性腎障害	0	0	0	1 (0.2%)

MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

[5.3.5.3-nAMD-1 t_ae_cod_NOCUL_DSC_SE_nAMD_HLS を改変]

表 2.7.4.7-35 データカットオフ日までに眼以外に発現した治験薬の投与中止に至った有害事象（DME 統合）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887)							
	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
Total number of patients with at least one adverse event	1 (0.2%)	9 (1.4%)	0	4 (0.6%)	1 (<0.1%)	13 (1.0%)	2 (0.3%)	7 (1.1%)
Overall total number of events	1	9	0	4	1	13	2	7
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）								
Total number of patients with at least one adverse event	1 (0.2%)	3 (0.5%)	0	3 (0.5%)	1 (<0.1%)	6 (0.5%)	0	1 (0.2%)
Total number of events	1	3	0	3	1	6	0	1
腺癌	0	0	0	0	0	0	0	1 (0.2%)
乳癌	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
結腸癌	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
遠隔転移を伴う結腸直腸癌	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
肺の悪性新生物	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
新生物	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
形質細胞性骨髄腫	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
神経系障害								
Total number of patients with at least one adverse event	0	2 (0.3%)	0	0	0	2 (0.2%)	0	3 (0.5%)
Total number of events	0	2	0	0	0	2	0	3
脳血管発作	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	1 (0.2%)
アルツハイマー型認知症	0	0	0	0	0	0	0	1 (0.2%)
虚血性脳卒中	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
脊髄圧迫	0	0	0	0	0	0	0	1 (0.2%)
心臓障害								
Total number of patients with at least one adverse event	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.2%)	0	0
Total number of events	0	1	0	1	0	2	0	0
うっ血性心不全	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
心筋梗塞	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-35 データカットオフ日までに眼以外に発現した治験薬の投与中止に至った有害事象（DME 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887)							
	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
感染症および寄生虫症								
Total number of patients with at least one adverse event	0	1 (0.2%)	0	0	0	1 (<0.1%)	1 (0.2%)	1 (0.2%)
Total number of events	0	1	0	0	0	1	1	1
伝染性単核症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
肺炎	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
免疫系障害								
Total number of patients with at least one adverse event	0	0	0	0	0	0	0	1 (0.2%)
Total number of events	0	0	0	0	0	0	0	1
造影剤アレルギー	0	0	0	0	0	0	0	1 (0.2%)
精神障害								
Total number of patients with at least one adverse event	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
Total number of events	0	0	0	0	0	0	1	1
錯乱状態	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
腎および尿路障害								
Total number of patients with at least one adverse event	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
Total number of events	0	1	0	0	0	1	0	0
腎不全	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
血管障害								
Total number of patients with at least one adverse event	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
Total number of events	0	1	0	0	0	1	0	0
末梢動脈血栓症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

[5.3.5.3-nAMD-1 t_ae_cod_NOCUL_SDSC_SE_DME_HLS を改変]

表 2.7.4.7-36 データカットオフ日までに眼以外に発現した治験中止に至った有害事象（DME 統合）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887)							
	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
Total number of patients with at least one adverse event	2 (0.3%)	16 (2.5%)	7 (1.1%)	17 (2.7%)	9 (0.7%)	33 (2.6%)	6 (1.0%)	14 (2.2%)
Overall total number of events	2	18	7	17	9	35	7	15
心臓障害								
Total number of patients with at least one adverse event	0	6 (1.0%)	1 (0.2%)	4 (0.6%)	1 (<0.1%)	10 (0.8%)	1 (0.2%)	4 (0.6%)
Total number of events	0	7	1	4	1	11	1	4
心筋梗塞	0	1 (0.2%)	1 (0.2%)	2 (0.3%)	1 (<0.1%)	3 (0.2%)	1 (0.2%)	2 (0.3%)
急性心筋梗塞	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	1 (0.2%)
心不全	0	0	0	2 (0.3%)	0	2 (0.2%)	0	0
心停止	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
うっ血性心不全	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
冠動脈疾患	0	0	0	0	0	0	0	1 (0.2%)
左房拡張	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
左室拡張	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
心膜炎	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
一般・全身障害および投与部位の状態								
Total number of patients with at least one adverse event	1 (0.2%)	3 (0.5%)	2 (0.3%)	5 (0.8%)	3 (0.2%)	8 (0.6%)	0	0
Total number of events	1	3	2	5	3	8	0	0
死亡	1 (0.2%)	2 (0.3%)	2 (0.3%)	5 (0.8%)	3 (0.2%)	7 (0.6%)	0	0
全身健康状態悪化	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-36 データカットオフ日までに眼以外に発現した治験中止に至った有害事象（DME 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887)							
	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）								
Total number of patients with at least one adverse event	0	2 (0.3%)	1 (0.2%)	4 (0.6%)	1 (<0.1%)	6 (0.5%)	1 (0.2%)	2 (0.3%)
Total number of events	0	2	1	4	1	6	1	2
遠隔転移を伴う膵癌	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	1 (0.2%)	1 (0.2%)
腺癌	0	0	0	0	0	0	0	1 (0.2%)
膀胱癌	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
結腸癌	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
肺の悪性新生物	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
新生物	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
形質細胞性骨髄腫	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
神経系障害								
Total number of patients with at least one adverse event	0	2 (0.3%)	2 (0.3%)	2 (0.3%)	2 (0.2%)	4 (0.3%)	0	2 (0.3%)
Total number of events	0	2	2	2	2	4	0	2
脳出血	0	1 (0.2%)	1 (0.2%)	1 (0.2%)	1 (<0.1%)	2 (0.2%)	0	0
虚血性脳卒中	0	1 (0.2%)	1 (0.2%)	1 (0.2%)	1 (<0.1%)	2 (0.2%)	0	0
アルツハイマー型認知症	0	0	0	0	0	0	0	1 (0.2%)
脊髄圧迫	0	0	0	0	0	0	0	1 (0.2%)
精神障害								
Total number of patients with at least one adverse event	0	0	0	0	0	0	2 (0.3%)	3 (0.5%)
Total number of events	0	0	0	0	0	0	2	3
自殺既遂	0	0	0	0	0	0	0	1 (0.2%)
錯乱状態	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
薬物乱用	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
感染症および寄生虫症								
Total number of patients with at least one adverse event	0	1 (0.2%)	0	0	0	1 (<0.1%)	1 (0.2%)	1 (0.2%)
Total number of events	0	1	0	0	0	1	1	1
肺炎	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
敗血症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-36 データカットオフ日までに眼以外に発現した治験中止に至った有害事象（DME 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887)							
	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
呼吸器、胸郭および縦隔障害								
Total number of patients with at least one adverse event	0	0	1 (0.2%)	2 (0.3%)	1 (<0.1%)	2 (0.2%)	0	0
Total number of events	0	0	1	2	1	2	0	0
誤嚥性肺炎	0	0	0	1 (0.2%)	0	1 (<0.1%)	0	0
肺線維症	0	0	1 (0.2%)	1 (0.2%)	1 (<0.1%)	1 (<0.1%)	0	0
胃腸障害								
Total number of patients with at least one adverse event	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
Total number of events	0	0	0	0	0	0	1	1
腸管虚血	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
免疫系障害								
Total number of patients with at least one adverse event	0	0	0	0	0	0	0	1 (0.2%)
Total number of events	0	0	0	0	0	0	0	1
造影剤アレルギー	0	0	0	0	0	0	0	1 (0.2%)
傷害、中毒および処置合併症								
Total number of patients with at least one adverse event	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
Total number of events	0	0	0	0	0	0	1	1
過量投与	0	0	0	0	0	0	1 (0.2%)	1 (0.2%)
代謝および栄養障害								
Total number of patients with at least one adverse event	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
Total number of events	0	1	0	0	0	1	0	0
糖尿病合併症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
腎および尿路障害								
Total number of patients with at least one adverse event	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0
Total number of events	1	1	0	0	1	1	0	0
腎不全	1 (0.2%)	1 (0.2%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.4.7-36 データカットオフ日までに眼以外に発現した治験中止に至った有害事象（DME 統合）（続）

MedDRA System Organ Class MedDRA Preferred Term	Pooled(YOSEMITE and RHINE) (N=1887)							
	Faricimab 6 mg Q8W (N=630)		Faricimab 6 mg PTI (N=632)		Faricimab 6 mg All (N=1262)		Aflibercept 2 mg Q8W (N=625)	
	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall	Onset after Week 56	Overall
血管障害								
Total number of patients with at least one adverse event	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0
Total number of events	0	1	0	0	0	1	0	0
塞栓症	0	1 (0.2%)	0	0	0	1 (<0.1%)	0	0

MedDRA = Medical Dictionary for Regulatory Activities; Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings. PTI = Personalized Treatment Interval (from Q4W up to Q16W).
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

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[5.3.5.3-nAMD-1 t_ae_cod_NOCUL_DSC_SE_DME_HLS を改変]

表 2.7.4.7-37　52週時（nAMD）又は56週時（DME）までに試験眼に発現した特定された眼内炎：重篤性，転帰，重症度，頻度（nAMD 統合，DME 統合，両疾患統合）

Important Identified Endophthalmitis Risks: Seriousness, Outcomes, Severity, Frequency with 95% CI through Week 56 DME, Week 52 nAMD in the Study Eye, Safety-Evaluable Population
Protocol: GR40349, GR40398, GR40306, GR40844
Clinical Cutoff Date: YOSEMITE 20OCT2020, RHINE 19OCT2020, TENAYA 19JAN2021 (global enrollment) 26MAY2021 (Japan extension), LUCERNE 28DEC2020

	nAMD (N=1407)		DME (N=1887)		POOLED(nAMD, DME) (N=3294)	
	Faricimab (N=704)	Aflibercept (N=703)	Faricimab (N=1262)	Aflibercept (N=625)	Faricimab (N=1966)	Aflibercept (N=1328)
Number (%) of patients with at least one AE	0	1 (0.1%)	4 (0.3%)	1 (0.2%)	4 (0.2%)	2 (0.2%)
95% CI for % of patients with at least one AE	(0.00%, 0.54%)	(0.03%, 0.80%)	(0.12%, 0.81%)	(0.03%, 0.90%)	(0.08%, 0.52%)	(0.04%, 0.55%)
Difference in % of patients with at least one AE	-0.1%		0.2%		0.1%	
95% CI for difference	(-0.80%, 0.41%)		(-0.61%, 0.67%)		(-0.36%, 0.39%)	
Total number of AEs	0	1	4	1	4	2
Number (%) of patients with at least one AE by severity						
Mild	0	0	0	0	0	0
Moderate	0	1 (100%)	2 (50.0%)	0	2 (50.0%)	1 (50.0%)
Severe	0	0	2 (50.0%)	1 (100%)	2 (50.0%)	1 (50.0%)
Number (%) of patients with at least one serious AE	0	1 (0.1%)	4 (0.3%)	1 (0.2%)	4 (0.2%)	2 (0.2%)
Number (%) of patients with at least one AE by outcome						
Fatal	0	0	0	0	0	0
Not recovered/Resolved	0	0	0	0	0	0
Recovering/Resolving	0	0	1 (25.0%)	0	1 (25.0%)	0
Recovered/Resolved	0	1 (100%)	3 (75.0%)	0	3 (75.0%)	1 (50.0%)
Resolved with sequelae	0	0	0	1 (100%)	0	1 (50.0%)
Unknown outcome	0	0	0	0	0	0

Investigator text for DME AEs encoded using MedDRA version 23.1. Investigator text for nAMD AEs encoded using MedDRA version 24.0. Percentages for "Number of patients with at least one AE" and "Number of patients with at least one serious AE" are based on the N in the column headings. The percentages for AE severity and AE outcome are based on "Number of patients with at least one AE".
Table summary includes adverse events that started or worsened (for existing condition) on or after the date of the first injection of active study drug. Multiple occurrences of the same AE in one individual are counted once at the greatest intensity for this preferred term.
AE=adverse event; CI=Confidence Interval; 95% CI were computed using the Wilson method. Difference in frequency rates is relative to AFLIBERCEPT and 95% CI of the difference were computed using Newcombe Risk difference. Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst grade.
Faricimab dosing is Faricimab 6MG intravitreal Q8W and personalized treatment interval.
Aflibercept dosing is Aflibercept 2 mg Q8W.
Endophthalmitis terms = Endophthalmitis, Candida endophthalmitis, Mycotic endophthalmitis, Pseudoendophthalmitis.
nAMD pools GR40306 and GR40844; DME pools GR40349 and GR40398; POOLED(nAMD, DME) pools all four studies.

Program: root/clinical_studies/RO6867461/share/pool_rmp_Chugai/prod/program/t_saf_rmp.sas
Output: root/clinical_studies/RO6867461/share/pool_rmp_Chugai/prod/output/t_saf_rmp_ENDO_SE.out
23JUL2021 16:01

[5.3.5.3-nAMD-3 t_saf_rmp_ENDO_SE を再掲]

表 2.7.4.7-38　52週時（nAMD）又は56週時（DME）までに試験眼に発現した特定された眼内炎症：重篤性，転帰，重症度，頻度（nAMD 統合，DME 統合，両疾患統合）

Important Identified Intraocular Inflammation (IOI) Risks: Seriousness, Outcomes, Severity, Frequency with 95% CI through Week 56 DME, Week 52 nAMD in the Study Eye, Safety-Evaluable Population
Protocol: GR40349, GR40398, GR40306, GR40844
Clinical Cutoff Date: YOSEMITE 20OCT2020, RHINE 19OCT2020, TENAYA 19JAN2021 (global enrollment) 26MAY2021 (Japan extension), LUCERNE 28DEC2020

	nAMD (N=1407)		DME (N=1887)		POOLED(nAMD, DME) (N=3294)	
	Faricimab (N=704)	Aflibercept (N=703)	Faricimab (N=1262)	Aflibercept (N=625)	Faricimab (N=1966)	Aflibercept (N=1328)
Number (%) of patients with at least one AE	15 (2.1%)	11 (1.6%)	17 (1.3%)	4 (0.6%)	32 (1.6%)	15 (1.1%)
95% CI for % of patients with at least one AE	(1.30%, 3.49%)	(0.88%, 2.78%)	(0.84%, 2.15%)	(0.25%, 1.63%)	(1.16%, 2.29%)	(0.69%, 1.86%)
Difference in % of patients with at least one AE	0.6%		0.7%		0.5%	
95% CI for difference	(-0.91%, 2.09%)		(-0.41%, 1.60%)		(-0.37%, 1.29%)	
Total number of AEs	19	12	25	6	44	18
Number (%) of patients with at least one AE by severity						
Mild	9 (60.0%)	6 (54.5%)	9 (52.9%)	3 (75.0%)	18 (56.3%)	9 (60.0%)
Moderate	5 (33.3%)	5 (45.5%)	9 (52.9%)	1 (25.0%)	14 (43.8%)	6 (40.0%)
Severe	3 (20.0%)	1 (9.1%)	3 (17.6%)	0	6 (18.8%)	1 (6.7%)
Number (%) of patients with at least one serious AE	5 (0.7%)	2 (0.3%)	4 (0.3%)	0	9 (0.5%)	2 (0.2%)
Number (%) of patients with at least one AE by outcome						
Fatal	0	0	0	0	0	0
Not recovered/Resolved	1 (6.7%)	1 (9.1%)	2 (11.8%)	0	3 (9.4%)	1 (6.7%)
Recovering/Resolving	2 (13.3%)	0	5 (29.4%)	1 (25.0%)	7 (21.9%)	1 (6.7%)
Recovered/Resolved	13 (86.7%)	10 (90.9%)	12 (70.6%)	3 (75.0%)	25 (78.1%)	13 (86.7%)
Resolved with sequelae	0	0	1 (5.9%)	0	1 (3.1%)	0
Unknown outcome	0	0	0	0	0	0

Investigator text for DME AEs encoded using MedDRA version 23.1. Investigator text for nAMD AEs encoded using MedDRA version 24.0. Percentages for "Number of patients with at least one AE" and "Number of patients with at least one serious AE" are based on the N in the column headings. The percentages for AE severity and AE outcome are based on "Number of patients with at least one AE".
Table summary includes adverse events that started or worsened (for existing condition) on or after the date of the first injection of active study drug. Multiple occurrences of the same AE in one individual are counted once at the greatest intensity for this preferred term.
AE=adverse event; CI=Confidence Interval; 95% CI were computed using the Wilson method. Difference in frequency rates is relative to AFLIBERCEPT and 95% CI of the difference were computed using Newcombe Risk difference. Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst grade.
Intraocular inflammation (IOI) terms = Anterior chamber flare, Anterior Chamber inflammation, Chorioretinitis, Choroiditis, Cyclitis, Eye inflammation, Iridocyclitis, Iritis, Keratic precipitates, Keratouveitis, Noninfective chorioretinitis, Non-infectious Endophthalmitis, Ocular vasculitis, Post procedural inflammation, Retinal vasculitis, Uveitis, and Vitritis.
Faricimab dosing is Faricimab 6MG intravitreal Q8W and personalized treatment interval.
Aflibercept dosing is Aflibercept 2 mg Q8W.
nAMD pools GR40306 and GR40844; DME pools GR40349 and GR40398; POOLED(nAMD, DME) pools all four studies.

Program: root/clinical_studies/RO6867461/share/pool_rmp_Chugai/prod/program/t_saf_rmp.sas
Output: root/clinical_studies/RO6867461/share/pool_rmp_Chugai/prod/output/t_saf_rmp_IOI_SE.out
23JUL2021 16:05

[5.3.5.3-nAMD-3 t_saf_rmp_IOI_SE を再掲]

表 2.7.4.7-39 52週時（nAMD）又は56週時（DME）までに試験眼に発現した特定された網膜剥離及び網膜裂孔：重篤性，転帰，重症度，頻度（nAMD 統合，DME 統合，両疾患統合）

Important Identified Retinal Detachment and Retinal Tear Risks: Seriousness, Outcomes, Severity, Frequency with 95% CI through Week 56 DME, Week 52 nAMD in the Study Eye, Safety-Evaluable Population
Protocol: GR40349, GR40398, GR40306, GR40844
Clinical Cutoff Date: YOSEMITE 20OCT2020, RHINE 19OCT2020, TENAYA 19JAN2021 (global enrollment) 26MAY2021 (Japan extension), LUCERNE 28DEC2020

	nAMD (N=1407)		DME (N=1887)		POOLED(nAMD, DME) (N=3294)	
	Faricimab (N=704)	Aflibercept (N=703)	Faricimab (N=1262)	Aflibercept (N=625)	Faricimab (N=1966)	Aflibercept (N=1328)
Number (%) of patients with at least one AE	2 (0.3%)	1 (0.1%)	3 (0.2%)	0	5 (0.3%)	1 (<0.1%)
95% CI for % of patients with at least one AE	(0.08%, 1.03%)	(0.03%, 0.80%)	(0.08%, 0.70%)	(0.00%, 0.61%)	(0.11%, 0.59%)	(0.01%, 0.43%)
Difference in % of patients with at least one AE	0.1%		0.2%		0.2%	
95% CI for difference	(-0.55%, 0.90%)		(-0.39%, 0.70%)		(-0.20%, 0.52%)	
Total number of AEs	2	1	3	0	5	1
Number (%) of patients with at least one AE by severity						
Mild	0	1 (100%)	2 (66.7%)	0	2 (40.0%)	1 (100%)
Moderate	1 (50.0%)	0	0	0	1 (20.0%)	0
Severe	1 (50.0%)	0	1 (33.3%)	0	2 (40.0%)	0
Number (%) of patients with at least one serious AE	2 (0.3%)	0	3 (0.2%)	0	5 (0.3%)	0
Number (%) of patients with at least one AE by outcome						
Fatal	0	0	0	0	0	0
Not recovered/Resolved	0	0	1 (33.3%)	0	1 (20.0%)	0
Recovering/Resolving	0	1 (100%)	0	0	0	1 (100%)
Recovered/Resolved	2 (100%)	0	2 (66.7%)	0	4 (80.0%)	0
Resolved with sequelae	0	0	0	0	0	0
Unknown outcome	0	0	0	0	0	0

Investigator text for DME AEs encoded using MedDRA version 23.1. Investigator text for nAMD AEs encoded using MedDRA version 24.0. Percentages for "Number of patients with at least one AE" and "Number of patients with at least one serious AE" are based on the N in the column headings. The percentages for AE severity and AE outcome are based on "Number of patients with at least one AE".
Table summary includes adverse events that started or worsened (for existing condition) on or after the date of the first injection of active study drug. Multiple occurrences of the same AE in one individual are counted once at the greatest intensity for this preferred term.
AE=adverse event; CI=Confidence Interval; 95% CI were computed using the Wilson method. Difference in frequency rates is relative to AFLIBERCEPT and 95% CI of the difference were computed using Newcombe Risk difference. Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst grade.
Faricimab dosing is Faricimab 6MG intravitreal Q8W and personalized treatment interval.
Aflibercept dosing is Aflibercept 2 mg Q8W. NE = Not Evaluable.
Retinal detachment and retinal tear terms = Rhegmatogenous retinal detachment, Retinal detachment, Retinal tear.
nAMD pools GR40306 and GR40844; DME pools GR40349 and GR40398; POOLED(nAMD, DME) pools all four studies.

Program: root/clinical_studies/RO6867461/share/pool_rmp_Chugai/prod/program/t_saf_rmp.sas
Output: root/clinical_studies/RO6867461/share/pool_rmp_Chugai/prod/output/t_saf_rmp_RDT_SE.out
23JUL2021 16:07

[5.3.5.3-nAMD-3 t_saf_rmp_RDT_SE を再掲]

表 2.7.4.7-40　52週時（nAMD）又は56週時（DME）までに試験眼に発現した特定された網膜色素上皮裂孔：重篤性，転帰，重症度，頻度（nAMD 統合，DME 統合，両疾患統合）

Important Identified Retinal Pigment Epithelial Tear Risks: Seriousness, Outcomes, Severity, Frequency with 95% CI through Week 56 DME, Week 52 nAMD in the Study Eye, Safety-Evaluable Population
Protocol: GR40349, GR40398, GR40306, GR40844
Clinical Cutoff Date: YOSEMITE 20OCT2020, RHINE 19OCT2020, TENAYA 19JAN2021 (global enrollment) 26MAY2021 (Japan extension), LUCERNE 28DEC2020

	nAMD (N=1407)		DME (N=1887)		POOLED(nAMD, DME) (N=3294)	
	Faricimab (N=704)	Aflibercept (N=703)	Faricimab (N=1262)	Aflibercept (N=625)	Faricimab (N=1966)	Aflibercept (N=1328)
Number (%) of patients with at least one AE	19 (2.7%)	9 (1.3%)	0	0	19 (1.0%)	9 (0.7%)
95% CI for % of patients with at least one AE	(1.73%, 4.18%)	(0.67%, 2.42%)	(0.00%, 0.30%)	(0.00%, 0.61%)	(0.62%, 1.50%)	(0.36%, 1.28%)
Difference in % of patients with at least one AE	1.4%		NE		0.3%	
95% CI for difference	(-0.07%, 3.02%)		NE		(-0.41%, 0.92%)	
Total number of AEs	19	9	0	0	19	9
Number (%) of patients with at least one AE by severity						
Mild	12 (63.2%)	7 (77.8%)	0	0	12 (63.2%)	7 (77.8%)
Moderate	5 (26.3%)	2 (22.2%)	0	0	5 (26.3%)	2 (22.2%)
Severe	2 (10.5%)	0	0	0	2 (10.5%)	0
Number (%) of patients with at least one serious AE	4 (0.6%)	0	0	0	4 (0.2%)	0
Number (%) of patients with at least one AE by outcome						
Fatal	0	0	0	0	0	0
Not recovered/Resolved	16 (84.2%)	8 (88.9%)	0	0	16 (84.2%)	8 (88.9%)
Recovering/Resolving	0	1 (11.1%)	0	0	0	1 (11.1%)
Recovered/Resolved	2 (10.5%)	0	0	0	2 (10.5%)	0
Resolved with sequelae	0	0	0	0	0	0
Unknown outcome	1 (5.3%)	0	0	0	1 (5.3%)	0

Investigator text for DME AEs encoded using MedDRA version 23.1. Investigator text for nAMD AEs encoded using MedDRA version 24.0. Percentages for "Number of patients with at least one AE" and "Number of patients with at least one serious AE" are based on the N in the column headings. The percentages for AE severity and AE outcome are based on "Number of patients with at least one AE".
Table summary includes adverse events that started or worsened (for existing condition) on or after the date of the first injection of active study drug. Multiple occurrences of the same AE in one individual are counted once at the greatest intensity for this preferred term.
AE=adverse event; CI=Confidence Interval; 95% CI were computed using the Wilson method. Difference in frequency rates is relative to AFLIBERCEPT and 95% CI of the difference were computed using Newcombe Risk difference. Multiple occurrences of qualifying events in a patient are counted only once at the patient's worst grade.
Faricimab dosing is Faricimab 6MG intravitreal Q8W and personalized treatment interval.
Aflibercept dosing is Aflibercept 2 mg Q8W. NE = Not Evaluable.
nAMD pools GR40306 and GR40844; DME pools GR40349 and GR40398; POOLED(nAMD, DME) pools all four studies.

Program: root/clinical_studies/RO6867461/share/pool_rmp_Chugai/prod/program/t_saf_rmp.sas
Output: root/clinical_studies/RO6867461/share/pool_rmp_Chugai/prod/output/t_saf_rmp_RPE_SE.out
23JUL2021 16:08

[5.3.5.3-nAMD-3 t_saf_rmp_RPE_SE を再掲]

表 2.7.4.7-41　52週時までの ADA の発現状況（nAMD 統合）

Baseline Prevalence and Incidence of Treatment Emergent ADA, IG Population
Protocol: GR40306 & GR40844
Clinical Cutoff Date: TENAYA 19JAN2021 (global enrollment) 26MAY2021 (Japan extension), LUCERNE 28DEC2020

	Faricimab 6 mg (N=704)
Baseline Prevalence of ADA*	
Baseline evaluable patients	680
Patients with a positive sample at time of entry into the study	12 (1.7%)
Patients with no positive sample at time of entry into the study	668
Incidence of Treatment Emergent ADA**	
Post-baseline evaluable patients***	697
Patients with ADA-positive	84
Patients with treatment-emergent ADA-positive	77 (11.0%)
Patients with treatment-induced ADA-positive	76 (10.9%)
Patients with treatment-boosted ADA-positive	1 (0.1%)
Patients with treatment-unaffected ADA-positive	7 (1.0%)
Patients with ADA-negative	613

* All baseline evaluable patients including patients who did not receive study treatment.
**Only patients who received at least one dose of study treatment are included.
*** Denominator used for incidence calculation.
ADA = Anti-Drug Antibodies (is also referred to as ATA, or Anti-Therapeutic Antibodies).
Baseline evaluable patient = Patients with evaluable baseline samples.
Post-baseline evaluable patient = Patients with at least one post-dose sample.
Patients with ADA-positive = Post-baseline evaluable patients determined to be treatment-induced ADA-positive, treatment-boosted ADA-positive or treatment-unaffected ADA-positive during the study period.
Patients with treatment-emergent ADA-positive = Post-baseline evaluable patients determined to be treatment-induced ADA-positive or treatment-boosted ADA-positive during the study period.
Patients with treatment-induced ADA-positive= Post-baseline evaluable patients with an ADA-negative sample or missing sample at baseline and any post-baseline positive sample.
Patients with treatment-boosted ADA-positive = Post-baseline evaluable patients with an ADA-positive sample at baseline and any post-baseline samples with a titer that is equal or greater than 4-fold baseline titer.
Patients with treatment-unaffected ADA-positive = Post-baseline evaluable patients with ADA-positive sample post-baseline having Titer lower than 4-fold the ADA-positive baseline Titer.
Patients with ADA-negative = Post-baseline evaluable patients without positive ADA during the study period or if they are ADA positive at baseline but without positive ADA post baseline.
For any positive sample with titer result less than the minimum reportable titer or any positive sample where a titer cannot be obtained, titer value is imputed as equal to the minimum reportable titer.

Program: root/clinical_studies/RO6867461/CDPT7716/share/pool_CTD_safety_update/prod/program/t_ada_base.sas
Output: root/clinical_studies/RO6867461/CDPT7716/share/pool_CTD_safety_update/prod/output/t_ada_base_IG_nAMD_JPN.out
13JAN2022 8:38 Page 1 of 1

表 2.7.4.7-42　52週時までに試験眼に発現した眼内炎症（Definition 2，nAMD 統合，GR40306試験及び GR40844試験，ADA 陽性患者）

Safety Summary through Week 52, Study Eye, ADA Positive, Intraocular Inflammation Revised Definition 2
Protocol: GR40306 & GR40844
Clinical Cutoff Date: TENAYA 19JAN2021 (global enrollment) 26MAY2021 (Japan extension), LUCERNE 28DEC2020

	GR40306(TENAYA) (N=44)	GR40844(LUCERNE) (N=40)	Pooled(TENAYA and LUCERNE) (N=84)
	Faricimab 6 mg (N=44)	Faricimab 6 mg (N=40)	Faricimab 6 mg (N=84)
AE			
AE	7 (15.9%)	2 (5.0%)	9 (10.7%)
SAE	2 (4.5%)	1 (2.5%)	3 (3.6%)
Severe AE	2 (4.5%)	0	2 (2.4%)
AE of Special Interest			
Drop in VA score >=30	2 (4.5%)	0	2 (2.4%)
Associated with severe IOI	0	0	0
Intervention req. to prevent permanent vision loss	0	0	0
Total number of patients with IOI at least 2 times	1 (2.3%)	1 (2.5%)	2 (2.4%)

AE=Adverse Event. SAE=Serious Adverse Event.
Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once.
Drop in VA score >=30 is defined as causing a decrease of >=30 VA score (compared with the last of VA prior to the most recent assessment) lasting more than 1 hour.
Intervention req. to prevent permanent vision loss is defined as required surgical or medical intervention to prevent permanent loss of sight.
Intraocular inflammation (IOI) terms = Anterior chamber inflammation, Chorioretinitis, Iridocyclitis, Iritis, Keratic precipitates, Keratouveitis, Post procedural inflammation, Uveitis, Vitritis, Non-infectious endophthalmitis, Anterior chamber flare, Eye inflammation, Ocular vasculitis, Retinal vasculitis, Cyclitis, Choroiditis, Noninfective chorioretinitis, Anterior chamber cell, Anterior chamber fibrin, Hypopyon, Retinitis, Toxic anterior segment syndrome, Viral keratouveitis, Viral uveitis, Vitreous abscess, Vitreous haze, Vitritis, Retinal occlusive vasculitis.
Includes AEs with onset up to Day 377 (last day of Week 52 analysis visit window).

Program: root/clinical_studies/RO6867461/CDPT7716/share/pool_CTD_safety_update/prod/program/t_ae_oview4.sas
Output: root/clinical_studies/RO6867461/CDPT7716/share/pool_CTD_safety_update/prod/output/t_ae_oview4_SOCUL_IOI2_ADAP_W52_SE_nAMD_JPN.out
05OCT2021 11:13

表 2.7.4.7-43　52週時までに試験眼に発現した眼内炎症（Definition 2，nAMD 統合，GR40306試験及び GR40844試験，ADA 陰性患者）

Safety Summary through Week 52, Study Eye, ADA Negative, Intraocular Inflammation Revised Definition 2
Protocol: GR40306 & GR40844
Clinical Cutoff Date: TENAYA 19JAN2021 (global enrollment) 26MAY2021 (Japan extension), LUCERNE 28DEC2020

	GR40306(TENAYA) (N=324)	GR40844(LUCERNE) (N=289)	Pooled(TENAYA and LUCERNE) (N=613)
	Faricimab 6 mg (N=324)	Faricimab 6 mg (N=289)	Faricimab 6 mg (N=613)
AE			
AE	1 (0.3%)	7 (2.4%)	8 (1.3%)
SAE	0	3 (1.0%)	3 (0.5%)
Severe AE	0	2 (0.7%)	2 (0.3%)
AE of Special Interest			
Drop in VA score >=30	0	1 (0.3%)	1 (0.2%)
Associated with severe IOI	0	1 (0.3%)	1 (0.2%)
Intervention req. to prevent permanent vision loss	0	0	0
Total number of patients with IOI at least 2 times	0	2 (0.7%)	2 (0.3%)

AE=Adverse Event. SAE=Serious Adverse Event.
Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once.
Drop in VA score >=30 is defined as causing a decrease of >=30 VA score (compared with the last of VA prior to the most recent assessment) lasting more than 1 hour.
Intervention req. to prevent permanent vision loss is defined as required surgical or medical intervention to prevent permanent loss of sight.
Intraocular inflammation (IOI) terms = Anterior chamber inflammation, Chorioretinitis, Iridocyclitis, Iritis, Keratic precipitates, Keratouveitis, Post procedural inflammation, Uveitis, Vitritis, Non-infectious endophthalmitis, Anterior chamber flare, Eye inflammation, Ocular vasculitis, Retinal vasculitis, Cyclitis, Choroiditis, Noninfective chorioretinitis, Anterior chamber cell, Anterior chamber fibrin, Hypopyon, Retinitis, Toxic anterior segment syndrome, Viral keratouveitis, Viral uveitis, Vitreous abscess, Vitreous haze, Vitritis, Retinal occlusive vasculitis.
Includes AEs with onset up to Day 377 (last day of Week 52 analysis visit window).

Program: root/clinical_studies/RO6867461/CDPT7716/share/pool_CTD_safety_update/prod/program/t_ae_oview4.sas
Output: root/clinical_studies/RO6867461/CDPT7716/share/pool_CTD_safety_update/prod/output/t_ae_oview4_SOCUL_IOI2_ADAN_W52_SE_nAMD_JPN.out
05OCT2021 11:15

表 2.7.4.7-44　56週時までに試験眼に発現した眼内炎症（Definition 2，DME 統合，GR40349試験及び GR40398試，ADA 陽性患者）

Safety Summary through Week 56, Study Eye, ADA Positive, Intraocular Inflammation Revised Definition 2
Protocol: GR40349 & GR40398
Clinical Cutoff Date: YOSEMITE 20OCT2020 and RHINE 19OCT2020

	GR40349(YOSEMITE) (N=67)		GR40398(RHINE) (N=46)		Pooled(YOSEMITE and RHINE) (N=113)		
	Faricimab 6 mg Q8W (N=34)	Faricimab 6 mg PTI (N=33)	Faricimab 6 mg Q8W (N=23)	Faricimab 6 mg PTI (N=23)	Faricimab 6 mg Q8W (N=57)	Faricimab 6 mg PTI (N=56)	Faricimab 6 mg All (N=113)
AE							
AE	4 (11.8%)	7 (21.2%)	0	1 (4.3%)	4 (7.0%)	8 (14.3%)	12 (10.6%)
SAE	1 (2.9%)	4 (12.1%)	0	0	1 (1.8%)	4 (7.1%)	5 (4.4%)
Severe AE	1 (2.9%)	2 (6.1%)	0	0	1 (1.8%)	2 (3.6%)	3 (2.7%)
AE of Special Interest							
Drop in VA score >=30	0	0	0	0	0	0	0
Associated with severe IOI	1 (2.9%)	3 (9.1%)	0	0	1 (1.8%)	3 (5.4%)	4 (3.5%)
Intervention req. to prevent permanent vision loss	0	1 (3.0%)	0	0	0	1 (1.8%)	1 (0.9%)
Total number of patients with IOI at least 2 times	0	4 (12.1%)	0	0	0	4 (7.1%)	4 (3.5%)

AE=Adverse Event. SAE=Serious Adverse Event.
Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once.
Drop in VA score >=30 is defined as causing a decrease of >=30 VA score (compared with the last of VA prior to the most recent assessment) lasting more than 1 hour.
Intervention req. to prevent permanent vision loss is defined as required surgical or medical intervention to prevent permanent loss of sight.
Intraocular inflammation (IOI) terms = Anterior chamber inflammation, Chorioretinitis, Iridocyclitis, Iritis, Keratic precipitates, Keratouveitis, Post procedural inflammation, Uveitis, Vitritis, Non-infectious endophthalmitis, Anterior chamber flare, Eye inflammation, Ocular vasculitis, Retinal vasculitis, Cyclitis, Choroiditis, Noninfective chorioretinitis, Anterior chamber cell, Anterior chamber fibrin, Hypopyon, Retinitis, Toxic anterior segment syndrome, Viral keratouveitis, Viral uveitis, Vitreous abscess, Vitreous haze, Vitritis.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).
PTI = Personalized Treatment Interval (from Q4W up to Q16W).

Program: root/clinical_studies/RO6867461/CDT70122/share/pool_DME_SCE_SCS/prod/program/t_ae_oview4.sas
Output: root/clinical_studies/RO6867461/CDT70122/share/pool_DME_SCE_SCS/prod/output/t_ae_oview4_SOCUL_IOI2_ADAP_W56_SE_DME_HLS.out
05OCT2021 11:27

表 2.7.4.7-45　56週時までに試験眼に発現した眼内炎症（Definition 2，DME 統合，GR40349試験及び GR40398試，ADA 陰性患者）

Safety Summary through Week 56, Study Eye, ADA Negative, Intraocular Inflammation Revised Definition 2
Protocol: GR40349 & GR40398
Clinical Cutoff Date: YOSEMITE 20OCT2020 and RHINE 19OCT2020

	GR40349(YOSEMITE) (N=552)		GR40398(RHINE) (N=578)		Pooled(YOSEMITE and RHINE) (N=1130)		
	Faricimab 6 mg Q8W (N=275)	Faricimab 6 mg PTI (N=277)	Faricimab 6 mg Q8W (N=287)	Faricimab 6 mg PTI (N=291)	Faricimab 6 mg Q8W (N=562)	Faricimab 6 mg PTI (N=568)	Faricimab 6 mg All (N=1130)
AE							
AE	2 (0.7%)	0	3 (1.0%)	1 (0.3%)	5 (0.9%)	1 (0.2%)	6 (0.5%)
SAE	0	0	0	0	0	0	0
Severe AE	0	0	0	0	0	0	0
AE of Special Interest							
Drop in VA score >=30	0	0	0	0	0	0	0
Associated with severe IOI	0	0	0	0	0	0	0
Intervention req. to prevent permanent vision loss	0	0	0	0	0	0	0
Total number of patients with IOI at least 2 times	0	0	1 (0.3%)	0	1 (0.2%)	0	1 (<0.1%)

AE=Adverse Event. SAE=Serious Adverse Event.
Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once.
Drop in VA score >=30 is defined as causing a decrease of >=30 VA score (compared with the last of VA prior to the most recent assessment) lasting more than 1 hour.
Intervention req. to prevent permanent vision loss is defined as required surgical or medical intervention to prevent permanent loss of sight.
Intraocular inflammation (IOI) terms = Anterior chamber inflammation, Chorioretinitis, Iridocyclitis, Iritis, Keratic precipitates, Keratouveitis, Post procedural inflammation, Uveitis, Vitritis, Non-infectious endophthalmitis, Anterior chamber flare, Eye inflammation, Ocular vasculitis, Retinal vasculitis, Cyclitis, Choroiditis, Noninfective chorioretinitis, Anterior chamber cell, Anterior chamber fibrin, Hypopyon, Retinitis, Toxic anterior segment syndrome, Viral keratouveitis, Viral uveitis, Vitreous abscess, Vitreous haze, Vitritis.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).
PTI = Personalized Treatment Interval (from Q4W up to Q16W).

Program: root/clinical_studies/RO6867461/CDT70122/share/pool_DME_SCE_SCS/prod/program/t_ae_oview4.sas
Output: root/clinical_studies/RO6867461/CDT70122/share/pool_DME_SCE_SCS/prod/output/t_ae_oview4_SOCUL_IOI2_ADAN_W56_SE_DME_HLS.out
05OCT2021 11:29

表 2.7.4.7-46 52週時までに試験眼に発現した眼内炎症（Definition 2，nAMD 統合，GR40306試験及び GR40844試験）

Safety Summary through Week 52, Study Eye, Intraocular inflammation Revised Definition 2
Protocol: GR40306 & GR40844
Clinical Cutoff Date: TENAYA 19JAN2021 (global enrollment) 26MAY2021 (Japan extension), LUCERNE 28DEC2020

	GR40306(TENAYA) (N=750)		GR40844(LUCERNE) (N=657)		Pooled(TENAYA and LUCERNE) (N=1407)	
	Faricimab 6 mg (N=373)	Aflibercept 2 mg (N=377)	Faricimab 6 mg (N=331)	Aflibercept 2 mg (N=326)	Faricimab 6 mg (N=704)	Aflibercept 2 mg (N=703)
AE						
AE	8 (2.1%)	3 (0.8%)	9 (2.7%)	8 (2.5%)	17 (2.4%)	11 (1.6%)
AE - Related	5 (1.3%)	2 (0.5%)	5 (1.5%)	6 (1.8%)	10 (1.4%)	8 (1.1%)
Death	0	0	0	0	0	0
SAE	2 (0.5%)	0	4 (1.2%)	2 (0.6%)	6 (0.9%)	2 (0.3%)
SAE - Related	1 (0.3%)	0	3 (0.9%)	2 (0.6%)	4 (0.6%)	2 (0.3%)
SAE other than death	2 (0.5%)	0	4 (1.2%)	2 (0.6%)	6 (0.9%)	2 (0.3%)
SAE other than death - Related	1 (0.3%)	0	3 (0.9%)	2 (0.6%)	4 (0.6%)	2 (0.3%)
AE leading to study treatment discontinuation	1 (0.3%)	0	4 (1.2%)	2 (0.6%)	5 (0.7%)	2 (0.3%)
AE by severity						
Mild	6 (1.6%)	1 (0.3%)	3 (0.9%)	5 (1.5%)	9 (1.3%)	6 (0.9%)
Mild - Related	4 (1.1%)	0	2 (0.6%)	3 (0.9%)	6 (0.9%)	3 (0.4%)
Moderate	1 (0.3%)	2 (0.5%)	6 (1.8%)	3 (0.9%)	7 (1.0%)	5 (0.7%)
Moderate - Related	1 (0.3%)	2 (0.5%)	3 (0.9%)	3 (0.9%)	4 (0.6%)	5 (0.7%)
Severe	2 (0.5%)	0	2 (0.6%)	1 (0.3%)	4 (0.6%)	1 (0.1%)
Severe - Related	1 (0.3%)	0	1 (0.3%)	1 (0.3%)	2 (0.3%)	1 (0.1%)

AE=Adverse Event. SAE=Serious Adverse Event.
Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once.
Intraocular inflammation (IOI) terms = Anterior chamber inflammation, Chorioretinitis, Iridocyclitis, Iritis, Keratic precipitates, Keratouveitis, Post procedural inflammation, Uveitis, Vitritis, Non-infectious endophthalmitis, Anterior chamber flare, Eye inflammation, Ocular vasculitis, Retinal vasculitis, Cyclitis, Choroiditis, Noninfective chorioretinitis, Anterior chamber cell, Anterior chamber fibrin, Hypopyon, Retinitis, Toxic anterior segment syndrome, Viral keratouveitis, Viral uveitis, Vitreous abscess, Vitreous haze, Vitritis, Retinal occlusive vasculitis.
Includes AEs with onset up to Day 377 (last day of Week 52 analysis visit window).

Program: root/clinical_studies/RO6867461/CDPT7716/share/pool_CTD_safety_update/prod/program/t_ae_oview3.sas
Output: root/clinical_studies/RO6867461/CDPT7716/share/pool_CTD_safety_update/prod/output/t_ae_oview3_SOCUL_IOI2_W52_SE_nAMD_JPN.out
28SEP2021 13:21

表 2.7.4.7-47　52週時までに試験眼に発現した眼圧上昇（Definition 2，nAMD 統合，GR40306試験及び GR40844試験）

Safety Summary through Week 52, Study Eye, Intraocular Pressure Increased Revised Definition 2
Protocol: GR40306 & GR40844
Clinical Cutoff Date: TENAYA 19JAN2021 (global enrollment) 26MAY2021 (Japan extension), LUCERNE 28DEC2020

	GR40306(TENAYA) (N=750)		GR40844(LUCERNE) (N=657)		Pooled(TENAYA and LUCERNE) (N=1407)	
	Faricimab 6 mg (N=373)	Aflibercept 2 mg (N=377)	Faricimab 6 mg (N=331)	Aflibercept 2 mg (N=326)	Faricimab 6 mg (N=704)	Aflibercept 2 mg (N=703)
AE						
AE	11 (2.9%)	11 (2.9%)	10 (3.0%)	9 (2.8%)	21 (3.0%)	20 (2.8%)
AE - Related	0	5 (1.3%)	2 (0.6%)	1 (0.3%)	2 (0.3%)	6 (0.9%)
Death	0	0	0	0	0	0
SAE	0	0	1 (0.3%)	0	1 (0.1%)	0
SAE - Related	0	0	0	0	0	0
SAE other than death	0	0	1 (0.3%)	0	1 (0.1%)	0
SAE other than death - Related	0	0	0	0	0	0
AE leading to study treatment discontinuation	0	0	0	0	0	0
AE by severity						
Mild	10 (2.7%)	9 (2.4%)	6 (1.8%)	6 (1.8%)	16 (2.3%)	15 (2.1%)
Mild - Related	0	5 (1.3%)	2 (0.6%)	0	2 (0.3%)	5 (0.7%)
Moderate	2 (0.5%)	2 (0.5%)	3 (0.9%)	4 (1.2%)	5 (0.7%)	6 (0.9%)
Moderate - Related	0	0	0	1 (0.3%)	0	1 (0.1%)
Severe	0	0	2 (0.6%)	1 (0.3%)	2 (0.3%)	1 (0.1%)
Severe - Related	0	0	0	0	0	0

AE=Adverse Event. SAE=Serious Adverse Event.
Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once.
Intraocular Pressure Increased terms = Intraocular pressure increased, Intraocular pressure fluctuation, Intraocular pressure test abnormal, Ocular hypertension.
Includes AEs with onset up to Day 377 (last day of Week 52 analysis visit window).

Program: root/clinical_studies/RO6867461/CDPT7716/share/pool_CTD_safety_update/prod/program/t_ae_oview3.sas
Output: root/clinical_studies/RO6867461/CDPT7716/share/pool_CTD_safety_update/prod/output/t_ae_oview3_SOCUL_IPI2_W52_SE_nAMD_JPN.out
10SEP2021 15:17

表 2.7.4.7-48　52週時までに試験眼に発現した網膜色素上皮裂孔（nAMD 統合，GR40306試験及び GR40844試験）

Safety Summary through Week 52, Study Eye, Retinal Pigment Epithelium Tears
Protocol: GR40306 & GR40844
Clinical Cutoff Date: TENAYA 19JAN2021 (global enrollment) 26MAY2021 (Japan extension), LUCERNE 28DEC2020

	GR40306(TENAYA) (N=750)		GR40844(LUCERNE) (N=657)		Pooled(TENAYA and LUCERNE) (N=1407)	
	Faricimab 6 mg (N=373)	Aflibercept 2 mg (N=377)	Faricimab 6 mg (N=331)	Aflibercept 2 mg (N=326)	Faricimab 6 mg (N=704)	Aflibercept 2 mg (N=703)
AE						
AE	9 (2.4%)	6 (1.6%)	10 (3.0%)	3 (0.9%)	19 (2.7%)	9 (1.3%)
AE - Related	5 (1.3%)	1 (0.3%)	3 (0.9%)	1 (0.3%)	8 (1.1%)	2 (0.3%)
Death	0	0	0	0	0	0
SAE	2 (0.5%)	0	2 (0.6%)	0	4 (0.6%)	0
SAE - Related	2 (0.5%)	0	2 (0.6%)	0	4 (0.6%)	0
SAE other than death	2 (0.5%)	0	2 (0.6%)	0	4 (0.6%)	0
SAE other than death - Related	2 (0.5%)	0	2 (0.6%)	0	4 (0.6%)	0
AE leading to study treatment discontinuation	0	0	1 (0.3%)	0	1 (0.1%)	0
AE by severity						
Mild	5 (1.3%)	6 (1.6%)	7 (2.1%)	1 (0.3%)	12 (1.7%)	7 (1.0%)
Mild - Related	3 (0.8%)	1 (0.3%)	1 (0.3%)	0	4 (0.6%)	1 (0.1%)
Moderate	4 (1.1%)	0	1 (0.3%)	2 (0.6%)	5 (0.7%)	2 (0.3%)
Moderate - Related	2 (0.5%)	0	1 (0.3%)	1 (0.3%)	3 (0.4%)	1 (0.1%)
Severe	0	0	2 (0.6%)	0	2 (0.3%)	0
Severe - Related	0	0	1 (0.3%)	0	1 (0.1%)	0

AE=Adverse Event. SAE=Serious Adverse Event.
Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once.
Includes AEs with onset up to Day 377 (last day of Week 52 analysis visit window).

Program: root/clinical_studies/RO6867461/CDPT7716/share/pool_CTD_safety_update/prod/program/t_ae_oview3.sas
Output: root/clinical_studies/RO6867461/CDPT7716/share/pool_CTD_safety_update/prod/output/t_ae_oview3_SOCUL_RPE_W52_SE_nAMD_JPN.out
09SEP2021 20:22

表 2.7.4.7-49 52週時までに発現した VEGF 阻害作用に関連する全身性の有害事象（Definition 2，nAMD 統合，GR40306試験及び GR40844試験）

Non-Ocular Adverse Events Related to anti-VEGF Effect Revised Definition 2 through Week 52
Protocol: GR40306 & GR40844
Clinical Cutoff Date: TENAYA 19JAN2021 (global enrollment) 26MAY2021 (Japan extension), LUCERNE 28DEC2020

	GR40306(TENAYA) (N=750)		GR40844(LUCERNE) (N=657)		Pooled(TENAYA and LUCERNE) (N=1407)	
MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg (N=373)	Aflibercept 2 mg (N=377)	Faricimab 6 mg (N=331)	Aflibercept 2 mg (N=326)	Faricimab 6 mg (N=704)	Aflibercept 2 mg (N=703)
Total number of patients with at least one adverse event	40 (10.7%)	39 (10.3%)	27 (8.2%)	42 (12.9%)	67 (9.5%)	81 (11.5%)
Overall total number of events	47	43	33	53	80	96
Hypertension						
Total number of patients with at least one adverse event	20 (5.4%)	16 (4.2%)	11 (3.3%)	15 (4.6%)	31 (4.4%)	31 (4.4%)
Total number of events	20	17	11	16	31	33
高血圧	19 (5.1%)	10 (2.7%)	8 (2.4%)	10 (3.1%)	27 (3.8%)	20 (2.8%)
血圧上昇	0	3 (0.8%)	1 (0.3%)	5 (1.5%)	1 (0.1%)	8 (1.1%)
本態性高血圧症	1 (0.3%)	1 (0.3%)	0	0	1 (0.1%)	1 (0.1%)
コントロール不良の血圧	0	1 (0.3%)	0	0	0	1 (0.1%)
起立性高血圧	0	1 (0.3%)	0	0	0	1 (0.1%)
高血圧クリーゼ	0	0	1 (0.3%)	0	1 (0.1%)	0
収縮期血圧上昇	0	0	1 (0.3%)	0	1 (0.1%)	0

AE=Adverse Event. SAE=Serious Adverse Event.
Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once.
Non-ocular adverse events Related to anti-VEGF Effect Revised Definition 2 (APTC2) terms = Hypertension (SMQ), Haemorrhages (SMQ), Conditions associated with central nervous system haemorrhages and cerebrovascular accidents (SMQ), Haemorrhagic central nervous system vascular conditions (SMQ), Embolic and thrombotic events, arterial (SMQ), Myocardial infarction (SMQ), Other ischaemic heart disease (SMQ), Ischaemic central nervous system vascular conditions (SMQ), Embolic and thrombotic events, venous (SMQ).
Hypertension terms = Hypertension (narrow).
Hemorrhage terms = Conditions associated with central nervous system haemorrhages and cerebrovascular accidents (narrow), Haemorrhagic central nervous system vascular conditions (narrow).
Embolic and thrombotic events, arterial terms = Embolic and thrombotic events, arterial (narrow), Myocardial infarction (narrow), Other ischaemic heart disease (narrow), Ischaemic central nervous system vascular conditions (narrow)
Embolic and thrombotic events, venous terms = Embolic and thrombotic events, venous (narrow).
Includes AEs with onset up to Day 377 (last day of Week 52 analysis visit window).

Program: root/clinical_studies/RO6867461/CDPT7716/share/pool_CTD_safety_update/prod/program/t_ae_cat.sas
Output: root/clinical_studies/RO6867461/CDPT7716/share/pool_CTD_safety_update/prod/output/t_ae_cat_NOCUL_APTC2_W52_SE_nAMD_JPN.out
22SEP2021 15:43

表 2.7.4.7-49 52週時までに発現した VEGF 阻害作用に関連する全身性の有害事象（Definition 2, nAMD 統合, GR40306試験及び GR40844試験）（続）

Non-Ocular Adverse Events Related to anti-VEGF Effect Revised Definition 2 through Week 52
Protocol: GR40306 & GR40844
Clinical Cutoff Date: TENAYA 19JAN2021 (global enrollment) 26MAY2021 (Japan extension), LUCERNE 28DEC2020

MedDRA System Organ Class MedDRA Preferred Term	GR40306(TENAYA) (N=750)		GR40844(LUCERNE) (N=657)		Pooled(TENAYA and LUCERNE) (N=1407)	
	Faricimab 6 mg (N=373)	Aflibercept 2 mg (N=377)	Faricimab 6 mg (N=331)	Aflibercept 2 mg (N=326)	Faricimab 6 mg (N=704)	Aflibercept 2 mg (N=703)
Haemorrhages						
Total number of patients with at least one adverse event	14 (3.8%)	16 (4.2%)	6 (1.8%)	13 (4.0%)	20 (2.8%)	29 (4.1%)
Total number of events	16	16	9	14	25	30
挫傷	3 (0.8%)	5 (1.3%)	4 (1.2%)	6 (1.8%)	7 (1.0%)	11 (1.6%)
血尿	2 (0.5%)	3 (0.8%)	0	0	2 (0.3%)	3 (0.4%)
血腫	0	2 (0.5%)	1 (0.3%)	1 (0.3%)	1 (0.1%)	3 (0.4%)
胃腸出血	0	2 (0.5%)	0	1 (0.3%)	0	3 (0.4%)
骨挫傷	1 (0.3%)	1 (0.3%)	0	1 (0.3%)	1 (0.1%)	2 (0.3%)
上部消化管出血	1 (0.3%)	1 (0.3%)	0	1 (0.3%)	1 (0.1%)	2 (0.3%)
眼挫傷	2 (0.5%)	0	0	0	2 (0.3%)	0
くも膜下出血	0	0	1 (0.3%)	0	1 (0.1%)	0
カテーテル留置部位血腫	0	0	0	1 (0.3%)	0	1 (0.1%)
下部消化管出血	1 (0.3%)	0	0	0	1 (0.1%)	0
外傷性血腫	0	1 (0.3%)	0	0	0	1 (0.1%)
口腔粘膜血腫	1 (0.3%)	0	0	0	1 (0.1%)	0
痔出血	0	0	0	1 (0.3%)	0	1 (0.1%)
出血性膀胱炎	0	0	0	1 (0.3%)	0	1 (0.1%)
頭蓋内出血	1 (0.3%)	0	0	0	1 (0.1%)	0
尿潜血陽性	1 (0.3%)	0	0	0	1 (0.1%)	0
尿中血陽性	0	1 (0.3%)	0	0	0	1 (0.1%)
脳出血	0	0	0	1 (0.3%)	0	1 (0.1%)
鼻出血	1 (0.3%)	0	0	0	1 (0.1%)	0
不正子宮出血	1 (0.3%)	0	0	0	1 (0.1%)	0
膣出血	1 (0.3%)	0	0	0	1 (0.1%)	0

AE=Adverse Event. SAE=Serious Adverse Event.
Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once.
Non-ocular adverse events Related to anti-VEGF Effect Revised Definition 2 (APTC2) terms = Hypertension (SMQ), Haemorrhages (SMQ), Conditions associated with central nervous system haemorrhages and cerebrovascular accidents (SMQ), Haemorrhagic central nervous system vascular conditions (SMQ), Embolic and thrombotic events, arterial (SMQ), Myocardial infarction (SMQ), Other ischaemic heart disease (SMQ), Ischaemic central nervous system vascular conditions (SMQ), Embolic and thrombotic events, venous (SMQ).
Hypertension terms = Hypertension (narrow).
Hemorrhage terms = Conditions associated with central nervous system haemorrhages and cerebrovascular accidents (narrow), Haemorrhagic central nervous system vascular conditions (narrow).
Embolic and thrombotic events, arterial terms = Embolic and thrombotic events, arterial (narrow), Myocardial infarction (narrow), Other ischaemic heart disease (narrow), Ischaemic central nervous system vascular conditions (narrow)
Embolic and thrombotic events, venous terms = Embolic and thrombotic events, venous (narrow).
Includes AEs with onset up to Day 377 (last day of Week 52 analysis visit window).

Program: root/clinical_studies/RO6867461/CDPT7716/share/pool_CTD_safety_update/prod/program/t_ae_cat.sas
Output: root/clinical_studies/RO6867461/CDPT7716/share/pool_CTD_safety_update/prod/output/t_ae_cat_NOCUL_APTC2_W52_SE_nAMD_JPN.out
22SEP2021 15:43

表 2.7.4.7-49 52週時までに発現した VEGF 阻害作用に関連する全身性の有害事象（Definition 2, nAMD 統合, GR40306試験及び GR40844試験）（続）

Non-Ocular Adverse Events Related to anti-VEGF Effect Revised Definition 2 through Week 52
Protocol: GR40306 & GR40844
Clinical Cutoff Date: TENAYA 19JAN2021 (global enrollment) 26MAY2021 (Japan extension), LUCERNE 28DEC2020

MedDRA System Organ Class MedDRA Preferred Term	GR40306(TENAYA) (N=750)		GR40844(LUCERNE) (N=657)		Pooled(TENAYA and LUCERNE) (N=1407)	
	Faricimab 6 mg (N=373)	Aflibercept 2 mg (N=377)	Faricimab 6 mg (N=331)	Aflibercept 2 mg (N=326)	Faricimab 6 mg (N=704)	Aflibercept 2 mg (N=703)
Arterial thrombotic events						
Total number of patients with at least one adverse event	8 (2.1%)	6 (1.6%)	10 (3.0%)	14 (4.3%)	18 (2.6%)	20 (2.8%)
Total number of events	9	6	10	20	19	26
脳血管発作	3 (0.8%)	1 (0.3%)	2 (0.6%)	4 (1.2%)	5 (0.7%)	5 (0.7%)
冠動脈疾患	1 (0.3%)	0	2 (0.6%)	2 (0.6%)	3 (0.4%)	2 (0.3%)
一過性脳虚血発作	2 (0.5%)	0	1 (0.3%)	1 (0.3%)	3 (0.4%)	1 (0.1%)
狭心症	1 (0.3%)	0	2 (0.6%)	1 (0.3%)	3 (0.4%)	1 (0.1%)
急性心筋梗塞	1 (0.3%)	1 (0.3%)	1 (0.3%)	0	2 (0.3%)	1 (0.1%)
冠動脈硬化症	0	1 (0.3%)	0	1 (0.3%)	0	2 (0.3%)
虚血性脳卒中	0	0	0	2 (0.6%)	0	2 (0.3%)
心筋梗塞	1 (0.3%)	0	0	1 (0.3%)	1 (0.1%)	1 (0.1%)
ラクナ脳卒中	0	0	0	1 (0.3%)	0	1 (0.1%)
頚動脈狭窄	0	0	0	1 (0.3%)	0	1 (0.1%)
血栓性脳梗塞	0	0	1 (0.3%)	0	1 (0.1%)	0
心筋虚血	0	0	1 (0.3%)	0	1 (0.1%)	0
脳梗塞	0	1 (0.3%)	0	0	0	1 (0.1%)
肺動脈血栓症	0	0	0	1 (0.3%)	0	1 (0.1%)
不安定狭心症	0	1 (0.3%)	0	0	0	1 (0.1%)
末梢動脈閉塞性疾患	0	1 (0.3%)	0	0	0	1 (0.1%)
Venous thrombotic events						
Total number of patients with at least one adverse event	2 (0.5%)	3 (0.8%)	2 (0.6%)	3 (0.9%)	4 (0.6%)	6 (0.9%)
Total number of events	2	4	3	3	5	7
肺塞栓症	0	2 (0.5%)	1 (0.3%)	1 (0.3%)	1 (0.1%)	3 (0.4%)
血栓性静脈炎	0	0	2 (0.6%)	0	2 (0.3%)	0
深部静脈血栓症	0	2 (0.5%)	0	0	0	2 (0.3%)
表在性血栓性静脈炎	1 (0.3%)	0	0	1 (0.3%)	1 (0.1%)	1 (0.1%)
肝静脈血栓症	0	0	0	1 (0.3%)	0	1 (0.1%)
四肢静脈血栓症	1 (0.3%)	0	0	0	1 (0.1%)	0

AE=Adverse Event. SAE=Serious Adverse Event.
Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once.
Non-ocular adverse events Related to anti-VEGF Effect Revised Definition 2 (APTC2) terms = Hypertension (SMQ), Haemorrhages (SMQ), Conditions associated with central nervous system haemorrhages and cerebrovascular accidents (SMQ), Haemorrhagic central nervous system vascular conditions (SMQ), Embolic and thrombotic events, arterial (SMQ), Myocardial infarction (SMQ), Other ischaemic heart disease (SMQ), Ischaemic central nervous system vascular conditions (SMQ), Embolic and thrombotic events, venous (SMQ).
Hypertension terms = Hypertension (narrow).
Hemorrhage terms = Conditions associated with central nervous system haemorrhages and cerebrovascular accidents (narrow), Haemorrhagic central nervous system vascular conditions (narrow).
Embolic and thrombotic events, arterial terms = Embolic and thrombotic events, arterial (narrow), Myocardial infarction (narrow), Other ischaemic heart disease (narrow), Ischaemic central nervous system vascular conditions (narrow)
Embolic and thrombotic events, venous terms = Embolic and thrombotic events, venous (narrow).
Includes AEs with onset up to Day 377 (last day of Week 52 analysis visit window).

Program: root/clinical_studies/RO6867461/CDPT7716/share/pool_CTD_safety_update/prod/program/t_ae_cat.sas
Output: root/clinical_studies/RO6867461/CDPT7716/share/pool_CTD_safety_update/prod/output/t_ae_cat_NOCUL_APTC2_W52_SE_nAMD_JPN.out
22SEP2021 15:43

表 2.7.4.7-50　56週時までに試験眼に発現した眼内炎症（Definition 2，DME 統合，GR40349試験及び GR40398試験）

Safety Summary through Week 56, Study Eye, Intraocular inflammation Revised Definition 2
Protocol: GR40349 & GR40398
Clinical Cutoff Date: YOSEMITE 20OCT2020 and RHINE 19OCT2020

	GR40349(YOSEMITE) (N=937)			GR40398(RHINE) (N=950)		
	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Aflibercept 2 mg Q8W (N=311)	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Aflibercept 2 mg Q8W (N=314)
AE						
AE	6 (1.9%)	7 (2.2%)	3 (1.0%)	3 (0.9%)	2 (0.6%)	1 (0.3%)
AE - Related	2 (0.6%)	6 (1.9%)	2 (0.6%)	1 (0.3%)	0	0
Death	0	0	0	0	0	0
SAE	1 (0.3%)	4 (1.3%)	0	0	0	0
SAE - Related	0	4 (1.3%)	0	0	0	0
SAE other than death	1 (0.3%)	4 (1.3%)	0	0	0	0
SAE other than death - Related	0	4 (1.3%)	0	0	0	0
AE leading to study treatment discontinuation	1 (0.3%)	2 (0.6%)	0	0	0	0
AE by severity						
Mild	2 (0.6%)	4 (1.3%)	3 (1.0%)	3 (0.9%)	1 (0.3%)	0
Mild - Related	0	2 (0.6%)	2 (0.6%)	1 (0.3%)	0	0
Moderate	3 (1.0%)	5 (1.6%)	0	0	1 (0.3%)	1 (0.3%)
Moderate - Related	1 (0.3%)	4 (1.3%)	0	0	0	0
Severe	1 (0.3%)	2 (0.6%)	0	0	0	0
Severe - Related	1 (0.3%)	2 (0.6%)	0	0	0	0

AE=Adverse Event. SAE=Serious Adverse Event.
Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once.
Intraocular inflammation (IOI) terms = Anterior chamber inflammation, Chorioretinitis, Iridocyclitis, Iritis, Keratic precipitates, Keratouveitis, Post procedural inflammation, Uveitis, Vitritis, Non-infectious endophthalmitis, Anterior chamber flare, Eye inflammation, Ocular vasculitis, Retinal vasculitis, Cyclitis, Choroiditis, Noninfective chorioretinitis, Anterior chamber cell, Anterior chamber fibrin, Hypopyon, Retinitis, Toxic anterior segment syndrome, Viral keratouveitis, Viral uveitis, Vitreous abscess, Vitreous haze, Vitritis.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).
PTI = Personalized Treatment Interval (from Q4W up to Q16W).

Program: root/clinical_studies/RO6867461/CDT70122/share/pool_DME_SCE_SCS/prod/program/t_ae_oview3.sas
Output: root/clinical_studies/RO6867461/CDT70122/share/pool_DME_SCE_SCS/prod/output/t_ae_oview3_SOCUL_IOI2_W56_SE_DME_HLS.out
28SEP2021 11:09

表 2.7.4.7-50　56週時までに試験眼に発現した眼内炎症（Definition 2，DME 統合，GR40349試験及び GR40398試験）（続）

Safety Summary through Week 56, Study Eye, Intraocular inflammation Revised Definition 2
Protocol: GR40349 & GR40398
Clinical Cutoff Date: YOSEMITE 20OCT2020 and RHINE 19OCT2020

	Pooled(YOSEMITE and RHINE) (N=1887)			
	Faricimab 6 mg Q8W (N=630)	Faricimab 6 mg PTI (N=632)	Faricimab 6 mg All (N=1262)	Aflibercept 2 mg Q8W (N=625)
AE				
AE	9 (1.4%)	9 (1.4%)	18 (1.4%)	4 (0.6%)
AE - Related	3 (0.5%)	6 (0.9%)	9 (0.7%)	2 (0.3%)
Death	0	0	0	0
SAE	1 (0.2%)	4 (0.6%)	5 (0.4%)	0
SAE - Related	0	4 (0.6%)	4 (0.3%)	0
SAE other than death	1 (0.2%)	4 (0.6%)	5 (0.4%)	0
SAE other than death - Related	0	4 (0.6%)	4 (0.3%)	0
AE leading to study treatment discontinuation	1 (0.2%)	2 (0.3%)	3 (0.2%)	0
AE by severity				
Mild	5 (0.8%)	5 (0.8%)	10 (0.8%)	3 (0.5%)
Mild - Related	1 (0.2%)	2 (0.3%)	3 (0.2%)	2 (0.3%)
Moderate	3 (0.5%)	6 (0.9%)	9 (0.7%)	1 (0.2%)
Moderate - Related	1 (0.2%)	4 (0.6%)	5 (0.4%)	0
Severe	1 (0.2%)	2 (0.3%)	3 (0.2%)	0
Severe - Related	1 (0.2%)	2 (0.3%)	3 (0.2%)	0

AE=Adverse Event. SAE=Serious Adverse Event.
Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once.
Intraocular inflammation (IOI) terms = Anterior chamber inflammation, Chorioretinitis, Iridocyclitis, Iritis, Keratic precipitates, Keratouveitis, Post procedural inflammation, Uveitis, Vitritis, Non-infectious endophthalmitis, Anterior chamber flare, Eye inflammation, Ocular vasculitis, Retinal vasculitis, Cyclitis, Choroiditis, Noninfective chorioretinitis, Anterior chamber cell, Anterior chamber fibrin, Hypopyon, Retinitis, Toxic anterior segment syndrome, Viral keratouveitis, Viral uveitis, Vitreous abscess, Vitreous haze, Vitritis.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).
PTI = Personalized Treatment Interval (from Q4W up to Q16W).

Program: root/clinical_studies/RO6867461/CDT70122/share/pool_DME_SCE_SCS/prod/program/t_ae_oview3.sas
Output: root/clinical_studies/RO6867461/CDT70122/share/pool_DME_SCE_SCS/prod/output/t_ae_oview3_SOCUL_IOI2_W56_SE_DME_HLS.out
28SEP2021 11:09

表 2.7.4.7-51　56週時までに試験眼に発現した眼圧上昇（Definition 2，DME 統合，GR40349試験及び GR40398試験）

Safety Summary through Week 56, Study Eye, Intraocular Pressure Increased Revised Definition 2
Protocol: GR40349 & GR40398
Clinical Cutoff Date: YOSEMITE 20OCT2020 and RHINE 19OCT2020

	GR40349(YOSEMITE) (N=937)			GR40398(RHINE) (N=950)		
	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Aflibercept 2 mg Q8W (N=311)	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Aflibercept 2 mg Q8W (N=314)
AE						
AE	10 (3.2%)	9 (2.9%)	5 (1.6%)	13 (4.1%)	12 (3.8%)	9 (2.9%)
AE - Related	5 (1.6%)	2 (0.6%)	1 (0.3%)	2 (0.6%)	4 (1.3%)	3 (1.0%)
Death	0	0	0	0	0	0
SAE	0	1 (0.3%)	0	0	2 (0.6%)	0
SAE - Related	0	0	0	0	1 (0.3%)	0
SAE other than death	0	1 (0.3%)	0	0	2 (0.6%)	0
SAE other than death - Related	0	0	0	0	1 (0.3%)	0
AE leading to study treatment discontinuation	1 (0.3%)	0	0	0	1 (0.3%)	0
AE by severity						
Mild	7 (2.2%)	4 (1.3%)	5 (1.6%)	9 (2.8%)	6 (1.9%)	8 (2.5%)
Mild - Related	3 (1.0%)	1 (0.3%)	1 (0.3%)	1 (0.3%)	1 (0.3%)	3 (1.0%)
Moderate	2 (0.6%)	6 (1.9%)	0	4 (1.3%)	6 (1.9%)	2 (0.6%)
Moderate - Related	1 (0.3%)	1 (0.3%)	0	1 (0.3%)	2 (0.6%)	0
Severe	1 (0.3%)	0	0	0	1 (0.3%)	0
Severe - Related	1 (0.3%)	0	0	0	1 (0.3%)	0

AE=Adverse Event. SAE=Serious Adverse Event.
Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once.
Intraocular Pressure Increased terms = Intraocular pressure increased, Intraocular pressure fluctuation, Intraocular pressure test abnormal, Ocular hypertension.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).
PTI = Personalized Treatment Interval (from Q4W up to Q16W).

Program: root/clinical_studies/RO6867461/CDT70122/share/pool_DME_SCE_SCS/prod/program/t_ae_oview3.sas
Output: root/clinical_studies/RO6867461/CDT70122/share/pool_DME_SCE_SCS/prod/output/t_ae_oview3_SOCUL_IPI2_W56_SE_DME_HLS.out
10SEP2021 15:30

表 2.7.4.7-51　56週時までに試験眼に発現した眼圧上昇（Definition 2，DME 統合，GR40349試験及び GR40398試験）（続）

Safety Summary through Week 56, Study Eye, Intraocular Pressure Increased Revised Definition 2
Protocol: GR40349 & GR40398
Clinical Cutoff Date: YOSEMITE 20OCT2020 and RHINE 19OCT2020

	Pooled(YOSEMITE and RHINE) (N=1887)			
	Faricimab 6 mg Q8W (N=630)	Faricimab 6 mg PTI (N=632)	Faricimab 6 mg All (N=1262)	Aflibercept 2 mg Q8W (N=625)
AE				
AE	23 (3.7%)	21 (3.3%)	44 (3.5%)	14 (2.2%)
AE - Related	7 (1.1%)	6 (0.9%)	13 (1.0%)	4 (0.6%)
Death	0	0	0	0
SAE	0	3 (0.5%)	3 (0.2%)	0
SAE - Related	0	1 (0.2%)	1 (<0.1%)	0
SAE other than death	0	3 (0.5%)	3 (0.2%)	0
SAE other than death - Related	0	1 (0.2%)	1 (<0.1%)	0
AE leading to study treatment discontinuation	1 (0.2%)	1 (0.2%)	2 (0.2%)	0
AE by severity				
Mild	16 (2.5%)	10 (1.6%)	26 (2.1%)	13 (2.1%)
Mild - Related	4 (0.6%)	2 (0.3%)	6 (0.5%)	4 (0.6%)
Moderate	6 (1.0%)	12 (1.9%)	18 (1.4%)	2 (0.3%)
Moderate - Related	2 (0.3%)	3 (0.5%)	5 (0.4%)	0
Severe	1 (0.2%)	1 (0.2%)	2 (0.2%)	0
Severe - Related	1 (0.2%)	1 (0.2%)	2 (0.2%)	0

AE=Adverse Event. SAE=Serious Adverse Event.
Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once.
Intraocular Pressure Increased terms = Intraocular pressure increased, Intraocular pressure fluctuation, Intraocular pressure test abnormal, Ocular hypertension.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).
PTI = Personalized Treatment Interval (from Q4W up to Q16W).

Program: root/clinical_studies/RO6867461/CDT70122/share/pool_DME_SCE_SCS/prod/program/t_ae_oview3.sas
Output: root/clinical_studies/RO6867461/CDT70122/share/pool_DME_SCE_SCS/prod/output/t_ae_oview3_SOCUL_IPI2_W56_SE_DME_HLS.out
10SEP2021 15:30

表 2.7.4.7-52　56週時までに試験眼に発現した網膜色素上皮裂孔（DME 統合，GR40349試験及び GR40398試験）

Safety Summary through Week 56, Study Eye, Retinal Pigment Epithelium Tears
Protocol: GR40349 & GR40398
Clinical Cutoff Date: YOSEMITE 20OCT2020 and RHINE 19OCT2020

Null Report: No observations met the reporting criteria for inclusion in this output.

AE=Adverse Event. SAE=Serious Adverse Event.
Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).
PTI = Personalized Treatment Interval (from Q4W up to Q16W).

Program: root/clinical_studies/RO6867461/CDT70122/share/pool_DME_SCE_SCS/prod/program/t_ae_oview3.sas
Output: root/clinical_studies/RO6867461/CDT70122/share/pool_DME_SCE_SCS/prod/output/t_ae_oview3_SOCUL_RPE_W56_SE_DME_HLS.out
09SEP2021 20:25 Page 1 of 1

表 2.7.4.7-53 56週時までに発現したVEGF阻害作用に関連する全身性の有害事象（Definition 2，DME統合，GR40349試験及びGR40398試験）

Non-Ocular Adverse Events Related to anti-VEGF Effect Revised Definition 2 through Week 56
Protocol: GR40349 & GR40398
Clinical Cutoff Date: YOSEMITE 20OCT2020 and RHINE 19OCT2020

MedDRA System Organ Class MedDRA Preferred Term	GR40349(YOSEMITE) (N=937)			GR40398(RHINE) (N=950)			Pooled(YOSEMITE and RHINE) (N=1887)			
	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Aflibercept 2 mg Q8W (N=311)	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Aflibercept 2 mg Q8W (N=314)	Faricimab 6 mg Q8W (N=630)	Faricimab 6 mg PTI (N=632)	Faricimab 6 mg All (N=1262)	Aflibercept 2 mg Q8W (N=625)
Total number of patients with at least one adverse event	46 (14.7%)	42 (13.4%)	48 (15.4%)	29 (9.1%)	39 (12.2%)	32 (10.2%)	75 (11.9%)	81 (12.8%)	156 (12.4%)	80 (12.8%)
Overall total number of events	61	54	66	35	52	36	96	106	202	102
Hypertension										
Total number of patients with at least one adverse event	19 (6.1%)	24 (7.7%)	29 (9.3%)	16 (5.0%)	23 (7.2%)	19 (6.1%)	35 (5.6%)	47 (7.4%)	82 (6.5%)	48 (7.7%)
Total number of events	23	26	32	16	24	19	39	50	89	51
高血圧	17 (5.4%)	18 (5.8%)	25 (8.0%)	15 (4.7%)	19 (6.0%)	12 (3.8%)	32 (5.1%)	37 (5.9%)	69 (5.5%)	37 (5.9%)
血圧上昇	1 (0.3%)	2 (0.6%)	3 (1.0%)	1 (0.3%)	2 (0.6%)	4 (1.3%)	2 (0.3%)	4 (0.6%)	6 (0.5%)	7 (1.1%)
高血圧クリーゼ	0	1 (0.3%)	0	0	2 (0.6%)	1 (0.3%)	0	3 (0.5%)	3 (0.2%)	1 (0.2%)

AE=Adverse Event. SAE=Serious Adverse Event.
Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once.
Non-ocular adverse events Related to anti-VEGF Effect Revised Definition 2 (APTC2) terms = Hypertension (SMQ), Haemorrhages (SMQ), Conditions associated with central nervous system haemorrhages and cerebrovascular accidents (SMQ), Haemorrhagic central nervous system vascular conditions (SMQ), Embolic and thrombotic events, arterial (SMQ), Myocardial infarction (SMQ), Other ischaemic heart disease (SMQ), Ischaemic central nervous system vascular conditions (SMQ), Embolic and thrombotic events, venous (SMQ).
Hypertension terms = Hypertension (narrow).
Hemorrhage terms = Conditions associated with central nervous system haemorrhages and cerebrovascular accidents (narrow), Haemorrhagic central nervous system vascular conditions (narrow).
Embolic and thrombotic events, arterial terms = Embolic and thrombotic events, arterial (narrow), Myocardial infarction (narrow), Other ischaemic heart disease (narrow), Ischaemic central nervous system vascular conditions (narrow)
Embolic and thrombotic events, venous terms = Embolic and thrombotic events, venous (narrow).
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).
PTI = Personalized Treatment Interval (from Q4W up to Q16W).

Program: root/clinical_studies/RO6867461/CDT70122/share/pool_DME_SCE_SCS/prod/program/t_ae_cat.sas
Output: root/clinical_studies/RO6867461/CDT70122/share/pool_DME_SCE_SCS/prod/output/t_ae_cat_NOCUL_APTC2_W56_SE_DME_HLS.out
22SEP2021 15:15

表 2.7.4.7-53 56週時までに発現したVEGF阻害作用に関連する全身性の有害事象（Definition 2，DME統合，GR40349試験及びGR40398試験）（続）

Non-Ocular Adverse Events Related to anti-VEGF Effect Revised Definition 2 through Week 56
Protocol: GR40349 & GR40398
Clinical Cutoff Date: YOSEMITE 20OCT2020 and RHINE 19OCT2020

	GR40349(YOSEMITE) (N=937)			GR40398(RHINE) (N=950)			Pooled(YOSEMITE and RHINE) (N=1887)			
MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Aflibercept 2 mg Q8W (N=311)	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Aflibercept 2 mg Q8W (N=314)	Faricimab 6 mg Q8W (N=630)	Faricimab 6 mg PTI (N=632)	Faricimab 6 mg All (N=1262)	Aflibercept 2 mg Q8W (N=625)
高血圧切迫症	0	0	0	0	1 (0.3%)	1 (0.3%)	0	1 (0.2%)	1 (<0.1%)	1 (0.2%)
コントロール不良の血圧	0	0	1 (0.3%)	0	0	0	0	0	0	1 (0.2%)
拡張期血圧上昇	0	1 (0.3%)	0	0	0	0	0	1 (0.2%)	1 (<0.1%)	0
高血圧緊急症	1 (0.3%)	0	0	0	0	0	1 (0.2%)	0	1 (<0.1%)	0
高血圧性心疾患	0	1 (0.3%)	0	0	0	0	0	1 (0.2%)	1 (<0.1%)	0
高血圧性脳症	0	1 (0.3%)	0	0	0	0	0	1 (0.2%)	1 (<0.1%)	0
収縮期血圧上昇	0	0	0	0	0	1 (0.3%)	0	0	0	1 (0.2%)
代謝症候群	0	1 (0.3%)	0	0	0	0	0	1 (0.2%)	1 (<0.1%)	0
Arterial thrombotic events Total number of patients with at least one adverse event	21 (6.7%)	15 (4.8%)	17 (5.5%)	12 (3.8%)	17 (5.3%)	10 (3.2%)	33 (5.2%)	32 (5.1%)	65 (5.2%)	27 (4.3%)

AE=Adverse Event. SAE=Serious Adverse Event.
Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once.
Non-ocular adverse events Related to anti-VEGF Effect Revised Definition 2 (APTC2) terms = Hypertension (SMQ), Haemorrhages (SMQ), Conditions associated with central nervous system haemorrhages and cerebrovascular accidents (SMQ), Haemorrhagic central nervous system vascular conditions (SMQ), Embolic and thrombotic events, arterial (SMQ), Myocardial infarction (SMQ), Other ischaemic heart disease (SMQ), Ischaemic central nervous system vascular conditions (SMQ), Embolic and thrombotic events, venous (SMQ).
Hypertension terms = Hypertension (narrow).
Hemorrhage terms = Conditions associated with central nervous system haemorrhages and cerebrovascular accidents (narrow), Haemorrhagic central nervous system vascular conditions (narrow).
Embolic and thrombotic events, arterial terms = Embolic and thrombotic events, arterial (narrow), Myocardial infarction (narrow), Other ischaemic heart disease (narrow), Ischaemic central nervous system vascular conditions (narrow)
Embolic and thrombotic events, venous terms = Embolic and thrombotic events, venous (narrow).
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).
PTI = Personalized Treatment Interval (from Q4W up to Q16W).

Program: root/clinical_studies/RO6867461/CDT70122/share/pool_DME_SCE_SCS/prod/program/t_ae_cat.sas
Output: root/clinical_studies/RO6867461/CDT70122/share/pool_DME_SCE_SCS/prod/output/t_ae_cat_NOCUL_APTC2_W56_SE_DME_HLS.out
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表 2.7.4.7-53　56週時までに発現したVEGF阻害作用に関連する全身性の有害事象（Definition 2，DME統合，GR40349試験及びGR40398試験）（続）

Non-Ocular Adverse Events Related to anti-VEGF Effect Revised Definition 2 through Week 56
Protocol: GR40349 & GR40398
Clinical Cutoff Date: YOSEMITE 20OCT2020 and RHINE 19OCT2020

MedDRA System Organ Class MedDRA Preferred Term	GR40349(YOSEMITE) (N=937)			GR40398(RHINE) (N=950)			Pooled(YOSEMITE and RHINE) (N=1887)			
	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Aflibercept 2 mg Q8W (N=311)	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Aflibercept 2 mg Q8W (N=314)	Faricimab 6 mg Q8W (N=630)	Faricimab 6 mg PTI (N=632)	Faricimab 6 mg All (N=1262)	Aflibercept 2 mg Q8W (N=625)
Total number of events	27	20	22	14	23	10	41	43	84	32
冠動脈疾患	3 (1.0%)	5 (1.6%)	3 (1.0%)	1 (0.3%)	4 (1.3%)	1 (0.3%)	4 (0.6%)	9 (1.4%)	13 (1.0%)	4 (0.6%)
心筋梗塞	1 (0.3%)	3 (1.0%)	4 (1.3%)	3 (0.9%)	1 (0.3%)	2 (0.6%)	4 (0.6%)	4 (0.6%)	8 (0.6%)	6 (1.0%)
急性心筋梗塞	2 (0.6%)	2 (0.6%)	4 (1.3%)	0	1 (0.3%)	2 (0.6%)	2 (0.3%)	3 (0.5%)	5 (0.4%)	6 (1.0%)
狭心症	1 (0.3%)	1 (0.3%)	1 (0.3%)	1 (0.3%)	3 (0.9%)	2 (0.6%)	2 (0.3%)	4 (0.6%)	6 (0.5%)	3 (0.5%)
脳血管発作	2 (0.6%)	3 (1.0%)	1 (0.3%)	1 (0.3%)	1 (0.3%)	1 (0.3%)	3 (0.5%)	4 (0.6%)	7 (0.6%)	2 (0.3%)
心筋虚血	3 (1.0%)	1 (0.3%)	1 (0.3%)	1 (0.3%)	0	1 (0.3%)	4 (0.6%)	1 (0.2%)	5 (0.4%)	2 (0.3%)
一過性脳虚血発作	1 (0.3%)	1 (0.3%)	1 (0.3%)	2 (0.6%)	1 (0.3%)	0	3 (0.5%)	2 (0.3%)	5 (0.4%)	1 (0.2%)
頚動脈硬化症	2 (0.6%)	1 (0.3%)	0	0	2 (0.6%)	0	2 (0.3%)	3 (0.5%)	5 (0.4%)	0
虚血性脳卒中	3 (1.0%)	0	1 (0.3%)	0	0	0	3 (0.5%)	0	3 (0.2%)	1 (0.2%)
冠動脈硬化症	0	1 (0.3%)	0	0	1 (0.3%)	1 (0.3%)	0	2 (0.3%)	2 (0.2%)	1 (0.2%)
虚血性心筋症	0	0	0	0	3 (0.9%)	0	0	3 (0.5%)	3 (0.2%)	0

AE=Adverse Event. SAE=Serious Adverse Event.
Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once.
Non-ocular adverse events Related to anti-VEGF Effect Revised Definition 2 (APTC2) terms = Hypertension (SMQ), Haemorrhages (SMQ), Conditions associated with central nervous system haemorrhages and cerebrovascular accidents (SMQ), Haemorrhagic central nervous system vascular conditions (SMQ), Embolic and thrombotic events, arterial (SMQ), Myocardial infarction (SMQ), Other ischaemic heart disease (SMQ), Ischaemic central nervous system vascular conditions (SMQ), Embolic and thrombotic events, venous (SMQ).
Hypertension terms = Hypertension (narrow).
Hemorrhage terms = Conditions associated with central nervous system haemorrhages and cerebrovascular accidents (narrow), Haemorrhagic central nervous system vascular conditions (narrow).
Embolic and thrombotic events, arterial terms = Embolic and thrombotic events, arterial (narrow), Myocardial infarction (narrow), Other ischaemic heart disease (narrow), Ischaemic central nervous system vascular conditions (narrow)
Embolic and thrombotic events, venous terms = Embolic and thrombotic events, venous (narrow).
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).
PTI = Personalized Treatment Interval (from Q4W up to Q16W).

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表 2.7.4.7-53 56週時までに発現したVEGF阻害作用に関連する全身性の有害事象（Definition 2，DME統合，GR40349試験及びGR40398試験）（続）

Non-Ocular Adverse Events Related to anti-VEGF Effect Revised Definition 2 through Week 56
Protocol: GR40349 & GR40398
Clinical Cutoff Date: YOSEMITE 20OCT2020 and RHINE 19OCT2020

MedDRA System Organ Class MedDRA Preferred Term	GR40349(YOSEMITE) (N=937)			GR40398(RHINE) (N=950)			Pooled(YOSEMITE and RHINE) (N=1887)			
	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Aflibercept 2 mg Q8W (N=311)	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Aflibercept 2 mg Q8W (N=314)	Faricimab 6 mg Q8W (N=630)	Faricimab 6 mg PTI (N=632)	Faricimab 6 mg All (N=1262)	Aflibercept 2 mg Q8W (N=625)
脳梗塞	1 (0.3%)	0	0	1 (0.3%)	1 (0.3%)	0	2 (0.3%)	1 (0.2%)	3 (0.2%)	0
冠動脈狭窄	1 (0.3%)	0	1 (0.3%)	0	0	0	1 (0.2%)	0	1 (<0.1%)	1 (0.2%)
頚動脈閉塞	1 (0.3%)	0	1 (0.3%)	0	0	0	1 (0.2%)	0	1 (<0.1%)	1 (0.2%)
不安定狭心症	0	0	0	1 (0.3%)	1 (0.3%)	0	1 (0.2%)	1 (0.2%)	2 (0.2%)	0
末梢動脈閉塞	1 (0.3%)	0	1 (0.3%)	0	0	0	1 (0.2%)	0	1 (<0.1%)	1 (0.2%)
末梢動脈閉塞性疾患	0	1 (0.3%)	0	1 (0.3%)	0	0	1 (0.2%)	1 (0.2%)	2 (0.2%)	0
トロポニン増加	0	0	1 (0.3%)	0	0	0	0	0	0	1 (0.2%)
ラクナ脳卒中	0	0	0	0	1 (0.3%)	0	0	1 (0.2%)	1 (<0.1%)	0
冠動脈閉塞	0	0	1 (0.3%)	0	0	0	0	0	0	1 (0.2%)
急性冠動脈症候群	0	0	0	0	1 (0.3%)	0	0	1 (0.2%)	1 (<0.1%)	0
頚動脈狭窄	1 (0.3%)	0	0	0	0	0	1 (0.2%)	0	1 (<0.1%)	0
心内膜下虚血	0	0	0	1 (0.3%)	0	0	1 (0.2%)	0	1 (<0.1%)	0

AE=Adverse Event. SAE=Serious Adverse Event.
Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once.
Non-ocular adverse events Related to anti-VEGF Effect Revised Definition 2 (APTC2) terms = Hypertension (SMQ), Haemorrhages (SMQ), Conditions associated with central nervous system haemorrhages and cerebrovascular accidents (SMQ), Haemorrhagic central nervous system vascular conditions (SMQ), Embolic and thrombotic events, arterial (SMQ), Myocardial infarction (SMQ), Other ischaemic heart disease (SMQ), Ischaemic central nervous system vascular conditions (SMQ), Embolic and thrombotic events, venous (SMQ).
Hypertension terms = Hypertension (narrow).
Hemorrhage terms = Conditions associated with central nervous system haemorrhages and cerebrovascular accidents (narrow), Haemorrhagic central nervous system vascular conditions (narrow).
Embolic and thrombotic events, arterial terms = Embolic and thrombotic events, arterial (narrow), Myocardial infarction (narrow), Other ischaemic heart disease (narrow), Ischaemic central nervous system vascular conditions (narrow)
Embolic and thrombotic events, venous terms = Embolic and thrombotic events, venous (narrow).
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).
PTI = Personalized Treatment Interval (from Q4W up to Q16W).

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表 2.7.4.7-53　56週時までに発現したVEGF阻害作用に関連する全身性の有害事象（Definition 2，DME統合，GR40349試験及びGR40398試験）（続）

Non-Ocular Adverse Events Related to anti-VEGF Effect Revised Definition 2 through Week 56
Protocol: GR40349 & GR40398
Clinical Cutoff Date: YOSEMITE 20OCT2020 and RHINE 19OCT2020

	GR40349(YOSEMITE) (N=937)			GR40398(RHINE) (N=950)			Pooled(YOSEMITE and RHINE) (N=1887)			
MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Aflibercept 2 mg Q8W (N=311)	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Aflibercept 2 mg Q8W (N=314)	Faricimab 6 mg Q8W (N=630)	Faricimab 6 mg PTI (N=632)	Faricimab 6 mg All (N=1262)	Aflibercept 2 mg Q8W (N=625)
低酸素性虚血性脳症	1 (0.3%)	0	0	0	0	0	1 (0.2%)	0	1 (<0.1%)	0
動脈閉塞性疾患	0	0	0	0	1 (0.3%)	0	0	1 (0.2%)	1 (<0.1%)	0
脳血管障害	0	1 (0.3%)	0	0	0	0	0	1 (0.2%)	1 (<0.1%)	0
末梢動脈血栓症	1 (0.3%)	0	0	0	0	0	1 (0.2%)	0	1 (<0.1%)	0
Haemorrhages										
Total number of patients with at least one adverse event	8 (2.6%)	7 (2.2%)	9 (2.9%)	3 (0.9%)	4 (1.3%)	5 (1.6%)	11 (1.7%)	11 (1.7%)	22 (1.7%)	14 (2.2%)
Total number of events	9	8	10	3	4	5	12	12	24	15
挫傷	1 (0.3%)	3 (1.0%)	3 (1.0%)	1 (0.3%)	0	0	2 (0.3%)	3 (0.5%)	5 (0.4%)	3 (0.5%)
鼻出血	0	0	1 (0.3%)	1 (0.3%)	1 (0.3%)	1 (0.3%)	1 (0.2%)	1 (0.2%)	2 (0.2%)	2 (0.3%)
胃腸出血	1 (0.3%)	1 (0.3%)	0	0	1 (0.3%)	0	1 (0.2%)	2 (0.3%)	3 (0.2%)	0

AE=Adverse Event. SAE=Serious Adverse Event.
Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once.
Non-ocular adverse events Related to anti-VEGF Effect Revised Definition 2 (APTC2) terms = Hypertension (SMQ), Haemorrhages (SMQ), Conditions associated with central nervous system haemorrhages and cerebrovascular accidents (SMQ), Haemorrhagic central nervous system vascular conditions (SMQ), Embolic and thrombotic events, arterial (SMQ), Myocardial infarction (SMQ), Other ischaemic heart disease (SMQ), Ischaemic central nervous system vascular conditions (SMQ), Embolic and thrombotic events, venous (SMQ).
Hypertension terms = Hypertension (narrow).
Hemorrhage terms = Conditions associated with central nervous system haemorrhages and cerebrovascular accidents (narrow), Haemorrhagic central nervous system vascular conditions (narrow).
Embolic and thrombotic events, arterial terms = Embolic and thrombotic events, arterial (narrow), Myocardial infarction (narrow), Other ischaemic heart disease (narrow), Ischaemic central nervous system vascular conditions (narrow)
Embolic and thrombotic events, venous terms = Embolic and thrombotic events, venous (narrow).
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).
PTI = Personalized Treatment Interval (from Q4W up to Q16W).

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表 2.7.4.7-53 56週時までに発現したVEGF阻害作用に関連する全身性の有害事象（Definition 2，DME統合，GR40349試験及びGR40398試験）（続）

Non-Ocular Adverse Events Related to anti-VEGF Effect Revised Definition 2 through Week 56
Protocol: GR40349 & GR40398
Clinical Cutoff Date: YOSEMITE 20OCT2020 and RHINE 19OCT2020

MedDRA System Organ Class MedDRA Preferred Term	GR40349(YOSEMITE) (N=937)			GR40398(RHINE) (N=950)			Pooled(YOSEMITE and RHINE) (N=1887)			
	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Aflibercept 2 mg Q8W (N=311)	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Aflibercept 2 mg Q8W (N=314)	Faricimab 6 mg Q8W (N=630)	Faricimab 6 mg PTI (N=632)	Faricimab 6 mg All (N=1262)	Aflibercept 2 mg Q8W (N=625)
血便排泄	2 (0.6%)	0	0	0	0	1 (0.3%)	2 (0.3%)	0	2 (0.2%)	1 (0.2%)
血腫	0	0	2 (0.6%)	0	0	0	0	0	0	2 (0.3%)
血尿	1 (0.3%)	0	1 (0.3%)	0	0	0	1 (0.2%)	0	1 (<0.1%)	1 (0.2%)
骨挫傷	0	1 (0.3%)	0	0	0	1 (0.3%)	0	1 (0.2%)	1 (<0.1%)	1 (0.2%)
点状出血	1 (0.3%)	0	1 (0.3%)	0	0	0	1 (0.2%)	0	1 (<0.1%)	1 (0.2%)
脳出血	1 (0.3%)	0	0	1 (0.3%)	0	0	2 (0.3%)	0	2 (0.2%)	0
紫斑	0	0	1 (0.3%)	0	0	0	0	0	0	1 (0.2%)
失血性貧血	1 (0.3%)	0	0	0	0	0	1 (0.2%)	0	1 (<0.1%)	0
出血性卒中	0	1 (0.3%)	0	0	0	0	0	1 (0.2%)	1 (<0.1%)	0
上部消化管出血	0	0	0	0	1 (0.3%)	0	0	1 (0.2%)	1 (<0.1%)	0
静脈破裂	0	0	0	0	0	1 (0.3%)	0	0	0	1 (0.2%)
直腸出血	0	0	0	0	1 (0.3%)	0	0	1 (0.2%)	1 (<0.1%)	0

AE=Adverse Event. SAE=Serious Adverse Event.
Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once.
Non-ocular adverse events Related to anti-VEGF Effect Revised Definition 2 (APTC2) terms = Hypertension (SMQ), Haemorrhages (SMQ), Conditions associated with central nervous system haemorrhages and cerebrovascular accidents (SMQ), Haemorrhagic central nervous system vascular conditions (SMQ), Embolic and thrombotic events, arterial (SMQ), Myocardial infarction (SMQ), Other ischaemic heart disease (SMQ), Ischaemic central nervous system vascular conditions (SMQ), Embolic and thrombotic events, venous (SMQ).
Hypertension terms = Hypertension (narrow).
Hemorrhage terms = Conditions associated with central nervous system haemorrhages and cerebrovascular accidents (narrow), Haemorrhagic central nervous system vascular conditions (narrow).
Embolic and thrombotic events, arterial terms = Embolic and thrombotic events, arterial (narrow), Myocardial infarction (narrow), Other ischaemic heart disease (narrow), Ischaemic central nervous system vascular conditions (narrow)
Embolic and thrombotic events, venous terms = Embolic and thrombotic events, venous (narrow).
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).
PTI = Personalized Treatment Interval (from Q4W up to Q16W).

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表 2.7.4.7-53　56週時までに発現したVEGF阻害作用に関連する全身性の有害事象（Definition 2，DME統合，GR40349試験及びGR40398試験）（続）

Non-Ocular Adverse Events Related to anti-VEGF Effect Revised Definition 2 through Week 56
Protocol: GR40349 & GR40398
Clinical Cutoff Date: YOSEMITE 20OCT2020 and RHINE 19OCT2020

	GR40349(YOSEMITE) (N=937)			GR40398(RHINE) (N=950)			Pooled(YOSEMITE and RHINE) (N=1887)			
MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Aflibercept 2 mg Q8W (N=311)	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Aflibercept 2 mg Q8W (N=314)	Faricimab 6 mg Q8W (N=630)	Faricimab 6 mg PTI (N=632)	Faricimab 6 mg All (N=1262)	Aflibercept 2 mg Q8W (N=625)
斑状出血	0	0	1 (0.3%)	0	0	0	0	0	0	1 (0.2%)
不全片麻痺	1 (0.3%)	0	0	0	0	0	1 (0.2%)	0	1 (<0.1%)	0
喀血	0	1 (0.3%)	0	0	0	0	0	1 (0.2%)	1 (<0.1%)	0
膣出血	0	0	0	0	0	1 (0.3%)	0	0	0	1 (0.2%)

AE=Adverse Event. SAE=Serious Adverse Event.
Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once.
Non-ocular adverse events Related to anti-VEGF Effect Revised Definition 2 (APTC2) terms = Hypertension (SMQ), Haemorrhages (SMQ), Conditions associated with central nervous system haemorrhages and cerebrovascular accidents (SMQ), Haemorrhagic central nervous system vascular conditions (SMQ), Embolic and thrombotic events, arterial (SMQ), Myocardial infarction (SMQ), Other ischaemic heart disease (SMQ), Ischaemic central nervous system vascular conditions (SMQ), Embolic and thrombotic events, venous (SMQ).
Hypertension terms = Hypertension (narrow).
Hemorrhage terms = Conditions associated with central nervous system haemorrhages and cerebrovascular accidents (narrow), Haemorrhagic central nervous system vascular conditions (narrow).
Embolic and thrombotic events, arterial terms = Embolic and thrombotic events, arterial (narrow), Myocardial infarction (narrow), Other ischaemic heart disease (narrow), Ischaemic central nervous system vascular conditions (narrow)
Embolic and thrombotic events, venous terms = Embolic and thrombotic events, venous (narrow).
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).
PTI = Personalized Treatment Interval (from Q4W up to Q16W).

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表 2.7.4.7-53 56週時までに発現したVEGF阻害作用に関連する全身性の有害事象（Definition 2，DME統合，GR40349試験及びGR40398試験）（続）

Non-Ocular Adverse Events Related to anti-VEGF Effect Revised Definition 2 through Week 56
Protocol: GR40349 & GR40398
Clinical Cutoff Date: YOSEMITE 20OCT2020 and RHINE 19OCT2020

	GR40349(YOSEMITE) (N=937)			GR40398(RHINE) (N=950)			Pooled(YOSEMITE and RHINE) (N=1887)			
MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Aflibercept 2 mg Q8W (N=311)	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Aflibercept 2 mg Q8W (N=314)	Faricimab 6 mg Q8W (N=630)	Faricimab 6 mg PTI (N=632)	Faricimab 6 mg All (N=1262)	Aflibercept 2 mg Q8W (N=625)
Venous thrombotic events										
Total number of patients with at least one adverse event	2 (0.6%)	0	1 (0.3%)	2 (0.6%)	1 (0.3%)	2 (0.6%)	4 (0.6%)	1 (0.2%)	5 (0.4%)	3 (0.5%)
Total number of events	2	0	2	2	1	2	4	1	5	4
深部静脈血栓症	0	0	1 (0.3%)	0	1 (0.3%)	1 (0.3%)	0	1 (0.2%)	1 (<0.1%)	2 (0.3%)
肺塞栓症	2 (0.6%)	0	1 (0.3%)	0	0	0	2 (0.3%)	0	2 (0.2%)	1 (0.2%)
頚静脈血栓症	0	0	0	1 (0.3%)	0	0	1 (0.2%)	0	1 (<0.1%)	0
血栓性静脈炎	0	0	0	0	0	1 (0.3%)	0	0	0	1 (0.2%)
鎖骨下静脈血栓症	0	0	0	1 (0.3%)	0	0	1 (0.2%)	0	1 (<0.1%)	0

AE=Adverse Event. SAE=Serious Adverse Event.
Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once.
Non-ocular adverse events Related to anti-VEGF Effect Revised Definition 2 (APTC2) terms = Hypertension (SMQ), Haemorrhages (SMQ), Conditions associated with central nervous system haemorrhages and cerebrovascular accidents (SMQ), Haemorrhagic central nervous system vascular conditions (SMQ), Embolic and thrombotic events, arterial (SMQ), Myocardial infarction (SMQ), Other ischaemic heart disease (SMQ), Ischaemic central nervous system vascular conditions (SMQ), Embolic and thrombotic events, venous (SMQ).
Hypertension terms = Hypertension (narrow).
Hemorrhage terms = Conditions associated with central nervous system haemorrhages and cerebrovascular accidents (narrow), Haemorrhagic central nervous system vascular conditions (narrow).
Embolic and thrombotic events, arterial terms = Embolic and thrombotic events, arterial (narrow), Myocardial infarction (narrow), Other ischaemic heart disease (narrow), Ischaemic central nervous system vascular conditions (narrow)
Embolic and thrombotic events, venous terms = Embolic and thrombotic events, venous (narrow).
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).
PTI = Personalized Treatment Interval (from Q4W up to Q16W).

Program: root/clinical_studies/RO6867461/CDT70122/share/pool_DME_SCE_SCS/prod/program/t_ae_cat.sas
Output: root/clinical_studies/RO6867461/CDT70122/share/pool_DME_SCE_SCS/prod/output/t_ae_cat_NOCUL_APTC2_W56_SE_DME_HLS.out
22SEP2021 15:15

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3) 2.7.3 で引用した文献
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略語一覧

略語	英名	和名
ADA	anti drug antibody	抗薬物抗体
AE	adverse event	有害事象
AMD	age-related macular degeneration	加齢黄斑変性
Ang-2	angiopoietin-2	アンジオポエチン2
AUC	area under the concentration-time curve	薬物濃度-時間曲線下面積
AUC_{0-x}	area under the concentration-time curve from Time 0 to x hours	投与後0時間から x 時間までの薬物濃度-時間曲線下面積
AUC_{inf}	area under the concentration−time curve from Time 0 to infinity	投与後0時間から無限大までの薬物濃度-時間曲線下面積
AUC_{tau}	area under the concentration-time curve during one dosing interval	投与間隔での薬物濃度-時間曲線下面積
BCVA	best corrected visual acuity	最高矯正視力
BLQ	below limit of quantification	定量下限値未満
CI	confidence interval	信頼区間
CI-DME	center-involving diabetic macular edema	中心窩を含む糖尿病黄斑浮腫
C_{max}	maximum observed serum/plasma concentration	最高血清/血漿中薬物濃度
CNV	choroidal neovascularization	脈絡膜新生血管
COVID-19	Coronavirus Disease 2019	新型コロナウイルス感染症
DLE	dose-limiting events	用量制限有害事象
DME	diabetic macular edema	糖尿病黄斑浮腫
DRSS	diabetic retinopathy severity scale	—
ETDRS	Early Treatment Diabetic Retinopathy Study	—
FFA	fundus fluorescein angiography	フルオレセイン蛍光眼底造影
GCP	good clinical practice	医薬品の臨床試験の実施の基準に関する省令
ICGA	indocyanine green angiography	インドシアニングリーン蛍光眼底造影
ITT	intent-to-treat	—
IVT	intravitreal	硝子体内
IxRS	interactive voice or web-based response system	双方向音声認識又はウェブ応答システム
LLD	low luminance deficit	低輝度条件下での視力低下
MAD	multiple-ascending dose	反復投与用量漸増
MMRM	mixed model for repeated measurement	経時測定データに対する混合効果モデル
nAMD	neovascular age-related macular degeneration	新生血管を伴う加齢黄斑変性
NEI VFQ-25	National Eye Institute 25-Item Visual Function Questionnaire	—
NGSP	National Glycohemoglobin Standardization Program	—
NPDR	non-proliferative diabetic retinopathy	非増殖性糖尿病網膜症
OCT	optical coherence tomography	光干渉断層撮影
PCV	polypoidal choroidal vasculopathy	ポリープ状脈絡膜血管症
PTI	personalized treatment interval	—
Q4W	every 4 weeks	4週間隔
Q8W	every 8 weeks	8週間隔
Q12W	every 12 weeks	12週間隔
Q16W	every 16 weeks	16週間隔
QOL	quality of life	生活の質

略語	英名	和名
RAP	retinal angiomatous proliferation	網膜血管腫状増殖
SAD	single ascending dose	単回投与用量漸増
SD-OCT	spectral-domain optical coherence tomography	スペクトラルドメイン光干渉断層撮影
SS-OCT	swept source-optical coherence tomography	波長掃引型光干渉断層撮影
$t_{1/2}$	elimination half-life	消失半減期
T_{max}	time to maximum concentration	最高濃度到達時間
VEGF	vascular endothelial growth factor	血管内皮増殖因子
VEGF-A	vascular endothelial growth factor A	血管内皮増殖因子 A
wAMD	wet age-related macular degeneration	滲出型加齢黄斑変性

2.7.6 個々の試験のまとめ

2.7.6は，ファリシマブ（遺伝子組換え）（以降，ファリシマブ又は別名，RO6867461）硝子体内注射液（以降，本剤）の以下の2つの適応症に対する承認申請（以降，本申請）の臨床データパッケージに含まれる臨床試験の一覧を表2.7.6-1に示し，以降に個々の試験のまとめを記載した。

- 中心窩下脈絡膜新生血管を伴う加齢黄斑変性（nAMD，別名，滲出型加齢黄斑変性，wAMD）
- 糖尿病黄斑浮腫（DME）

表2.7.6-1 臨床試験一覧表

地域	試験番号 資料番号 位置づけ	試験デザイン	対象患者	目的	投与量，投与方法，投与期間	割付・解析例数	試験の進捗状況
海外	BP28936 5.3.3.2-1 評価資料	第 I 相，多施設共同非ランダム化非遮蔽単回及び反復用量漸増並行群間比較試験	nAMD 患者	安全性，忍容性，薬物動態及び薬力学	パート A：（単回投与）：0.5，1.5，3.0又は6.0 mg を IVT 投与 パート B：（反復投与）：3.0又は6.0 mg を Q4W で3回 IVT 投与	計24例 パート a：12例 各群3例 パート b：12例 各群6例	完了
国内	JP39844 5.3.3.2-2 評価資料	第 I 相，多施設共同，非ランダム化，非遮蔽，反復用量漸増投与，非対照試験	nAMD 又は DME 患者	安全性，忍容性，薬物動態及び薬力学	1.5又は6.0 mg を Q4W で IVT 投与（Day 1，29及び57の3回）	計12例 1.5 mg 投与群：6例（内，nAMD 患者は2例） 6.0 mg 投与群：6例（内，nAMD 患者は2例）	完了
海外	BP29647 5.3.5.1-nAMD-1 評価資料	第 II 相，多施設共同，反復投与・複数用法，ランダム化，実薬対照，二重遮蔽，5群並行群間比較，36週間の試験	nAMD 患者	安全性，忍容性，薬物動態及び有効性	A 群：ラニビズマブ0.5 mg を Q4W で32週間（9回）IVT 投与 B 群：本剤1.5 mg を Q4W で32週間（9回）IVT 投与 C 群：本剤6.0 mg を Q4W で32週間（9回）IVT 投与 D 群：本剤6.0 mg を Q4W で12週時まで（4回）IVT 投与，以降は本剤 6.0 mg を Q8W で（すなわち20及び28週時の2回）IVT 投与 E 群：ラニビズマブ0.5 mg を Q4W で8週時まで（3回）IVT 投与，以降は本剤 6.0 mg を Q4W で（6回）IVT 投与	計273例 A 群：68例 B 群：46例 C 群：39例 D 群：46例 E 群：64例 （10例［1施設］は GCP 違反により解析から除外）	完了

表2.7.6-1 臨床試験一覧表（続き）

地域	試験番号 資料番号 位置づけ	試験デザイン	対象患者	目的	投与量，投与方法，投与期間	割付・解析例数	試験の進捗状況
海外	CR39521 5.3.5.1-nAMD-2 評価資料	第 II 相，多施設共同，複数用法，ランダム化，実薬対照，患者・評価者遮蔽，3群並行群間比較試験（52週間の試験）	nAMD 患者	有効性，安全性及び薬物動態	Q12W 群：本剤6.0 mg を Q4W で12週時まで（4回）IVT 投与，以降は本剤6.0 mg を Q12W で48週時まで（24，36及び48週時の3回）IVT 投与 Q16W 群：本剤6.0 mg を Q4W で12週時まで（4回）IVT 投与，以降は24週時の疾患活動性評価により本剤 6.0 mg を12～Q16W で48週時まで IVT 投与 ラニビズマブ Q4W 群：ラニビズマブ0.5 mg を Q4W で48週間（13回）IVT 投与	計76例 A 群：29例 B 群：31例 C 群：16例 （5例［1施設］は GCP 違反により解析から除外）	完了
国際共同	GR40306 5.3.5.1-nAMD-3 評価資料	第 III 相，ランダム化，二重遮蔽，実薬対照，2並行群間比較試験（112週間の試験）	nAMD 患者	有効性，安全性，薬物動態及び薬力学	A 群（本剤群）：本剤6.0 mg を12週時まで Q4W で IVT 投与。20週時，24週時の疾患活動性評価により本剤6.0 mg を60週時まで Q8W～Q16W で IVT 投与。以降は本剤6.0 mg を108週時まで PTI で IVT 投与。（112週時に最終来院） B 群（アフリベルセプト群）：アフリベルセプト2.0 mg を8週時まで Q4W で IVT 投与。以降，アフリベルセプト2.0 mg を108週時まで Q8W で IVT 投与。（112週時に最終来院）	計671例 A 群：334例 B 群：337例	実施中
海外	GR40844 5.3.5.1-nAMD-4 評価資料					計658例 A 群：331例 B 群：327例	実施中

表2.7.6-1 臨床試験一覧表（続き）

地域	試験番号 資料番号 位置づけ	試験デザイン	対象患者	目的	投与量，投与方法，投与期間	割付・解析例数	試験の進捗状況
海外	BP30099 5.3.5.1-DME-1 評価資料	第 II 相，多施設共同，複数用法，ランダム化，実薬対照，二重遮蔽，3並行群間比較，36週間の試験	DME 患者	安全性，忍容性，薬物動態及び有効性	A 群：ラニビズマブ0.3 mg を Q4W で20週間（6回）IVT 投与 B 群：本剤1.5 mg を Q4W で20週間（6回）IVT 投与 C 群：本剤6.0 mg を Q4W で20週間（6回）IVT 投与	未治療患者 計168例 A 群：59例 B 群：54例 C 群：55例 抗 VEGF 薬既治療患者 計61例 A 群：31例 B 群：1例 C 群：29例 （2例［1施設］は GCP 違反により解析から除外）	完了
国際共同	GR40349 5.3.5.1-DME-2 評価資料	第 III 相，ランダム化，二重遮蔽，実薬対照，3並行群間比較試験（100週間の試験）	DME 患者	有効性，安全性，薬物動態及び薬力学	A 群（本剤 Q8W 群）：本剤6.0 mg を20週時まで Q4W で IVT 投与。以降は本剤6.0 mg を96週時まで Q8W で IVT 投与。（100週時に最終来院） B 群（本剤 PTI 群）：本剤6.0 mg を12週時まで Q4W で IVT 投与。以降は本剤6.0 mg を96週時まで PTI で IVT 投与。（100週時に最終来院） C 群（アフリベルセプト Q8W 群）：アフリベルセプト2.0 mg を16週時まで Q4W で IVT 投与。以降はアフリベルセプト2.0 mg を96週時まで Q8W で IVT 投与。（100週時に最終来院）	計940例 A 群：315例 B 群：313例 C 群：312例	実施中
海外	GR40398 5.3.5.1-DME-3 評価資料					計951例 A 群：317例 B 群：319例 C 群：315例	実施中

DME = 糖尿病黄斑浮腫，IVT = 硝子体内投与，nAMD = 新生血管を伴う加齢黄斑変性，PTI = 個別化投与間隔，Q4W = 4 週間隔，Q8W = 8 週間隔，Q12W = 12 週間隔， Q16W = 16 週間隔，LPI = 最後の患者の組入れ

2.7.6.1　概要

2.7.6.1.1　海外第 I 相臨床試験（nAMD 患者への単回，反復投与：BP28936試験）

（評価資料：5.3.3.2-1）

2.7.6.1.1.1　概要表

表 2.7.6.1.1.1-1 概要表（BP28936試験）

治験の標題：nAMD 患者における硝子体内投与後のファリシマブの安全性，忍容性，薬物動態及び薬力学を検討するための多施設共同，非ランダム化，非遮蔽，単回及び反復用量漸増，並行群間比較試験	
施設及び国：米国（5施設），英国（3施設）	
公表文献（引用文献）：なし	
第1症例の登録日：2013年12月2日 最終症例の最終観察日：2015年2月26日	開発のフェーズ：第 I 相
目　　的： 主要目的 nAMD 患者における本剤の単回及び反復硝子体内投与の安全性と忍容性を評価する。 副次的目的 本剤の単回及び反復投与時の全身薬物動態を検討する。 探索的目的 • 最高矯正視力（BCVA）及び解剖学的アウトカムに対する本剤の単回及び反復硝子体内投与の効果を検討する。 • 本剤の濃度を検討し，サンプル量が許せば，房水サンプルにおける炎症性及び血管新生促進因子を検討する。 • 血漿中抗ファリシマブ抗体の発現を検討する。	
治 験 方 法： 加齢黄斑変性（AMD）に続発した脈絡膜新生血管（CNV）を有する患者を対象とした多施設共同，非ランダム化，非対照，非遮蔽，単回及び反復用量漸増，並行群間比較試験。	
症　例　数： 目標例数：最大48例；パート A には最大30例，パート B には最大18例 登録例数：24例：パート A に12例（0.5，1.5，3.0，6.0 mg 各群3例），パート B に12例（3.0及び6.0 mg 各群6例）	
診断及び主要な組入基準： 50歳以上の nAMD 患者で，過去にいずれかの抗血管内皮増殖因子（VEGF）単剤療法による治療を受けたことのある患者。	
被験薬，用量及び投与方法： (1) 被験薬：ファリシマブ製剤 プラセボ（ファリシマブ製剤の適切な用量への希釈にのみ使用） (2) 用量及び投与方法： パート A：0.5 mg，硝子体内，単回投与　パート B：3.0 mg，硝子体内，3回投与，Q4W 1.5 mg，硝子体内，単回投与　6.0 mg，硝子体内，3回投与，Q4W 3.0 mg，硝子体内，単回投与 6.0 mg，硝子体内，単回投与	

対照薬，用量及び投与方法：
(1) 対照薬：該当なし

(2) 用量及び投与方法：該当なし

治 療 期 間：
パート A の各患者の治験の総期間は最長16週であり，その内訳は以下のとおりであった。
- スクリーニング：最長 4 週間
- 入院期間：Day 1
- 安全性のフォローアップ期間：Day 3 から Day 84（12 週時）まで

患者は投与後最長12週間，パート A に留まり，最後の必須の安全性フォローアップ来院は4週時までとした。治験責任医師が評価した医学的要件に基づいて，4週時から12週時までの間に標準治療へ切替えが許容された。懸念のある患者における最後のフォローアップ来院は，患者が標準治療に切り替えられた日に行われた。

パート B の各患者の治験の総期間（スクリーニングから試験完了まで）は最長24週であり，その内訳は以下のとおりであった。
- スクリーニング：最長 4 週間
- 治験薬投与期間：8 週間
- 安全性のフォローアップ期間：最長 12 週間

治験責任医師が評価した医学的要件に基づいて，治験薬の最終投与の4週後から12週後までの間に標準治療へ切替えが許容された。最後のフォローアップ来院は，患者が標準治療に切り替えられた日に行われた。

評 価 基 準：
(1) 薬物動態学的評価項目
主要パラメータ：
最高血漿中薬物濃度（C_{max}），投与後0時間から無限大までの薬物濃度-時間曲線下面積（AUC_{inf}），投与間隔での薬物濃度-時間曲線下面積（AUC_{tau}，パート B のみ）
副次的パラメータ：
最高濃度到達時間（T_{max}），消失半減期（$t_{1/2}$）
探索的パラメータ：
- 必要に応じて硝子体内濃度を評価するためのコンパートメント解析
- 追加で同意が得られた患者における房水サンプル中のファリシマブ濃度

(2) 薬力学的評価項目
機能評価（BCVA 及びコントラスト感度テスト），解剖学的評価項目［スペクトラルドメイン光干渉断層撮影（SD-OCT），フルオレセイン蛍光眼底造影（FFA），インドシアニングリーン蛍光眼底造影（ICGA）］，血漿/房水中バイオマーカー

(3) 安全性評価項目
- BCVA［Early Treatment Diabetic Retinopathy Study（ETDRS）視力表］，細隙灯顕微鏡検査，散瞳下高倍率の双眼倒像鏡検査，コントラスト感度，眼圧，眼底写真，及び SD-OCT 又は血管造影から得られたあらゆる安全性に関連する所見
- 眼の有害事象の発現頻度及び重症度
- 眼以外の有害事象の発現頻度及び重症度
- 血液学的検査，血液生化学的検査及び尿検査に基づく臨床検査値異常の発現頻度
- 抗ファリシマブ抗体の発現頻度
- 心電図
- バイタルサイン
- その他の安全性バイオマーカー

統 計 手 法：
正式な統計学的仮説検定は実施されなかった。
記述統計量及び症例一覧を作成する。

2.7.6.1.1.2 患者の内訳

CNV を伴う AMD 患者24例（パート A：12例；0.5 mg，1.5 mg，3.0 mg 及び6.0 mg に各3例，パート B：12例；3.0 mg 及び6.0 mg に各6例）が登録された。

パート A 6.0 mg 群の1例は，薬物動態データから治験薬を投与されたというエビデンスが得られなかった。パート A 3.0 mg 群の1例が治験薬投与後に有害事象のため試験を中止した。患者は，無症候性冠動脈疾患を抑えるための選択的心胸部手術のために入院を予定していたことから中止した。パート A で他に中止例はいなかった。

パート B では全患者がフォローアップを完了した。

2.7.6.1.1.3 患者背景

年齢の平均値（標準偏差）はパート A で77.3歳（9.4），パート B で74.6歳（7.4）であった。

体重の平均値（標準偏差）はパート A で70.53 kg（17.04），パート B で86.91 kg（25.08）であった。

2.7.6.1.1.4 薬物動態

血漿，及び追加で同意が得られた患者における房水中の薬物動態を評価した。

表 2.7.6.1.1.4-1 本剤の主な血漿中薬物動態パラメータの概要（BP28936試験）

用量/スケジュール	n	C_{max}（μg/mL）	AUC（μg·h/mL）	$t_{1/2}$（日）
0.5 mg SAD	3	0.0162 [0.00746-0.0409]	9.63 (n = 2) [8.79-10.5]	11.3 (n = 2) [7.29-15.4]
1.5 mg SAD	3	0.0600 [0.0316-0.0701]	17.9 [16.4-22.3]	6.02 [5.06-12.6]
3.0 mg SAD	3	0.160 [0.0725-0.171]	51.1 [42.7-65.0]	7.41 [6.16-11.8]
3.0 mg MAD	6	0.152 (34) [0.0725-0.210]	36.5 (23) [24.8-46.3]	5.91 (51) [3.14-10.6]
6.0 mg SAD	2	0.187 [0.126，0.248]	54.2 [43.6-64.7]	7.24 [6.76-7.71]
6.0 mg MAD	6	0.116 (37) [0.0734-0.176]	35.2 (31) [23.5-50.4]	7.34 (14) [6.50-9.29]

AUC = 薬物濃度-時間曲線下面積，AUC_{inf} = 投与後 0 時間から無限大までの薬物濃度-時間曲線下面積，AUC_{tau} = 1 回の投与間隔（0～Day 28）中の薬物濃度-時間曲線下面積，SAD = 単回投与用量漸増，MAD = 反復投与用量漸増。

注：SAD パートでは AUC_{inf}を算出し，MAD パートでは AUC_{tau}（0～Day 28）を算出した。

SAD パートでは中央値［範囲］を示し，MAD パートの 3 回目投与後では平均値（CV%）［範囲］を示した。

表 2.7.6.1.1.4-2 房水サンプルを採取した4例における個別の血漿及び房水中ファリシマブの見かけの消失半減期（BP28936試験）

パート，用量	血漿中 $t_{1/2}$（日）	房水中 $t_{1/2}$（日）
SAD，0.5 mg	15.4	13.4
SAD，6.0 mg	7.71	7.61
MAD，6.0 mg	6.61	6.08
MAD，6.0 mg	9.29	8.38

MAD = 反復投与用量漸増，SAD = 単回投与用量漸増，$t_{1/2}$ = 消失半減期。MAD パートにおいては3回目投与後より算出した。

2.7.6.1.1.5 薬力学

本試験の薬力学的評価項目は，機能評価（BCVA 及びコントラスト感度テスト），解剖学的評価項目（SD-OCT，FFA，ICGA）及び血漿/房水バイオマーカーであった。本項では，試験眼に関するデータのみを報告し，非試験眼に関するデータは総括報告書の付録に記載している。全体として，BCVA はベースラインから増加し，中心領域網膜厚の減少も観察された。しかし，一定の用量反応性は認められなかった。

6.0 mg SAD 群の1例は，薬物動態データから治験薬を投与されたというエビデンスが得られなかったため，薬力学的解析対象集団から除外された。

総 VEGF のアッセイは本剤に対して強い干渉を示したため，総 VEGF は血漿及び房水サンプルでは測定されなかった。

血漿遊離/総アンジオポエチン2（Ang-2）濃度は，SAD 及び MAD パートにおける本剤の硝子体内投与後に一時的な増加を示した。MAD パートのみでは，遊離 VEGF はベースラインからの一貫した変化を示さなかった。SAD パートの遊離 VEGF のデータは，必要とされる CTAD マトリックスが使用されておらず，内因性に放出される VEGF によってバイアスを受ける可能性があるため，慎重に解釈する必要がある。

房水中の遊離 VEGF 及び遊離 Ang-2濃度は，房水サンプルを採取した患者のほとんどで本剤の硝子体内投与後に抑制された。しかし，例数が少なく不完全なデータからは，Ang-2抑制と VEGF の抑制の関連性における結論は得られなかった。

2.7.6.1.1.6 安全性

有害事象の集計を表 2.7.6.2-1及び表 2.7.6.2-2に示した。

BP28936試験では，死亡，用量制限有害事象（DLE），眼の重篤な有害事象は報告されなかった。有害事象に明らかな用量関係は認められなかった。

すべての有害事象の発現頻度は，パート A では0.5 mg に認められず，1.5 mg に66.7%（2/3例，5件），3.0 mg に100%（3/3例，12件）及び6.0 mg に66.7%（2/3例，10件）であり，パート B では3.0 mg に83.3%（5/6例，20件）及び6.0 mg に33.3%（2/6例，4件）であった。副作用は，パート A では3.0 mg に33.3%（1/3例，1件，試験眼での虹彩毛様体炎），パート B では6.0 mg に16.7%（1/6例，1件，試験眼での眼圧上昇）であった。重篤な有害事象が1件報告されたが，眼以外の事象であり，治験責任医師により治験薬との因果関係なしと判断された。

試験眼の有害事象の発現頻度は，パート A では33.3%（4/12例，7件）であり，その内訳は，0.5 mg 及び1.5 mg に認められず，3.0 mg に66.7%（2/3例，4件）及び6.0 mg に66.7%（2/3例，3件）であった。パート B では41.7%（5/12例，7件）であり，その内訳は，3.0 mg に66.7%（4/6例，6件）及び6.0 mg に16.7%（1/6例，1件）であった。いずれかの投与群で2例以上認められた有害事象は，試験眼では，眼瞼炎（パート A 3.0 mg 群2例）であった。副作用はパート A 3.0 mg の1例に虹彩毛様体炎が1件，パート B 6.0 mg の1例に眼圧上昇が1件認められた。試験眼の有害事象の重症度は，中等度であった眼痛以外は軽度であった。試験眼で重篤な有害事象は認められなかった。

非試験眼の有害事象の発現頻度は，パート A では25.0%（3/12例，8件）であり，その内訳は，0.5 mg 及び6.0 mg に認められず，1.5 mg に33.3%（1/3例，2件）及び3.0 mg に66.7%（2/3例，6件）であった。パート B では16.7%（2/12例，2件）であり，その内訳は，3.0 mg 及び6.0 mg にいずれも16.7%（1/6例，1件）であった。いずれかの投与群で2例以上認められた有害事象は，非試験眼では，眼瞼炎（パート A 3.0 mg 群2例）であった。副作用は認められなかった。非試験眼の有害事象の重症度は，パート A では中等度であった網膜出血（1.5 mg）以外は軽度であった。非試験眼で重篤な有害事象は認められなかった。

眼以外の有害事象の発現頻度は，パート A では41.7%（5/12例，12件）であり，その内訳は，0.5 mg に認められず，1.5 mg に33.3%（1/3例，3件），3.0 mg に66.7%（2/3例，2件）及び6.0 mg に66.7%（2/3例，7件）であった。パート B では33.3%（4/12例，15件）であり，その内訳は，3.0 mg に50.0%（3/6例，13件）及び6.0 mg に16.7%（1/6例，2件）であった。いずれかの投与群で2例以上認められた有害事象は，眼以外では認められなかった。副作用は認められなかった。重症度が高度の眼以外の有害事象は，パート A では胃腸出血（重篤な有害事象）及び冠動脈疾患各1件であり，パート B では認められなかった。眼以外の重篤な有害事象は胃腸出血が1件報告され，治験責任医師により治験薬との因果関係なしと判断された。71歳の患者（パート A：1.5 mg）であり，アルコール乱用の既往があり，過度の飲酒後に事象が発現した。

試験中止に至った有害事象は，試験眼又は非試験眼では認められず，眼以外の有害事象でパート A 3.0 mg 群の1例（冠動脈疾患）に認められた。患者は，無症候性冠動脈疾患を抑えるための選択的心胸部手術のために入院を予定していたことから中止した。治験責任医師は，冠動脈疾患の事象は治験薬との因果関係なしと判断した。

硝子体内投与の手技に関連した予期せぬ有害事象は報告されなかった。治療を必要とする持続的な眼圧上昇は報告されなかった。

2.7.6.1.1.7 結論

nAMD 患者における本剤の単回及び反復硝子体内投与は，DLE 又は眼の重篤な有害事象が認められず，試験した最高用量である6.0 mg の単回投与及び6.0 mg の4週間隔3回投与まで良好な忍容性を示した。

全身曝露量は本剤3.0 mg までほぼ用量に比例して増加し，予想範囲内であった。4例の個別の血漿及び房水中濃度の時間プロファイルに基づき，血漿中濃度の時間プロファイルは硝子体内の保持時間（flip-flop 薬物動態）を表していた。

大多数の患者で BCVA の改善と中心領域網膜厚の減少が観察された。しかしながら，本試験の例数が少ないことにより予測されたとおり，一貫した用量反応性は認められなかった。

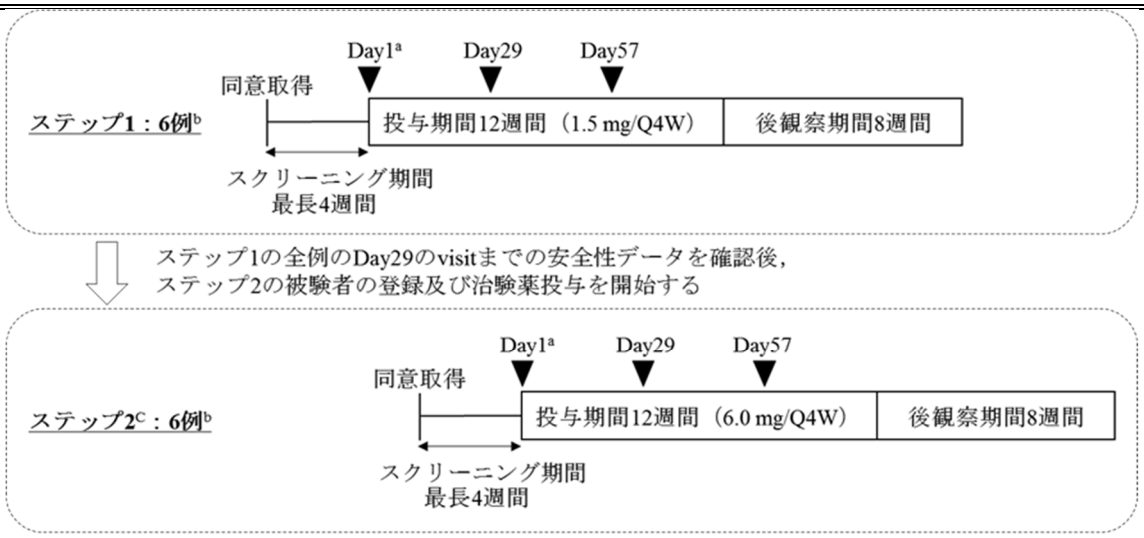
2.7.6.1.2 国内第 I 相臨床試験（nAMD 又は DME 患者への反復投与：JP39844試験）

（評価資料：5.3.3.2-2）

2.7.6.1.2.1 概要表

表 2.7.6.1.2.1-1 概要表（JP39844試験）

治験の標題：ファリシマブの日本人 nAMD 患者及び DME 患者を対象とした第 I 相臨床試験	
治験責任医師：計5名	
実施医療機関：計5施設	
公表文献（引用文献）：なし	
第1症例の同意日：2017年8月10日 最終症例の最終観察日：2018年6月27日	開発のフェーズ：第 I 相
目　　的： 主要目的 日本人 nAMD 患者及び DME 患者を対象とし，本剤を硝子体内注射で反復投与した時の安全性，忍容性を検討する。 副次的目的 日本人 nAMD 患者及び DME 患者を対象とし，本剤を硝子体内注射で反復投与した時の血漿中薬物動態を検討する。 探索的目的 日本人 nAMD 患者及び DME 患者を対象とし，本剤を硝子体内注射で反復投与した時の以下の項目について検討する。 • 最高矯正視力（BCVA）及び解剖学的変化に対する影響 • 血漿中の薬力学的バイオマーカー及び探索的バイオマーカー • 任意採取した房水中のファリシマブ濃度，薬力学的バイオマーカー • 血漿中抗薬物抗体（ADA）濃度	
治 験 方 法： nAMD 患者及び DME 患者を対象とした多施設共同，非遮蔽，非対照用量漸増試験。ステップ1では本剤1.5 mg を4週間隔（Q4W）で計3回，ステップ2では本剤6.0 mg を Q4W で計3回，試験眼（片眼）に硝子体内注射した。両眼が試験眼に対する選択基準を満たす場合は，視力のより低い眼を試験眼とした。視力が同じ場合は，治験責任医師又は治験分担医師が試験眼を選択した。適格と判断された患者をステップ1から順に登録した。	



▼：治験薬投与　Q4W：4週間隔投与
a 治験薬初回投与日をDay1とする
b 滲出型加齢黄斑変性，糖尿病黄斑浮腫患者を各疾患少なくとも2例以上登録する
c ステップ2には，ステップ1の治験薬投与を受けていない新たな症例を登録する

【DLE】
初回投与から Day 29の visit までを DLE 評価期間とし，各ステップにおいて1例に DLE に該当する事象が発現した場合には，当該ステップに3例（nAMD 患者及び DME 患者それぞれ少なくとも1例を含む計3例とする）の患者を新たに登録することとした。

＜DLE の定義＞
- 治験責任医師又は治験依頼者により治験薬との因果関係ありと判断され，用量が不耐容であると判断される眼以外の重篤な有害事象
- 治験責任医師又は治験依頼者により治験薬との因果関係ありと判断され，視力を脅かす重篤な眼に関連する有害事象
- 治験責任医師又は治験依頼者により治験薬との因果関係ありと判断された，以下の事象
  - 眼内の炎症（5.3.3.2-2 治験実施計画書 付録 4 前房フレア，細胞，硝子体出血密度，硝子体細胞の評価尺度で 2+以上と診断されるぶどう膜炎及び硝子体炎）
  - 持続性の眼圧上昇（>30 mmHg）
  - ETDRS 視力表による文字スコアで直近の測定時と比較し 15 文字を超える視力の低下

【DLE の発現状況に基づく患者の追加及びステップ移行基準】
1) DLE の発現が 6 例中 0 例であった場合
次ステップへ移行する。
2) DLE の発現が 6 例中 1 例に認められた場合
当該ステップに3例の患者を追加登録し，9例での検討を行う。
   a. DLE の発現が 9 例中 1 例であった（新たな DLE の発現が認められない）場合，次ステップへ移行する。
   b. DLE の発現が 9 例中 2 例以上であった（新たな DLE の発現が認められた）場合，次ステップへの移行を行わない。
3) DLE の発現が 6 例中 2 例以上に認められた場合
次ステップへの移行を行わない。

症　例　数： 目標例数：12例；1ステップ当たり6例（nAMD，DME の各疾患に少なくとも2例以上）の計2ステップ

登録例数：12例
投与例数：12例（各ステップともにnAMD2例，DME4例）
安全性解析対象例12例，薬物動態解析対象例12例，薬力学的解析対象例12例

診断及び組入基準：
以下の選択基準及び除外基準に従った。

(1) 選択基準
各疾患の基準のすべてに該当する患者を本治験に登録する。

【nAMD 患者に関する選択基準】
- 全般的な選択基準

1) 同意取得時の年齢が 50 歳以上 85 歳未満の日本人男性又は女性である
2) ＜女性の場合＞妊娠可能な女性の場合は，同意取得日から最終投与 57 日後まで，禁欲（異性間性交を避ける）又は適切な避妊法を使用することに同意している。
   – 初潮はむかえているが閉経後状態（閉経以外の原因が特定されていない 12 カ月以上の無月経）には達しておらず，不妊手術（卵巣摘出術及び／又は子宮摘出術）を受けたことがない女性を妊娠可能とみなす。
   – 許容される避妊法としては，両側卵管結紮，ホルモン避妊薬，子宮内避妊器具，バリア法，若しくはパートナーに対する男性不妊手術が挙げられる。
   – 禁欲の信頼性は，治験実施期間と患者の望ましい通常の生活習慣を考慮して判断する。周期的禁欲（カレンダー法，排卵日法，徴候体温法，排卵後法等）及び膣外射精は避妊法として許容しない。
3) ＜男性の場合＞同意取得日から最終投与 57 日後まで，禁欲（異性間性交を避ける）又は適切な避妊法を使用することに同意している。
   – 許容される避妊法としては，男性不妊手術，若しくは妊娠可能なパートナーに対する両側卵管結紮，ホルモン避妊薬，子宮内避妊器具，バリア法（周期的禁欲は除く）が挙げられる。

- 試験眼に関する選択基準

4) nAMD と診断されている
5) スクリーニング検査時に実施する BCVA が ETDRS 視力表による文字スコアで 78～19 文字である（Snellen 視力相当で約 20/32～20/400，小数視力相当で約 0.62～0.05）
6) 脈絡膜新生血管（CNV）による滲出が明らかである（網膜血管腫状増殖［RAP］とポリープ状脈絡膜血管症［PCV］を含む CNV も可）
7) 総病変サイズ（血液，萎縮／瘢痕及び血管新生を含む）が 12 乳頭径以下である
8) 網膜内及び／又は網膜下及び／又は網膜色素上皮下の滲出液が明らかである
9) 過去に 3 回以上の抗 VEGF 薬の硝子体内注射を受けており，最後の硝子体内注射は治験薬初回投与日の 4 週間以上前である
10) 確定診断のための良好な網膜所見が検出可能である（クリアな透光体と十分な瞳孔散大能を有する）

【DME 患者に関する選択基準】
- 全般的な選択基準

11) 同意取得時の年齢が 20 歳以上 85 歳未満の日本人男性又は女性である
12) 1 型又は 2 型の糖尿病と診断されている
13) ＜女性の場合＞妊娠可能な女性の場合は，同意取得日から最終投与 57 日後まで，禁欲（異性間性交を避ける）又は適切な避妊法を使用することに同意している。
   – 初潮はむかえているが閉経後状態（閉経以外の原因が特定されていない 12 カ月以上の無月経）には達しておらず，不妊手術（卵巣摘出術及び／又は子宮摘出術）を受けた

ことがない女性を妊娠可能とみなす。
- 許容される避妊法としては，両側卵管結紮，ホルモン避妊薬，子宮内避妊器具，バリア法，若しくはパートナーに対する男性不妊手術が挙げられる。
- 禁欲の信頼性は，治験実施期間と患者の望ましい通常の生活習慣を考慮して判断する。周期的禁欲（カレンダー法，排卵日法，徴候体温法，排卵後法等）及び膣外射精は避妊法として許容しない。

14) ＜男性の場合＞同意取得日から最終投与 57 日後まで，禁欲（異性間性交を避ける）又は適切な避妊法を使用することに同意している。
- 許容される避妊法としては，男性不妊手術，若しくは妊娠可能なパートナーに対する両側卵管結紮，ホルモン避妊薬，子宮内避妊器具，バリア法（周期的禁欲は除く）が挙げられる。

- 試験眼に関する選択基準

15) SD-OCT/SS-OCT によって黄斑中心を含む黄斑の肥厚が確認された，糖尿病網膜症を伴う黄斑浮腫である。スクリーニング検査時に Spectralis（Heidelberg 社）で中心領域網膜厚が ≥325 μm であることが確認されている（Spectralis を使用できない場合，以下の機器とその閾値が許容される）
   a. Cirrus：中心領域網膜厚 ≥315 μm
   b. Topcon：中心領域網膜厚 ≥315 μm
   c. Optovue：中心領域網膜厚 ≥295 μm
16) スクリーニング検査時に実施する BCVA が ETDRS 視力表による文字スコアで 78～19 文字である（Snellen 視力相当で約 20/32～20/400，小数視力相当で約 0.62～0.05）
17) 過去に 3 回以上の抗 VEGF 薬の硝子体内注射を受けており，最後の硝子体内注射は治験薬初回投与日の 4 週間以上前である
18) 確定診断のための良好な網膜所見が検出可能である（クリアな透光体と十分な瞳孔散大能を有する）

(2) 除外基準
各疾患の基準のいずれかに該当する患者は本治験の登録対象から除外する。

【nAMD 患者に関する除外基準】
- 全般的な除外基準

1) スクリーニング検査前 28 日間に臨床的に重大な肝疾患，消化器疾患，血液疾患，免疫疾患，神経疾患，肺疾患，甲状腺疾患等に罹患した
2) 他の疾患の病歴，代謝機能不全，身体検査所見，又は臨床検査結果から治験責任医師又は治験分担医師によって治験薬の使用が適切ではない，又は治験結果の解釈に影響を与える可能性があると判断されている
3) 治験薬初回投与前 12 カ月間に脳卒中や心筋梗塞の既往又は合併がある
4) スクリーニング検査時の HbA1c が 8.5% を超える（National Glycohemoglobin Standardization Program［NGSP］値）
5) 血圧のコントロールが不良である（スクリーニング検査時の収縮期血圧>180 mmHg 又は拡張期血圧>110 mmHg）。再検査は 30 分以上の間隔を空けた後，1 度まで可とする。降圧剤未治療で再検査時も当該基準を満たさなかった場合，降圧剤を 30 日間継続して投薬を受けた後に，再度適格性確認を実施することを可とする
6) 治験薬初回投与前 24 週間に腎臓移植や血液透析，腹膜透析が必要となる腎臓の障害を有する，若しくは血液透析や腹膜透析の治験期間中の開始が必要となると予想される
7) ラニビズマブ，アフリベルセプト，ペガプタニブ，フルオレセイン，インドシアニングリーン（ICG），若しくはそれらの製剤や添加剤に対して過敏症の既往又は合併がある
8) いずれかの眼が散瞳薬使用に対して禁忌である

9) 治験薬初回投与日前 12 週間に他の治験薬による治療を受けたことがある
10) ＜女性の場合＞妊娠検査で陽性である又は授乳中である

- 病変の特性に関する除外基準

11) スクリーニング検査時に試験眼に総病変の 50%を超える，若しくは 1 乳頭径（2.54 mm^2）を超える中心窩を含む網膜下出血が存在する
12) スクリーニング検査時にいずれかの眼に加齢黄斑変性以外の原因（例：眼ヒストプラズマ症，外傷又は病的近視）による CNV が存在する
13) スクリーニング検査時に試験眼に黄斑を含む網膜色素上皮裂孔が存在する
14) スクリーニング検査時に試験眼に中心窩を含む顕著な線維化若しくは萎縮が存在する

- 前治療若しくは併用療法に関する除外基準

15) 試験眼に対して治験薬初回投与前 12 週間に光線力学的療法を受けたことがある
16) 試験眼に対して治験薬初回投与前 4 週間に硝子体内注射を受けたことがある
17) 試験眼に対して治験薬初回投与前 12 週間に硝子体内，眼周囲若しくはテノン嚢へのステロイド投与を受けたことがある
18) 治験薬初回投与前 24 週間に全身性の抗 VEGF 療法を受けたことがある
19) 治験薬初回投与前 7 日間に非試験眼に対する抗 VEGF 薬の硝子体内注射を受けたことがある
20) 本剤の投与を受けたことがある

- 眼合併症状に関する除外基準

21) 試験眼の視力に影響する可能性がある他の眼科疾患がある
22) 治験責任医師又は治験分担医師により以下のいずれかに該当すると判断される試験眼における眼内合併症状がある（例：白内障，DR 又は網膜上膜の牽引）
    a. 治験期間中に当該合併症状に起因すると思われる視力低下を予防又は治療するために医学的又は外科的介入が必要
    b. 当該合併症状に対して無治療の継続が許容された場合，治験期間中に BCVA が少なくとも Snellen 指標で 2 列相当低下（例えば，Snellen 視力で 20/50［小数視力相当 0.4］が 20/100［小数視力相当 0.2］に低下）する可能性がある
23) 試験眼に活動性の眼内の炎症（5.3.3.2-2 治験実施計画書 付録 4 前房フレア，細胞，硝子体出血密度，硝子体細胞の評価尺度で Trace 以上）の合併がある
24) 試験眼の硝子体出血の合併がある
25) いずれかの眼に特発性又は自己免疫性のぶどう膜炎の既往又は合併がある
26) いずれかの眼に活動性の感染性結膜炎，角膜炎，強膜炎又は眼内炎の合併がある
27) 試験眼の等価球面度数が 8 ジオプター以上の近視で屈折異常がある
28) スクリーニング検査前 12 週間又は治験薬最終投与後 12 週以内に，試験眼に対する白内障を含む眼科手術及び／又はあらゆる分類のレーザー治療の実施が予定されている
29) 緑内障治療薬による治療にも関わらず，スクリーニング検査時の試験眼の眼圧が 30 mmHg 以上又は視野の欠損があるコントロール不良な緑内障
30) 治験薬初回投与前 1 年間に試験眼での緑内障に対する手術の既往がある
31) 治験薬初回投与前 1 年間に試験眼での角膜移植又はデスメ膜剥離角膜内皮移植術の既往がある

【DME 患者に関する除外基準】

- 全般的な除外基準

32) スクリーニング検査前 28 日間に臨床的に重大な肝疾患，消化器疾患，血液疾患，免疫疾患，神経疾患，肺疾患，甲状腺疾患等に罹患した
33) 他の疾患の病歴，代謝機能不全，身体検査所見，又は臨床検査結果から治験責任医師又は

治験分担医師によって治験薬の使用が適切ではない，又は治験結果の解釈に影響を与える可能性があると判断されている
34) 治験薬初回投与前 12 カ月間に脳卒中や心筋梗塞の既往又は合併がある
35) 血圧のコントロールが不良である（スクリーニング検査時の収縮期血圧>180 mmHg 又は拡張期血圧>100 mmHg）。再検査は 30 分以上の間隔を空けた後，1 度まで可とする。降圧剤未治療で再検査時も当該基準を満たさなかった場合，降圧剤を 30 日間継続して投薬を受けた後に，再度適格性確認を実施することを可とする。
36) スクリーニング検査時の HbA1c が 12%を超える（NGSP 値）
37) 未治療の糖尿病患者，若しくは治験薬初回投与日前 16 週間以内に経口抗糖尿病薬やインスリンによる治療を開始した，若しくは治験期間中に抗糖尿病治療の変更が見込まれる
38) 治験薬初回投与前 24 週間に腎臓移植や血液透析，腹膜透析が必要となる腎臓の障害を有する，若しくは血液透析や腹膜透析の治験期間中の開始が必要となると予想される
39) ラニビズマブ，アフリベルセプト，フルオレセイン，若しくはそれらの製剤や添加剤に対して過敏症の既往又は合併がある
40) いずれかの眼が散瞳薬使用に対して禁忌である
41) 治験薬初回投与前 12 週間に他の治験薬による治療を受けたことがある
42) ＜女性の場合＞妊娠検査で陽性である又は授乳中である

- 試験眼に関する除外基準

43) スクリーニング検査時に以下のようなハイリスクの増殖糖尿病網膜症（PDR）の徴候がある
  - 硝子体又は網膜前出血がある
  - 1/2 乳頭径以上の網膜新生血管（NVE）がある
  - 1/3 乳頭径以上の乳頭上新生血管（NVD）がある

- 前治療若しくは併用療法に関する除外基準

44) 試験眼に対して治験薬初回投与前 12 週間に硝子体内，眼周囲若しくはテノン嚢へのステロイド投与を受けたことがある
45) 試験眼に対してスクリーニング検査前 12 週間に汎網膜光凝固（PRP）療法を受けたことがある
46) 治験薬初回投与前 1 年間に試験眼に対する網膜硝子体の手術を受けたことがある
47) 治験薬初回投与前 24 週間に全身性の抗 VEGF 薬の投与を受けたことがある
48) 治験薬初回投与前 4 週間に全身性の副腎皮質ステロイド投与を受けたことがある
49) 治験薬初回投与前 7 日間に非試験眼に対する抗 VEGF 薬の硝子体内注射を受けたことがある
50) 本剤の投与を受けたことがある

- 眼合併症状に関する除外基準

51) 試験眼においてルベオーシスの既往又は合併がある
52) DME 以外の，黄斑の評価又は中央視野に影響するような試験眼の眼疾患（例：加齢黄斑変性，網膜静脈閉塞症，網膜色素線状，眼ヒストプラズマ症，活性化又は不活化サイトメガロウイルス症，病的近視，網膜剥離，黄斑牽引症，黄斑円孔等）の既往又は合併がある
53) いずれかの眼に特発性又は自己免疫性のぶどう膜炎の既往又は合併がある
54) 試験眼に活動性の眼内の炎症（5.3.3.2-2 治験実施計画書 付録 4 前房フレア，細胞，硝子体出血密度，硝子体細胞の評価尺度で Trace 以上）の合併がある
55) いずれかの眼に活動性の感染性結膜炎，角膜炎，強膜炎又は眼内炎の合併がある
56) 試験眼に視力の改善に影響を及ぼす可能性があると治験責任医師又は治験分担医師に判断される中心窩の萎縮，色素異常及び中心窩下の高濃度の滲出液等の合併がある
57) スクリーニング検査前 12 週間又は治験薬最終投与後 12 週以内に，試験眼に対する白内障

を含む眼科手術及び／又はあらゆる分類のレーザー治療の実施が予定されている 58) 緑内障治療薬による治療にも関わらず，スクリーニング検査時の試験眼の眼圧が 25 mmHg 以上又は視野の欠損があるコントロール不良な緑内障 59) 治験薬初回投与前 1 年間に試験眼での緑内障に対する手術の既往がある 60) 治験薬初回投与前 1 年間に試験眼での角膜移植又はデスメ膜剥離角膜内皮移植術の既往がある
被験薬，用量及び投与方法： (1) 被験薬：ファリシマブ ファリシマブ60 mg/0.5 mL（120 mg/mL）を充填した2 mL の単回使用バイアル製剤。 (2) 用量及び投与方法：ステップ1では本剤1.5 mg を Q4W で計3回，ステップ2では本剤6.0 mg を Q4W で計3回，試験眼（片眼）に硝子体内注射した。
治 療 期 間： 最初の患者に対する同意取得日（治験開始日）から最後の患者の最終後観察日（治験終了日）までとした。
評 価 基 準： (1) 安全性評価項目 眼の有害事象，眼以外の有害事象，眼圧，臨床検査値，12誘導心電図，バイタルサイン，血漿中 ADA 濃度 (2) 薬物動態学的評価項目 血漿中ファリシマブ濃度及びその薬物動態パラメータ（C_{max}，AUC，T_{max}，$t_{1/2}$等），任意採取した房水中ファリシマブ濃度 (3) 薬力学的評価項目 BCVA，SD-OCT/SS-OCT による解剖学的所見，血漿中の薬力学的バイオマーカー（VEGF，Ang-2濃度），血漿中の探索的バイオマーカー（Ang-1，Tie-2，VEGFR，PDGF 濃度），任意採取した房水中の薬力学的バイオマーカー（VEGF，Ang-2濃度）
統 計 手 法： (1) 安全性評価 有害事象は個別データの一覧を表示した。眼の有害事象と眼以外の有害事象でそれぞれ要約し，眼の有害事象は試験眼と非試験眼での事象も区別した。 眼圧，臨床検査（血液学的検査，血液生化学検査及び尿検査データ）及びバイタルサインデータは要約統計量を算出した。12誘導心電図は個別データの一覧を示した。 (2) 薬物動態学的評価 ファリシマブの血漿中薬物動態の指標として，C_{max}，AUC，T_{max}，$t_{1/2}$等の算出値及び要約統計量を算出し，推移図を作成した。反復投与時の定常状態，累積係数等を検討した。 (3) 薬力学的評価 SD-OCT/SS-OCT による解剖学的所見は個別データの一覧を表示した。①中心網膜厚，②平均中心領域網膜厚（1 mm 径），③総黄斑体積は眼（試験眼／非試験眼）ごとに要約統計量を算出した。

2.7.6.1.2.2　患者の内訳

1.5 mg 投与群又は6.0 mg 投与群にそれぞれ6例の計12例が登録された。全例が治験薬を投与され，治験実施計画書に基づく治験薬の投与及びその後の観察・検査を完遂した。

全例が DLE 評価可能と判断されたが，DLE の発現は認められなかった。

2.7.6.1.2.3 患者背景

年齢の中央値は1.5 mg 投与群で70.5歳（範囲：52～79歳），6.0 mg 投与群で69.5歳（範囲：52～81歳）であり，各群6例のうち2例が nAMD であった。

ベースライン時の試験眼の BCVA の中央値は，1.5 mg 投与群で60.5文字（範囲：8～73文字），6.0 mg 投与群で50.5文字（範囲：38～77文字），平均中心領域網膜厚は1.5 mg 投与群で368.0 μm（範囲：141～464 μm），6.0 mg 投与群で348.0 μm（範囲：193～475 μm）であった。また，ベースライン時の試験眼の眼圧の中央値は，1.5 mg 投与群で15.5 mmHg（範囲：10～17 mmHg），6.0 mg 投与群で16.5 mmHg（範囲：10～21 mmHg）であった。

2.7.6.1.2.4 薬物動態

平均血漿中ファリシマブ濃度は投与2日後に最高値を示し，その後1相性の消失を示した。濃度推移の形状は海外結果と同様であった。累積係数についてはおよそ1であった。すなわち，血漿中ファリシマブ濃度はほとんど蓄積しないと思われ，またこの結果は海外結果と同様であった。

2.7.6.1.2.5 薬力学

試験眼の BCVA は，1.5 mg 投与群では Day 1観察時から Day 29観察時に7.8 ± 7.5（mean ± SD）文字，Day 85観察時に5.2 ± 5.1文字の増加が認められた。6.0 mg 投与群では Day 1観察時から Day 29観察時に0.5 ± 7.6文字，Day 85観察時に5.3 ± 8.5文字の増加が認められた。

試験眼の平均中心領域網膜厚は，1.5 mg 投与群では Day 1観察時から Day 29観察時に68.7 ± 63.4 μm，Day 85観察時に39.5 ± 99.1 μm の減少が認められた。6.0 mg 投与群では Day 1観察時から Day 29観察時に42.5 ± 98.0 μm，Day 85観察時に91.0 ± 82.0 μm の減少が認められた。

2.7.6.1.2.6 安全性

有害事象は4例4件｛1.5 mg 投与群の1例1件（上咽頭炎），6.0 mg 投与群の3例3件［結膜出血（非試験眼），上咽頭炎，インフルエンザ］｝に認められた。重症度はいずれも軽度であり，いずれの有害事象も治験薬との因果関係は否定された。

死亡，重篤な有害事象，重篤な副作用，特に注目すべき有害事象，DLE は発現しなかった。

試験眼の有害事象はいずれの患者にも認められなかった。

非試験眼の有害事象は6.0 mg 投与群の1例に1件（結膜出血）認められた。

眼以外の有害事象は3例3件［1.5 mg 投与群の1例1件（上咽頭炎），6.0 mg 投与群の2例2件（上咽頭炎，インフルエンザ）］に認められた。

眼圧は，両群ともに試験眼で治験薬の投与直後の上昇及びその後の元の眼圧値への低下が確認された。バイタルサインや安静時12誘導心電図では，ベースライン時と比較して大きな変化は認められなかった。

以上の結果から，日本人の nAMD 及び DME 患者への本剤 1.5 mg 及び6.0 mg の Q4W，計3回の硝子体内投与は概ね安全で，忍容性は良好であった。

2.7.6.1.2.7 結論

日本人の nAMD 又は DME 患者への本剤 1.5 mg 又は6.0 mg の Q4W で計3回の硝子体内投与時の安全性，忍容性が確認された。日本人の本剤の全身曝露は概ね海外で得られた結果の範囲内であった。BCVA 及び平均中心領域網膜厚の改善傾向が示唆された。

2.7.6.1.3　海外第 II 相臨床試験（nAMD 患者：BP29647試験）

（評価資料：5.3.5.1- nAMD-1）

2.7.6.1.3.1　概要表

表 2.7.6.1.3.1-1 概要表（BP29647試験）

治験の標題：脈絡膜新生血管を伴う加齢黄斑変性患者にファリシマブを硝子体内投与した際の安全性，忍容性，薬物動態及び有効性を検討する多施設共同，反復投与及び複数用法，ランダム化，実薬対照，二重遮蔽，並行群間比較，36週間の試験	
施設及び国：米国（58施設）	
公表文献（引用文献）：なし	
第1症例の登録日：2015年8月11日 最終症例の最終来院日：2017年9月26日	開発のフェーズ：第 II 相
目　　的： 主要目的 未治療及び抗 VEGF 薬で効果不十分な CNV を伴う AMD 患者における本剤の有効性をラニビズマブ単独療法と比較評価する。 副次的目的 • 本剤の硝子体内反復投与の安全性を評価する。 • 本剤の全身薬物動態を評価する。 • 本剤の作用機序に関する情報を提供する薬力学及び解剖学的アウトカムを検討する。 • 血漿中抗ファリシマブ抗体の形成を検討する。 • 2 種類の本剤投与方法を検討する。	
治 験 方 法： 本試験は，CNV を伴う AMD 患者を対象とした多施設共同，反復投与及び複数用法，ランダム化，実薬対照，二重遮蔽，5群（A 群～E 群）並行群間比較，36週間の試験。 本試験は，未治療患者集団（A 群，B 群，C 群，D 群の比較）及び抗 VEGF 薬で効果不十分な患者集団における本剤の評価ができるようにデザインされた。 抗 VEGF 薬で効果不十分な患者集団は，12週時に BCVA が68文字以下であった A 群及び E 群の患者の部分集団（集団 C）と定義した。試験眼は，1例1眼のみとした。	
症　例　数： 目標例数；CNV を伴う AMD 患者を最大271例，3:2:2:2:3の比で登録する。 登録例数；未治療の nAMD 患者計273例を本試験に登録した。1施設での GCP 違反により10例が解析から除外された。解析対象となった投与群ごとの登録例数は以下のとおりであった。 登録例数　　intent-to-treat（ITT）解析対象例数 • A 群：68 例　　68 例 • B 群：47 例　　46 例 • C 群：42 例　　39 例 • D 群：47 例　　46 例 • E 群：69 例　　64 例	
診断及び主要な組入基準： 50歳以上で，未治療の CNV を伴う AMD の男女の患者	

被験薬，用量及び投与方法：
(1) 被験薬：本剤
本剤60 mg/0.5 mL（120 mg/mL）を充填した2 mL の単回使用バイアル製剤。

(2) 用量及び投与方法：以下のスケジュールに従って本剤又はラニビズマブを50 μL 硝子体内投与するか，又はシャム投与を行った。
- A 群：ラニビズマブ 0.5 mg を Q4W で 32 週間（9 回注射）硝子体内投与
- B 群：本剤 1.5 mg を Q4W で 32 週間（9 回注射）硝子体内投与
- C 群：本剤 6.0 mg を Q4W で 32 週間（9 回注射）硝子体内投与
- D 群：本剤 6.0 mg を Q4W で 12 週時まで（4 回注射）硝子体内投与後，本剤 6.0 mg を 8 週間隔（Q8W）で（すなわち 20 週時及び 28 週時に 2 回注射）硝子体内投与
- E 群：ラニビズマブ 0.5 mg を Q4W で 8 週時まで（3 回注射）硝子体内投与後，本剤 6.0 mg を Q4W で（6 回注射）硝子体内投与

試験眼は片眼のみとした。
本剤の6.0 mg 用量は，希釈せずに投与されたが，1.5 mg 用量は治験依頼者から提供されたプラセボで希釈された。

対照薬，用量及び投与方法：

(1) 対照薬：
- プラセボ（ファリシマブ製剤の適切な用量への希釈にのみ使用）
ファリシマブ製剤と同じ賦形剤組成を含むが本剤を含まない溶液を表示含量1.0 mL 充填した2 mL の単回使用バイアル。
- ラニビズマブ
ラニビズマブ0.5 mg/0.05 mL（10 mg/mL）を充填した2 mL の単回使用バイアル製剤。治験依頼者から提供された。

(2) 用量及び投与方法：
被験薬の「(2) 用量及び投与方法」参照。

治 療 期 間：
各患者の治験の総期間は最長40週であり，その内訳は以下のとおりであった。
- スクリーニング：最長 4 週間
- ベースライン：Day 1
- 治験薬投与期間：Day 1 から 32 週時まで
- 最終の安全性及び有効性の評価期間：32 週時から 36 週時まで

評 価 基 準：
(1) 有効性評価項目
- 主要評価項目
  - 未治療患者（集団 A；A 群，B 群，C 群及び D 群にランダム化された全患者）
    ETDRS 視力表を用いたベースラインから36週時までの BCVA の平均変化量
  - 抗 VEGF 薬で効果不十分な患者（集団 C；12 週時に BCVA が 68 文字以下であった A 群及び E 群にランダム化された全患者）
    12週時のベースラインから36週時までの BCVA の平均変化量

- 副次的評価項目
  BCVA
  - 36 週時に BCVA がベースライン時と比較して 15 文字以上改善した患者の割合
  - 36 週時における BCVA が 20/40 以上の患者の割合
  - 36 週時における BCVA が 20/200 以下の患者の割合

SD-OCT による解剖学的アウトカム指標
- 36 週時における中心窩厚のベースラインからの平均変化量
- 36 週時における平均中心領域網膜厚（直径 1 mm）のベースラインからの平均変化量
- 36 週時に網膜内滲出液，網膜下液，嚢胞又は色素上皮剥離がない患者の割合

FFA による解剖学的アウトカム指標
- 36 週時における CNV の総面積のベースラインからの平均変化量
- 36 週時における CNV 領域の総面積のベースラインからの平均変化量
- 36 週時における総漏出面積のベースラインからの平均変化量

(2) 薬物動態学的評価項目
主要パラメータ：クリアランス及び分布容積
副次的パラメータ：観察された最高濃度，AUC_{inf} 及び投与後0時間から t 時間までの AUC（AUC_{0-t}），T_{max} 及び $t_{1/2}$
必要に応じて，硝子体内濃度を評価するためのコンパートメント解析（探索的）
追加で同意が得られた患者における房水サンプル中のファリシマブ濃度（探索的）

(3) 安全性評価項目
- BCVA，細隙灯顕微鏡検査，散瞳下高倍率の双眼倒像鏡検査，眼圧，眼底写真，SD-OCT，血管造影から得られた関連する安全性所見
- 眼の有害事象の発現頻度及び重症度
- 眼以外の有害事象の発現頻度及び重症度
- 血液学的検査，血液化学的検査及び尿検査の結果に基づく臨床検査値異常の発現頻度
- 抗ファリシマブ抗体の発現頻度
- 心電図
- バイタルサイン

統 計 手 法：

ランダム化された全例が有効性，薬物動態及び薬力学解析対象集団とされた。ランダム化後に1施設で GCP 違反があったため，10例をすべての解析から除外した。

集団 A については，ベースラインから36週時までの BCVA の平均変化量により有効性の主要評価項目を評価した。各本剤用量又は用法群（B 群，C 群及び D 群）を対照群（A 群）と比較した主要な有効性解析は，経時測定データに対する混合効果モデル（MMRM）を用いて行った。モデルには，カテゴリー共変量として，投与群，来院，来院と投与群の交互作用，ランダム化層別因子（BCVA ≤ 68文字 ETDRS vs. >68文字及び RAP 又は PCV の有無），連続共変量としてベースライン時の BCVA を含めた。患者内相関を説明するために，無構造分散共分散構造を用いた。主要な統計学的検定は，ベースラインから36週時までの平均 BCVA 変化量について，投与群と対照群との間に差がないという帰無仮説（H_0）を検定することを目的とした。有効性の主要評価項目として，36週時における投与群と対照群の各群間の差のモデルに基づく推定値，80%信頼度及び対応する P 値も併せて報告した。多重検定に対する第1種の過誤の正式な調整は行わなかった。

集団 C における有効性の主要評価項目は，A 群と E 群における抗 VEGF 薬で効果不十分な患者集団での BCVA の12週時から36週時までの平均変化量で評価され，主要な有効性解析は MMRM を用いて行われた。モデルには，カテゴリー共変量として，投与群，来院，来院と投与群の交互作用，ランダム化層別因子（BCVA ≤ 68文字 ETDRS vs. >68文字及び RAP 又は PCV の有無），連続共変量として12週時の BCVA を含めた。患者内相関を説明するために，無構造分散共分散構造を用いた。主要な統計学的検定は，投与群と対照群との間に差がないという帰無仮説（H_0）を，12週時から36週時までの BCVA の平均変化量で検定することを目的とした。有効性の主要評価項目として，36週時の投与群と対照群との差のモデルに基づく推定値，80%信頼度及び対応する P 値を併せて報告した。多重検定の正式な調整は行わなかった。

2.7.6.1.3.2 患者の内訳

未治療の CNV を伴う AMD 患者273例が登録された。投与群別の内訳は，A 群：ラニビズマブ0.5 mg Q4W 投与群に68例，B 群：本剤1.5 mg Q4W 投与群に47例，C 群：本剤6.0 mg Q4W 投与群に42例，D 群：本剤6.0 mg を Q4W で12週時まで投与後，本剤6.0 mg を Q8W 投与する群に47例，E 群：ラニビズマブ0.5 mg を Q4W で8週時まで投与後，本剤6.0 mg を Q4W で投与する群に69例であった。1施設での GCP 違反により10例（A 群0例，B 群1例，C 群3例，D 群1例，E 群5例）が解析から除外され，解析対象は263例となった。除外された10例の安全性データはレビューされた。除外されたことにより結果に大きな影響はなかった。

試験を中止したのは263例中21例（A 群4例，B 群6例，C 群3例，D 群2例，E 群6例）であり，242例（92.0%）が試験を完了した。

死亡例が E 群に1例認められた。91歳であった本患者は Day 139に治験薬の最後の投与を受け，Day 174に死亡した。自然死であり，剖検は行われなかった。

2.7.6.1.3.3 患者背景

患者背景は全体的に投与群間でよく均衡が取れていた。年齢の平均値（標準偏差）は A 群［76.4歳（8.9）］が他の投与群［B 群で78.2歳（8.9），C 群で78.0歳（9.1），D 群で80.0歳（8.0），E 群で79.2歳（8.3）］に比べて低かった。白人がほとんど（98.1%）であり，女性（65.4%）が男性（34.6%）に比べて多かった。

ベースライン時の試験眼の BCVA の平均値（標準偏差）は，A 群で55.2文字（12.7），B 群で56.7文字（11.1），C 群で56.2文字（12.2），D 群で56.3文字（11.5）であり，投与群間でバランスがとれていた。中心領域網膜厚の平均値（標準偏差）は A 群で437.8 µm（122.4），B 群で446.2 µm（116.3），C 群で481.4 µm（151.6），D 群で464.4 µm（110.6）であり，数値に違いが認められた。また，治験実施計画書で定義された効果不十分な患者集団（A 群及び E 群でラニビズマブ0.5 mg を Q4W で12週間投与後に BCVA が68文字以下であった患者集団）における，12週時ベースラインの BCVA の平均値（標準偏差）は，E 群で56.2文字（11.1），対照群である A 群で54.5文字（13.2）であり，中心領域網膜厚の平均値（標準偏差）は E 群で300.9 µm（85.4），A 群で283.9 µm（67.9）であった。

2.7.6.1.3.4 有効性

主要評価項目である，ETDRS 視力表を用いたベースラインから36週時までの BCVA の平均変化量におけるラニビズマブ0.5 mg Q4W と比較して本剤で明らかに上回る有効性は認められなかった。未治療の CNV を伴う AMD 患者集団における BCVA アウトカムで，ラニビズマブ0.5 mg Q4W（A 群）を上回る差は本剤投与群のいずれにおいても認められなかった。

本剤6.0 mg Q8W（D 群）は，本剤6.0 mg Q4W（C 群）投与と数値的に類似した BCVA 結果を示した。本剤6.0 mg Q8W（D 群）はまた，ラニビズマブ0.5 mg Q4W（A 群）と比較して OCT パラメータに対して解剖学的な安定性を示した。

事前に規定した効果不十分例における解析：ラニビズマブ0.5 mg Q4W/本剤6.0 mg Q4W（E 群）は，治験実施計画書で定義された効果不十分な患者集団において，BCVA 又は OCT（中心領域網膜厚）のいずれにおいても，ラニビズマブ0.5 mg Q4W（A 群）と比較して追加のベネフィットを示さなかった。

2.7.6.1.3.5 薬物動態及び薬力学

薬物動態/薬力学データの解釈には母集団薬物動態及び薬力学解析が必要である。この解析は，本剤を用いた3つの第 II 相試験すべてを統合した解析で構成されるため，別途報告する。

観察されたデータに基づくと，血漿中ファリシマブ濃度は，本剤6.0 mg Q4W 群で本剤 1.5

mg Q4W 群に比較して約4倍高く，曝露量の用量比例的な増加が示された。本剤6.0 mg を投与されたすべての群で，全身遊離 VEGF 濃度は，ベースライン時のレベル，及びトラフ時の後の時点と比較して投与1週間後ではわずかに低かった。第1週の時点は，予想される最高血漿中ファリシマブ濃度付近であり，したがって，全身パラメータに対する潜在的な影響を評価するための最も感度の高い時点である。

投与後1週後（13週時）のわずかに高い濃度を除いて，いずれの投与群又は来院時においても，血漿中遊離又は総 Ang-2濃度の平均値にベースラインからの明らかな変化はなかった。総 Ang-2濃度の上昇は遊離 Ang-2濃度の低下と関連することが予想されるため，このことについて結論付けることはできなかった。

一部の患者から採取した房水サンプルにおける探索的薬力学的評価では，房水中の VEGF 及び Ang-2が本剤投与後8週までを含めて高度に抑制されたことが示された。しかし，ベースライン時に Ang-2濃度を定量できなかったサンプルが多かったため，Ang-2抑制データの解釈は限定的であった。

2.7.6.1.3.6 安全性

有害事象の概況を表 2.7.6.1.3.6-1に示し，すべての有害事象の集計を表 2.7.6.2-3に示した。試験眼の有害事象，非試験眼の有害事象及び眼以外の有害事象の集計をそれぞれ表 2.7.6.2-4，表 2.7.6.2-5及び表 2.7.6.2-6に示し，試験眼の副作用の集計を表 2.7.6.2-7に示した。

安全性解析対象集団は，治験を早期に中止したか否かにかかわらず，治験薬を少なくとも1回投与された全例とされ，262例であった（A 群の1例は治験薬を投与されなかったことから安全性解析集団には含まれなかった）。

また，1施設での GCP 違反により解析対象から除外された10例は，安全性解析対象集団に含まれなかった。これら10例のデータを削除しても，結果に大きな影響はなかった。

- 有害事象は計 81.7%（214 例）に発現し，有害事象の発現頻度は 5 つの投与群間で概ね同程度であった（表 2.7.6.2-3）。
- 眼の有害事象の大部分は試験眼に発現した。試験眼の有害事象は，全体で 47.7%（125 例），A 群の 41.8%（28 例），B 群の 45.7%（21 例），C 群の 53.8%（21 例），D 群の 58.7%（27 例）及び E 群の 43.8%（28 例）に認められた。発現頻度は投与群間で概ね同程度であったが，C 群及び D 群で高かった。全体で発現頻度が高かったのは，順に結膜出血，眼痛及び硝子体剥離であった。試験眼の副作用は全体で 5.0%（13 例），A 群の 4.5%（3 例 5 件，前房のフレア 3 例，前房内細胞 2 例），B 群の 8.7%（4 例 4 件，眼痛，網膜出血，視力障害，硝子体浮遊物各 1 例），C 群の 7.7%（3 例 3 件，網膜色素上皮裂孔，眼刺激，硝子体浮遊物各 1 例），D 群の 6.5%（3 例 3 件，網膜色素上皮裂孔 2 例，眼痛 1 例）に認められ，E 群では認められなかった（表 2.7.6.1.3.6-1，表 2.7.6.2-4 及び表 2.7.6.2-7）。試験眼の重篤な有害事象は全体で 1.9%（5 例），B 群の 6.5%（3 例に 4 件，角膜後面沈着物，網膜出血，視力低下及び眼内炎），E 群の 3.1%（2 例に 2 件，緑内障及び眼内炎）に認められた。この内，網膜出血は副作用であった。
- 非試験眼の有害事象は，全体で 32.1%（84 例），A 群の 31.3%（21 例），B 群の 34.8%（16 例），C 群の 23.1%（9 例），D 群の 39.1%（18 例）及び E 群の 31.3%（20 例）に認められた。全体で発現頻度が高かったのは，順に新生血管加齢黄斑変性，硝子体剥離及び網膜出血であった（表 2.7.6.2-5）。非試験眼の副作用は認められなかった。非試験眼の重篤な有害事象は全体で 1.1%（3 例），A 群の 1.5%（1 例，新生血管加齢黄斑変性），B 群の 2.2%（1 例，黄斑円孔）及び D 群の 2.2%（1 例，新生血管加齢黄斑変性）に認められた。
- 眼以外の有害事象は，全体で 64.9%（170 例），A 群の 55.2%（37 例），B 群の 80.4%（37 例），C 群の 59.0%（23 例），D 群の 65.2%（30 例）及び E 群 67.2%（43 例）に認められた。

発現頻度は投与群間で概ね同程度であったが，B 群で高かった。眼以外の副作用は認められなかった。眼以外の重篤な有害事象は全体で 12.6%（33 例）に認められた。

- 投与中止に至った有害事象は全体で 4.2%（11 例）に認められ，この内，試験眼の有害事象が 5 例（B 群 1 例，E 群 4 例），眼以外の有害事象が 5 例（A 群 1 例，B 群 2 例，E 群 2 例）であった。この内，副作用は網膜出血 1 例（B 群）であった。
- 死亡に至った有害事象が E 群（ラニビズマブ 0.5 mg を Q4W で 8 週時まで投与後，本剤 6.0 mg を Q4W で 32 週時まで投与）の 1 例（心肺停止）で眼以外の有害事象として報告された。この有害事象は治験薬との因果関係なしと判断された。
- 臨床検査値，心電図及びバイタルサインのデータを検討した結果，試験終了時には，投与群間で臨床検査値，心電図及びバイタルサインの平均パラメータに臨床的に重要な変化は認められなかった。
- 全体で，試験中のいずれかの時点で ADA 陽性であったのは 26 例であった。ADA 陽性の全身薬物動態に対する明らかな影響は認められず，ADA 陽性であった患者の大半（21/26 例）では眼内炎症を示唆する有害事象は認められなかった。

表 2.7.6.1.3.6-1 有害事象の概況（BP29647試験）

Overall Adverse Events Profile, Safety-Evaluable Patients
Protocol: BP29647

	0.5 mg ranibizumab Monthly (N=67)	1.5 mg RO6867461 Monthly (N=46)	6 mg RO6867461 Monthly (N=39)	6 mg RO6867461 Monthly(Wk12), Bi-Monthly (Wk28) (N=46)	0.5 mg ranibizumab Monthly(Wk8), 6 mg RO6867461 Monthly (Wk32) (N=64)
Total number of patients with at least one AE	51 (76.1%)	39 (84.8%)	31 (79.5%)	39 (84.8%)	54 (84.4%)
Total number of events	191	187	131	150	193
Total number of patients withdrawn due to an AE	1 (1.5%)	3 (6.5%)	0	0	5 (7.8%)
Total number of patients with at least one					
Ocular adverse events on the study eye	28 (41.8%)	21 (45.7%)	21 (53.8%)	27 (58.7%)	28 (43.8%)
Serious Ocular AE on study eye	0	3 (6.5%)	0	0	2 (3.1%)
Ocular AE on study eye leading to discontinuation	0	1 (2.2%)	0	0	4 (6.3%)
Systemic adverse events	37 (55.2%)	37 (80.4%)	23 (59.0%)	30 (65.2%)	43 (67.2%)
Serious Systemic AE	9 (13.4%)	7 (15.2%)	7 (17.9%)	4 (8.7%)	6 (9.4%)
Systemic AE leading to discontinuation	1 (1.5%)	2 (4.3%)	0	0	2 (3.1%)
AE with fatal outcome	0	0	0	0	1 (1.6%)
Serious AE	9 (13.4%)	11 (23.9%)	7 (17.9%)	5 (10.9%)	8 (12.5%)
Related Serious AE	0	1 (2.2%)	0	0	0
Related AE	3 (4.5%)	4 (8.7%)	3 (7.7%)	3 (6.5%)	0
Related Ocular AE on the study eye	3 (4.5%)	4 (8.7%)	3 (7.7%)	3 (6.5%)	0
Related Systemic AE	0	0	0	0	0
Ocular adverse events	39 (58.2%)	25 (54.3%)	23 (59.0%)	29 (63.0%)	37 (57.8%)
Ocular adverse events on the fellow eye	21 (31.3%)	16 (34.8%)	9 (23.1%)	18 (39.1%)	20 (31.3%)

Percentages are based on N.
Multiple occurences of the same Event in one individual counted only once.

Program: /opt/BIOSTAT/prod/cdt7716r/i29647c/t_ae_prof.sas / Output: /opt/BIOSTAT/prod/cdt7716r/i29647c/reports/t_ae_prof_SAF.out
02FEB2018 21:37　Page 1 of 1
One additional patient in Arm A (not listed in table) was withdrawn from the study, due to an ocular adverse event in the study eye, at the request of the Sponsor, in order to comply with protocol withdrawal criteria.

[5.3.5.1-nAMD-1 Table 27を再掲]

2.7.6.1.3.7 結論

第 II 相 BP29647試験は，ベースラインから36週時までの BCVA の平均変化量におけるラニビズマブ0.5 mg Q4W 投与と比較した本剤の明らかな有効性という事前に規定された主要評価項目を達成していなかったが，すべての投与群でベースラインからの BCVA の頑健な改善が認められた。

36週間の試験において，CNV を伴う AMD 患者に本剤を Q4W 及び Q8W で投与したとき，ラニビズマブ0.5 mg Q4W 投与と比較して同程度の有効性を示した。したがって，本剤は，同程度の視覚的及び解剖学的アウトカムを達成したまま，より頻度の少ない投与間隔（Q8W まで）での投与となる可能性がある。

本剤投与の忍容性は良好であった。本試験で認められた本剤の眼及び眼以外の安全性所見は，抗 VEGF 薬を硝子体内投与された nAMD 患者で報告されている安全性プロファイルと一致しており，新たな安全性シグナルは確認されなかった。ADA と薬物動態/薬力学，安全性アウトカムとの間に明らかな関係は認められなかった。

全体として，BP29647試験では，CNV を伴う AMD 患者において，ラニビズマブ0.5 mg Q4W 投与と同程度の本剤の安全性及び忍容性，並びに有効性が認められ，更に持続性が増大する可能性が示された。

2.7.6.1.4　海外第 II 相臨床試験（nAMD 患者：CR39521試験）

（評価資料：5.3.5.1- nAMD-2）

2.7.6.1.4.1　概要表

表 2.7.6.1.4.1-1 概要表（CR39521試験）

治験の標題：nAMD の治療における持続性延長のための二重特異的抗体ファリシマブによる Ang-2と VEGF-A の同時阻害	
施設及び国：米国（25施設）	
公表文献（引用文献）：なし	
第1症例の登録日：2017年1月27日 最終症例の最終来院日：2018年3月29日	開発のフェーズ：第 II 相
目　　的： 有効性の主要目的 本剤を12週間隔（Q12W）及び16週間隔（Q16W）で投与したときの視力に対する有効性を評価する。 有効性の副次的目的 その他の視力アウトカム並びに SD-OCT 及び FFA を用いた解剖学的アウトカム指標等に対する本剤の有効性を評価する。 有効性の探索的目的 24週時の疾患活動性の頻度を検討する。 安全性の目的 本剤の Q12W 及び Q16W の硝子体内反復投与を評価する。 薬物動態及び薬力学の探索的目的 本剤の全身薬物動態プロファイルを評価し，房水中の本剤，ラニビズマブ，遊離 VEGF-A 及び Ang-2プロファイルを評価する。	
治 験 方 法： 未治療の nAMD 患者を対象とした多施設共同，ランダム化，実薬対照（ラニビズマブ），患者及びアウトカム評価者遮蔽による並行群間比較（3投与群），52週間の試験。 以下の3群に2:2:1の比でランダムに割り付けた。 • 本剤 6.0 mg Q12W 投与群（Q12W 群）：12 週時まで本剤 6.0 mg を Q4W で硝子体内投与し，続いて 48 週時まで本剤 6.0 mg Q12W で硝子体内投与した。 • 本剤 6.0 mg Q16W 投与群（Q16W 群）：12 週時まで本剤 6.0 mg を Q4W（4 回の注射）で硝子体内投与し，続いて 48 週時まで本剤 6.0 mg を Q16W で硝子体内投与した。治験実施計画書に規定した 24 週時の疾患活動性の評価で，活動性疾患を有していた患者には残りの治験期間，本剤 6.0 mg を Q12W で投与した。 • 比較対照群（ラニビズマブ Q4W 群）：ラニビズマブ 0.5 mg を Q4W で 48 週間硝子体内投与した。 試験眼は片眼のみとした。試験期間を通して遮蔽を維持するために，Q12W 群及び Q16W 群にランダム化された患者にシャム硝子体内投与を行った。	
症　例　数： 目標例数：約75例；Q12W 群30例，Q16W 群30例，ラニビズマブ Q4W 群15例 登録例数：　76例；Q12W 群29例，Q16W 群31例，ラニビズマブ Q4W 群16例 解析対象例数：71例；Q12W 群24例，Q16W 群31例，ラニビズマブ Q4W 群16例 1施設で GCP 違反が認められたため，5例（すべて Q12W 群）を解析から除外した。	

診断及び主要な組入基準：
未治療の CNV を伴う AMD 患者

被験薬，用量及び投与方法：

(1) 被験薬：ファリシマブ製剤
本剤60 mg/0.5 mL（120 mg/mL）を充填した2 mL の単回使用バイアル製剤。

(2) 用量及び投与方法：
- Q12W 群：12 週時まで本剤 6.0 mg を Q4W で硝子体内投与し，続いて 48 週時まで本剤 6.0 mg を Q12W で硝子体内投与した。
- Q16W 群：12 週時まで本剤 6.0 mg を Q4W（4 回の注射）で硝子体内投与し，続いて 48 週時まで本剤 6.0 mg を Q16W で硝子体内投与した。治験実施計画書に規定した 24 週時の疾患活動性の評価で，活動性疾患を有していた患者には残りの治験期間，本剤 6.0 mg を Q12W で投与した。

対照薬，用量及び投与方法：
(1) 対照薬：
- ラニビズマブ
ラニビズマブ0.5 mg/0.05 mL（10 mg/mL）を充填した2 mL の単回使用バイアル製剤。治験依頼者から提供された。

(2) 用量及び投与方法：
ラニビズマブ Q4W 群：ラニビズマブ0.5 mg を Q4W で48週間硝子体内投与した。

治 療 期 間：
各患者の治験の試験期間は最長56週間とし，その内訳は，スクリーニング（ランダム化日又はその4週間前から），ランダム化（Day 1），治験薬投与（Day 1～48週時）及び最終来院（52週時）であった。

評 価 基 準：
(1) 有効性評価項目
- 主要評価項目
ETDRS 視力表を用いた BCVA のベースラインから40週時の平均変化量
- 副次評価項目
BCVA
  - ETDRS 視力表を用いた BCVA のベースラインからの平均変化量の推移
  - BCVA でベースラインから 0，5，10 又は 15 文字以上改善した患者の割合の推移
  - BCVA でベースラインから 0，5，10 又は 15 文字以上悪化を回避した患者の割合の推移
  - BCVA が 20/40 以上であった患者の割合の推移
  - BCVA が 20/200 以下となった患者の割合の推移

SD-OCT による解剖学的アウトカム指標
  - 中心窩厚のベースラインからの平均変化量の推移
  - 中心領域網膜厚のベースラインからの平均変化量の推移
  - 網膜内滲出液，網膜下液，嚢胞又は色素上皮剥離がある患者の割合の推移

FFA による解剖学的アウトカム指標
  - 40 週時及び 52 週時の CNV の総面積のベースラインからの平均変化量
  - 40 週時及び 52 週時における CNV 領域の総面積のベースラインからの平均変化量
  - 40 週時及び 52 週時の総漏出面積のベースラインからの平均変化量
- 探索的評価項目

24週時に疾患活動性を示した患者の割合

(2) 薬物動態学的評価項目
規定した時点の血漿中ファリシマブ濃度

(3) 薬力学的評価項目
- 房水中ファリシマブ濃度又は薬物動態パラメータと遊離 VEGF-A 及び Ang-2 濃度との関係
- 房水中ラニビズマブ濃度又は薬物動態パラメータと遊離 VEGF-A 及び Ang-2 濃度との関係
- 房水中の遊離 VEGF-A 及び Ang-2 濃度の推移

(4) 安全性評価項目
- 眼の有害事象の発現頻度及び重症度
- 眼以外の有害事象の発現頻度及び重症度
- 治験中止理由，臨床検査，併用薬などの他の安全性データ

統 計 手 法：
主要有効性解析，副次的有効性解析，探索的有効性解析は，ITT 解析集団（割り付けられた全患者と定義）を対象に実施され，患者は割り付けられた治療に従って群分けされた。
安全性解析では，治験を早期に中止したか否かにかかわらず，治験薬を少なくとも1回投与され，投与された治療（本剤又はラニビズマブ）に従って群分けされた患者を対象とした。
1施設で GCP 違反が認められたため，割り付けられた5例のデータはすべての解析から除外された。
主要有効性解析は，MMRM を用いて行った。モデルには，カテゴリー共変量として，投与群，来院，来院と投与群の交互作用，連続共変量としてベースラインの BCVA を含めた。患者内相関を説明するために，無構造分散共分散構造を用いた。
本剤群とラニビズマブ群の平均値，ラニビズマブに対する平均値の差，対応する80%信頼区間（CI）を算出した。多重検定に対する第1種の過誤の正式な調整は行わなかった。
副次的有効性評価項目についても，上記の MMRM を用いて解析した。繰り返し測定されたカテゴリーアウトカムは，二項分布，ロジットリンク関数，無構造分散共分散構造を持つ一般化推定方程式を用いて解析された。モデルには，カテゴリー共変量として，投与群，来院，来院と投与群の交互作用を含めた。最小二乗平均とその80%CI，及びオッズ比を算出した。
探索的有効性評価項目は，投与群ごとに対応する80% Wilson スコア CI で報告した。
24週時の疾患活動性別の BCVA 及び中心領域網膜厚の平均変化量は，上記の MMRM を用いて推定した。

2.7.6.1.4.2 患者の内訳

未治療の nAMD 患者76例（Q12W 群29例，Q16W 群31例，ラニビズマブ Q4W 群16例）が登録された。1施設で GCP 違反が認められたため，5例（すべて Q12W 群）を解析から除外した。
試験を中止した患者は71例中6例（Q12W 群3例，Q16W 群3例）であり，65例（91.5%）が試験を完了した。
死亡例が3例（Q12W 群1例，Q16W 群2例）認められた（2.7.6.1.4.6）。

2.7.6.1.4.3 患者背景

患者背景は全体的に投与群間でよく均衡が取れていた。年齢の平均値（標準偏差）は Q12W 群［80.3歳（7.2）］が他の投与群［Q16W 群で77.7歳（8.4），ラニビズマブ Q4W 群で77.3歳

（10.3）］に比べてわずかに高かった。白人がほとんど（97.2%）であり，女性（57.7%）が男性（42.3%）に比べて多かった。

ベースライン時の試験眼の BCVA の平均値（標準偏差）は，Q12W 群で57.8文字（10.5），Q16W 群で60.4文字（10.8），ラニビズマブ Q4W 群で55.3文字（12.1），中心領域網膜厚の平均値（標準偏差）は Q12W 群で417.9 µm（84.3），Q16W 群で382.2 µm（80.9），ラニビズマブ Q4W 群で443.1 µm（125.0）であり，投与群間で違いがあった。

2.7.6.1.4.4 有効性

CR39521試験では，主要評価項目である40週時及び52週時の試験終了時に，本剤6.0 mg を Q12W 及び Q16W で硝子体内投与した両投与群において，臨床的に意味のあるベースラインからの BCVA の改善及び維持が示された。本剤が投与された両投与群の患者における BCVA アウトカムは，試験期間を通してラニビズマブ Q4W 群のアウトカムと同程度であった。BCVA アウトカムは，解剖学的アウトカムでの対応する効果により支持された。

40週時の主要評価項目の解析では，Q12W 群とラニビズマブ Q4W 群の調整済み平均値（MMRM）の差は−2.1文字（CI：−6.8，2.6）であり，Q16W 群とラニビズマブ Q4W 群の調整済み平均値の差は1.1文字（CI：−3.4，5.5）であった。52週時の最終解析時，Q12W 群とラニビズマブ Q4W 群の比較では0.5文字の差（CI：−4.3，5.3）が認められ，Q16W 群とラニビズマブ Q4W 群の比較では1.8文字の差（CI：−2.7，6.4）が認められた。

40週時の主要評価項目のデータ及び52週時の試験終了時のデータは，ベースラインの BCVA からの0，5，10又は15文字以上（ETDRS）の改善又は悪化を回避した患者の割合，中心領域網膜厚のベースラインからの平均変化量の推移，並びに40週時及び52週時の CNV の総面積，CNV 領域の総面積及び総漏出面積のベースラインからの平均変化量といった，視力及び SD-OCT/FFA 所見による解剖学的な副次評価項目において，対照のラニビズマブ群と本剤が投与された両投与群との間で有効性が同程度であったことにより支持された。

有効性の評価項目ではないものの，52週間の試験期間におけるラニビズマブ Q4W 群の平均注入回数が12.9回であったのに対し，試験開始時に Q12W 及び Q16W の群にランダム化された患者の平均注入回数はそれぞれ6.7回及び6.2回であった中で，本剤が投与された両投与群では視覚機能面でラニビズマブ Q4W 群と同様に臨床的に意味のあるベネフィットが得られた。

2.7.6.1.4.5 薬物動態及び薬力学

薬物動態/薬力学データの解釈には母集団薬物動態及び薬力学的解析が必要である。この解析は，本剤を用いた3つの第 II 相試験すべてを統合した解析で構成されるため，別途報告する。

同意の得られた一部の患者からの房水サンプルにおける薬力学的評価では，本剤による VEGF 及び Ang-2の強い抑制が示されたが，ベースライン時に Ang-2濃度を定量できなかったサンプルが多数存在し，Ang-2抑制データの解釈は限定的であった。

2.7.6.1.4.6 安全性

有害事象の概況を表 2.7.6.1.4.6-1に示し，有害事象の集計を試験眼，非試験眼，眼以外についてそれぞれ表 2.7.6.2-8，表 2.7.6.2-9及び表 2.7.6.2-10に示した。副作用の集計を表 2.7.6.2-11に示した。

安全性解析対象集団は，治験を早期に中止したか否かにかかわらず，治験薬を少なくとも1回投与された患者71例であり，投与された治療に従って患者を群分けした。

- 有害事象は計 76.1%（54 例）に発現した。投与群間で，有害事象に臨床的に意味のある不均衡は認められなかった。
- 試験眼に有害事象が認められた患者は全体で 39.4%（28 例）であった。試験眼の有害事象の発現頻度は，本剤群の方がラニビズマブ群よりも数値的に低かった［Q12W 群 37.5%（9

例），Q16W 群 35.5%（11 例），ラニビズマブ Q4W 群 50.0%（8 例），表 2.7.6.2-8］。全体で発現頻度が高かった試験眼の有害事象は，順に結膜出血及び眼痛であり，他の事象は 2 例以下であった。試験眼の副作用は Q16W 群の 1 例に 1 件（虹彩炎）認められた（表 2.7.6.2-11）。試験眼の重篤な有害事象は認められなかった。

- 非試験眼に有害事象が認められた患者は全体で 23.9%（17 例）であった。非試験眼の有害事象の発現頻度は，Q12W 群 25.0%（6 例），Q16W 群 16.1%（5 例），ラニビズマブ Q4W 群 37.5%（6 例）であった。全体で発現頻度が高かった非試験眼の有害事象は新生血管加齢黄斑変性であり，他の事象は 2 例以下であった（表 2.7.6.2-9）。非試験眼において副作用及び重篤な有害事象は認められなかった。
- 眼以外の有害事象が少なくとも 1 件認められた患者は全体で 60.6%（43 例）であった。発現頻度は投与群間で同程度であった［Q12W 群 58.3%（14 例），Q16W 群 64.5%（20 例），ラニビズマブ Q4W 群 56.3%（9 例）］。全体で発現頻度が高かった眼以外の有害事象は上咽頭炎，転倒，尿路感染，インフルエンザ及び不安であり，他の事象は 2 例以下であった（表 2.7.6.2-10）。眼以外の副作用は認められなかった。眼以外の重篤な有害事象は，7 例に 10 件認められた。
- 投与中止に至った有害事象は試験眼，非試験眼，眼以外のいずれでも報告されなかった。治験薬の休薬に至った有害事象は Q12W 群の 2 例に 4 件報告された。この有害事象の内訳は，1 例での転倒，頭痛及び精神状態変化（いずれも眼以外の有害事象），及び他の 1 例での霰粒腫（試験眼での有害事象）であった。いずれも治験薬との因果関係なしと判断された。
- 死亡に至った有害事象が 3 例に認められた（Q12W 群の 1 例が虚血性脳卒中による死亡，Q16W 群の 2 例がそれぞれ敗血症及び遠隔転移を伴う新生物による死亡）。死亡に至った有害事象はいずれも治験薬との因果関係なしと判断された。

表 2.7.6.1.4.6-1 有害事象の概況（CR39521試験）

	RO6867461 Q12W (N=24)	RO6867461 Q16W (N=31)	Ranibizumab Q4W (N=16)	Pooled RO6867461 (N=55)
Total number of patients with at least one AE	18 (75.0%)	23 (74.2%)	13 (81.3%)	41 (74.5%)
Total number of AEs	60	82	57	142
Total number of deaths	1 (4.2%)	2 (6.5%)	0	3 (5.5%)
Total number of patients withdrawn from study due to an AE	0	0	0	0
Total number of patients with at least one				
Serious AE	4 (16.7%)	3 (9.7%)	0	7 (12.7%)
Serious AE leading to withdrawal from treatment	0	0	0	0
Serious AE leading to dose modification/interruption	1 (4.2%)	0	0	1 (1.8%)
Serious ocular AE	0	0	0	0
Serious non-ocular AE	4 (16.7%)	3 (9.7%)	0	7 (12.7%)
AE leading to withdrawal from treatment	0	0	0	0
AE leading to dose modification/interruption	2 (8.3%)	0	0	2 (3.6%)
Ocular AE in the study eye	9 (37.5%)	11 (35.5%)	8 (50.0%)	20 (36.4%)
Ocular AE in the fellow eye	6 (25.0%)	5 (16.1%)	6 (37.5%)	11 (20.0%)
Non-ocular AE	14 (58.3%)	20 (64.5%)	9 (56.3%)	34 (61.8%)
Ocular AEs of special interest				
Sight-threatening adverse events	1 (4.2%)	0	0	1 (1.8%)
Non-ocular AEs of special interest				
Cases of potential drug-induced liver injury	0	0	0	0
Suspected transmission of an infectious agent by the study drug	0	0	0	0

Adverse Events of Special Interest are defined from expedited events in eCRF.
Ocular / Non-Ocular AEs defined by location of event specified in eCRF. Events marked as 'Left' or 'Right' are considered as Ocular AEs. 'Not applicable' or unmarked events are considered as Non-Ocular AEs.
Withdrawal from treatment or dose modification/interruption categories consider actions taken with study drug and with sponsor supplied fellow eye Ranibizumab.

Program: /opt/BIOSTAT/prod/cdt7716a/i39521b/t_ae_ov.sas / Output: /opt/BIOSTAT/prod/cdt7716a/i39521d/reports/t_ae_ov_SE.out
08MAY2018 14:48

[5.3.5.1-nAMD-2 Table 23を再掲]

2.7.6.1.4.7 結論

nAMD 患者を対象とした本剤6.0 mg の Q12W 又は Q16W 投与は，52週までの期間を通してラニビズマブ0.5 mg Q4W 投与と比較して，同様の有効性を示し，眼及び眼以外の安全性は全体として概ね一致していた。結論として，本剤は，最初に Q4W で4回投与後，より頻度の少ない投与で，平均して，nAMD 患者における現在の標準治療と同様の視覚アウトカムの改善と維持並びに安全性プロファイルを保ちつつ， nAMD 疾患活動性を適切に管理可能であった。

2.7.6.1.5　国際共同第 III 相臨床試験（nAMD 患者：GR40306試験）

（評価資料：5.3.5.1- nAMD-3）

2.7.6.1.5.1　概要表

表 2.7.6.1.5.1-1 概要表（GR40306試験）

治験の標題：nAMD 患者を対象としたファリシマブの有効性及び安全性を検討する第 III 相多施設共同，ランダム化，実薬対照，二重遮蔽比較試験	
施設及び国：日本を含む15カ国（149施設）	
公表文献（引用文献）：なし	
第1症例の登録日：2019年2月19日 データカットオフ日：2020年10月26日	開発のフェーズ：第 III 相
目　　的： 有効性の主要目的 BCVA に対する本剤6.0 mg の硝子体内投与の有効性をアフリベルセプトと比較し評価する 有効性の副次的目的 • 追加の BCVA アウトカムに対する本剤の有効性を評価する • 治験薬の投与頻度を評価する • 光干渉断層撮影（OCT）を用いた解剖学的評価に対する本剤の有効性を評価する • FFA を用いた解剖学的評価に対する本剤の有効性を評価する 安全性の目的 • 本剤の眼及び眼以外の安全性及び忍容性を評価する 探索的有効性の目的 • National Eye Institute 25-Item Visual Function Questionnaire（NEI VFQ-25）を用いて，患者報告による視力関連機能及び生活の質（QOL）に対する本剤の有効性を評価する • OCT を用いた解剖学的評価に対する本剤の有効性を評価する 薬物動態の目的 • ファリシマブの全身薬物動態の特性を明らかにする 主な薬物動態及び薬力学的目的（探索的） • 房水（任意）及び硝子体（任意）におけるファリシマブの薬物動態の特性を明らかにする • 遊離 VEGF-A 及び遊離 Ang-2 の薬物濃度（曝露量）−反応関係を評価する 免疫原性の目的 ファリシマブに対する免疫応答を評価し，ADA の潜在的効果を評価する	
治 験 方 法： 治療歴のない nAMD 患者を対象に，本剤を最長 Q16W で投与したときの有効性，安全性，持続性，薬物動態を検討することを目的とした，第 III 相多施設共同ランダム化実薬（アフリベルセプト）対照二重遮蔽並行群間比較，112週間の試験。 患者は2つの投与群のいずれかに1:1の割合でランダムに割り付けられた。 • 本剤群：本剤群にランダムに割り付けられた患者に，本剤 6.0 mg を 12 週時まで Q4W で 4 回硝子体内投与した。20 週時に治験実施計画書に規定された疾患活動性の評価後，活動性疾患を有する本剤群の患者にはその来院時に本剤を投与し，Q8W の固定投	

与方法で継続した。24 週時に，治験実施計画書に規定された疾患活動性の 2 回目の評価後に，活動性疾患を有する本剤群の患者（20 週時に活動性疾患を有する患者は除く）にはその来院時に本剤を投与し，12 週間隔（Q12W）の固定投与方法で継続した。治験実施計画書に規定された基準に従い，20 週時及び 24 週時に活動性疾患を有さなかった本剤群の患者には，本剤の Q16W の固定投与方法で治療を行った。これらの固定投与方法による本剤投与は 60 週時まで継続され，補充療法は許容されなかった。

60週時（本剤群のすべての患者に本剤の投与を予定している場合）以降，108週時までは，本剤群のすべての患者に個別化した投与間隔に従って投与した。

- アフリベルセプト群：患者にアフリベルセプト 2 mg を 8 週時まで Q4W で 3 回硝子体内投与した。その後 108 週までアフリベルセプト 2 mg を Q8W で硝子体内投与した。
- 対象眼は片眼のみとした。投与群間の遮蔽を維持するために，該当する来院時に両投与群の患者にシャム注射を行った。
- ランダム化は，ベースライン時における以下の因子により層別化した
  - BCVA スコア（74 文字以上，73～55 文字，54 文字以下）
  - 低輝度条件下での視力低下（LLD，33 文字以上，33 文字未満）
  - 地域（米国及びカナダ，アジア，その他の地域）

主要解析は，グローバル登録期間の全例が48週時まで試験を完了したか又は48週時以前に試験を中止した時点で実施した。

症　例　数：
目標例数：約640例の患者を登録し，2つの投与群のいずれかに1:1の割合でランダムに割り付ける
登録例数：671例；本剤群に334例，アフリベルセプト群に337例

診断及び主要な組入基準：

50歳以上で，以下の試験眼に関する選択基準を満たす患者

- 未治療の CNV を伴う AMD（nAMD）
- FFA 又は OCT により CNV 活動性に関連する中心窩下成分が確認された，中心窩下 CNV 又は傍中心窩/中心窩外 CNV を認める（ここで CNV の活動とは，網膜下液，subretinal hyper-reflective material，もしくは漏出が確認できることと定義する）
- 以下のすべての特徴を示す CNV 病変（すなわち predominantly classic，minimally classic，又は occult）：FFA による病変全体の大きさが乳頭面積の 9 倍以下，FFA による CNV 病巣の面積が病変全体の大きさの 50%以上，FFA による活動性 CNV，及び OCT で確認された CNV からの滲出
- Day 1 に開始距離 4 m で評価する ETDRS 視力検査において，BCVA が 78～24 文字
- 中間透光体が十分にクリアで瞳孔は十分に散大し，確定診断のための良質な網膜画像の撮影が可能

被験薬，用量及び投与方法：
(1) 被験薬：ファリシマブ製剤
　単回使用バイアル製剤
(2) 用量及び投与方法：
　6.0 mg を最長 Q16W で硝子体内投与

対照薬，用量及び投与方法：
(1) 対照薬：アフリベルセプト
　単回使用バイアル製剤
(2) 用量及び投与方法：
　2 mg を Q8W で硝子体内投与

治 療 期 間：
- スクリーニング：最長 28 日間
- ベースライン：Day 1
- 治験薬投与期間：Day 1 から 108 週時まで
- 観察期間：108 週時から 112 週時

評 価 基 準：
(1) 有効性評価項目
- 主要評価項目

BCVA におけるベースライン値から40，44，48週時の各時点の平均変化量の平均値（以降，BCVA におけるベースラインから40/44/48週時点の変化量平均値）（ETDRS 視力表で測定）

- 副次的評価項目
  - BCVA のベースラインからの変化量の推移
  - 40週時，44週時及び48週時の平均並びに経時的な BCVA がベースラインから0，5，10又は15文字以上改善した患者の割合
  - 40週時，44週時及び48週時の平均並びに経時的な BCVA がベースラインから5，10又は15文字以上悪化を回避した患者の割合
  - 40週時，44週時及び48週時の平均並びに経時的な BCVA がベースラインから15文字以上の改善又は84文字以上の BCVA を達成した患者の割合
  - 40週時，44週時及び48週時の平均並びに経時的に Snellen 視標で20/40以上（ETDRS 視力で69文字以上）を達成した患者の割合
  - 40週時，44週時及び48週時の平均並びに経時的に Snellen 視標で20/200以下（ETDRS 視力で38文字以下）となった患者の割合
  - 48週時，60週時及び112週時の本剤群における Q8W，Q12W 及び Q16W 投与の患者の割合
  - 48週時，60週時及び112週時までの治験薬投与回数
  - 40週時，44週時及び48週時の平均並びに経時的な中心領域網膜厚のベースラインからの変化量
  - 経時的な網膜内液が認められなかった患者の割合の変化
  - 経時的な網膜下液が認められなかった患者の割合の変化
  - 経時的な網膜内液及び網膜下液が認められなかった患者の割合の変化
  - 経時的な網膜色素上皮剥離が認められなかった患者の割合の変化
  - 48週時及び112週時における CNV 領域の総面積のベースラインからの変化量
  - 48週時及び112週時の漏出領域の総面積のベースラインからの変化量

- 特定の探索的評価項目
  - NEI VFQ-25スコアのベースラインからの経時変化

(2) 薬物動態学的評価項目
- 血漿中ファリシマブ濃度推移
- ファリシマブの房水濃度（任意）及び硝子体液中濃度（任意）の経時変化（探索的）

(3) 薬力学的評価項目（探索的）
- ファリシマブの薬物動態と房水（任意），血漿中及び/又は硝子体液中（任意）遊離 Ang-2 及び遊離 VEGF-A 濃度との経時的関係

(4) 免疫原性
- ベースライン時における ADA の有無と比較した試験中の ADA の有無

• ADA の有無と有効性，安全性又は薬物動態のエンドポイントとの関係 (5) 安全性評価項目 • 眼の有害事象の発現頻度及び重症度 • 眼以外の有害事象の発現頻度及び重症度
統 計 手 法： 主要な比較は，ITT 集団におけるアフリベルセプトと比較した本剤の非劣性を検証することであった。非劣性試験は，片側有意水準を0.02485，非劣性マージンを4文字とした。 有効性の主要評価項目について，両群の調整済み平均値の差の両側95.03%CI の下限が−4文字（非劣性マージン）を上回った場合，本剤はアフリベルセプトに対して非劣性であるとみなした。 有効性解析は，特に指定のない限り，ITT 集団に基づいて実施した。主要評価項目については，per-protocol 集団に基づく補足的解析も実施した。ベースラインとは，割付け時又はその直前の測定値と定義した。ベースライン時の評価が欠測していた患者は補完されなかった。 特に記載のない限り，有効性評価の解析には，層別因子として投与1日目に測定されたベースラインの BCVA ETDRS 文字スコア（74文字以上，73～55文字，54文字以下），LLD（33文字未満，33文字以上）及び地域（米国及びカナダ，アジア，その他の地域）を用いた。双方向音声認識又はウェブ応答システム（IxRS）に記録された層別因子を用いた。 主要な比較は，実対照薬（アフリベルセプト）と本剤との比較とした。連続変数の解析には，MMRM を用いた。二値変数の解析には，二項割合に対する層別解析を用いた。推定値及び CI は，各投与群の平均値（連続変数の場合）又は割合（二値変数の場合）並びに2つの投与群間の平均値又は割合の差を算出した。CI はいずれも両側で95.03%レベルであった。 仮説の頑健性及び新型コロナウイルス感染症（COVID-19）パンデミックの影響を評価するために，異なる中間事象の取扱方法を用いた補足的解析を実施した。

この主要な総括報告書では，主要評価項目に用いた最終時点（48週時）に対応する主要解析の結果を示す。本剤群には，20週時及び24週時の疾患活動性評価による来院後に，Q8W，Q12W 又は Q16W の投与方法が60週時まで固定されている患者が含まれる。

2.7.6.1.5.2 患者の内訳

未治療の nAMD 患者計671例を本試験に1:1の割合でランダムに割り付けた。本剤群に334例，アフリベルセプト群に337例割り付けた。48週時前に治験薬の投与を中止した患者は計6.1%（41例）であり，その内訳は本剤群7.8%（26例），アフリベルセプト群4.5%（15例）であった。

2.7.6.1.5.3 患者背景

ITT 集団では，患者背景は投与群間で概ね同様であり，想定される患者集団と一致していた。全例の登録時の平均年齢は76.3歳（本剤群75.9歳，アフリベルセプト群76.7歳）であり，75歳以上の患者が大半（62.1%）であり，女性が大半（59.9%）であった。白人が90.2%，米国及びカナダ地域が54.5%，民族は非ヒスパニック系又は非ラテン系が91.1%であった。全体では，患者の8.0%がアジア人であり，その内日本人が大半（98.1%）であった。これは投与群間で同様であった。

ITT 集団の試験眼のベースライン時 BCVA の平均値（SD）は，本剤群では61.3文字（12.5文字），アフリベルセプト群では61.5文字（12.9文字）であった。ベースライン時 LLD は，本剤群では25.3文字（12.9文字），アフリベルセプト群では26.1文字（13.2文字）であった。ベース

ライン時の中心領域網膜厚の平均値（SD）は，本剤群では360.5 μm（124.1 μm），アフリベルセプト群では356.1 μm（107.0 μm）であった。試験眼におけるベースライン時の平均 BCVA 及びベースライン時の平均中心領域網膜厚は，投与群間で同様であった。

網膜内液が認められなかった患者は53.4%，網膜下液が認められなかった患者は32.8%，網膜色素上皮剥離がない患者は8.2%であった。CNV 領域は，中心窩下が57.7%，傍中心窩が26.2%，中心窩外が14.3%であった。CNV は，Occult Type が52.3%，Classic Type が23.4%，Minimally Classic Type が9.2%であり，これらは投与群間で同様であった。CNV 領域の面積の平均値は，本剤群で4.7 mm^2，アフリベルセプト群で4.5 mm^2であった。

2.7.6.1.5.4 有効性

ITT 集団（特に断りのない場合を除く）の主要な有効性の結果は以下のとおりであった（2.7.3.2.1.5.3）。

- ITT 集団において，BCVA におけるベースラインから 40/44/48 週時点の変化量平均値で定義された主要評価項目が達成された。最長 Q16W で本剤を投与した患者群（本剤群）では，Q8W でアフリベルセプトを投与した患者群（アフリベルセプト群）に対して，BCVA におけるベースラインから 40/44/48 週時点の変化量平均値の差の 95%CI（MMRM method）の下限が非劣性マージンである−4 文字より大きいため，非劣性が確認された。BCVA におけるベースラインから 40/44/48 週時点の変化量平均値は，本剤群では 5.8 文字（95%CI：4.6，7.1 文字），アフリベルセプト群では 5.1 文字（95%CI：3.9，6.4 文字）であった。本剤群及びアフリベルセプト群の差は 0.7 文字（95%CI：−1.1，2.5 文字）であった。
- 主要解析の結果は ITT 集団及び per-protocol 集団の間で一貫しており，感度分析及び補足的解析により裏付けられた。
- BCVA のベースライン時からの平均変化量の推移：本剤群はアフリベルセプト群と同様であった。
- ベースライン時から 40/44/48 週時までに BCVA が 15 文字以上改善した患者の割合：本剤群では 20.0%（95%CI：15.6，24.4%），アフリベルセプト群では 15.7%（95%CI：11.9，19.6%）であり，本剤群はアフリベルセプト群と同様であった。
- ベースライン時から 40/44/48 週時までに BCVA の 15 文字以上の悪化を回避した患者の割合：本剤群では 95.4%（95%CI：93.0，97.7%），アフリベルセプト群では 94.1%（95%CI：91.5，96.7%）であり，本剤群はアフリベルセプト群と同様であった。
- 40/44/48 週時点で BCVA の 15 文字以上の改善又は Snellen 視標で 20/20 以上（ETDRS 視力で 84 文字以上）を達成した患者の割合：本剤群では 24.3%（95%CI：19.5，29.1%），アフリベルセプト群では 21.3%（95%CI：16.8，25.7%）であり，本剤群はアフリベルセプト群と同様であった。
- 40/44/48 週時点で Snellen 視標で 20/40 以上（ETDRS 視力で 69 文字以上）を達成した患者の割合：本剤群では 56.4%（95%CI：51.5，61.4%），アフリベルセプト群では 57.0%（95%CI：51.9，62.1%）であり，本剤群はアフリベルセプト群と同様であった。
- 40/44/48 週時点で Snellen 視標で 20/200 以下（ETDRS 視力で 38 文字以下）となった患者の割合：本剤群では 6.4%（95%CI：3.7，9.1%），アフリベルセプト群では 6.9%（95%CI：4.2，9.5%）であり，本剤群はアフリベルセプト群と同様であった。
- ベースライン時から 40/44/48 週時までの中心領域網膜厚の変化量：本剤群では−136.8 μm（95%CI：−142.6，−131.0 μm），アフリベルセプト群では−129.4 μm（95%CI：−135.2，−123.5 μm）であり，本剤群ではアフリベルセプト群と比べて，40/44/48 週時点の中心領域網膜厚の同程度の減少が認められた。
- 本剤群における 48 週に到達した患者の 48 週時点の本剤投与間隔ごとの患者の割合：本剤群の投与間隔は，Q8W が 20.3%，Q12W が 34.0%，Q16W が 45.7%であった。

- 48 週時点までの治験薬の平均投与回数：本剤群では 6.9 回（中央値：7.0 回），アフリベルセプト群では 7.8 回（中央値：8.0 回）であった。
- 40 週，44 週，48 週時点で網膜下液，網膜内液，網膜下液及び網膜内液，又は網膜色素上皮剥離が認められなかった患者の割合：網膜下液が認められなかった患者の割合は，40 週時では本剤群 78.5%（95%CI：73.9，83.1%），アフリベルセプト群 67.3%（95%CI：61.9，72.7%），44 週時では本剤群 69.6%（95%CI：64.3，74.9%），アフリベルセプト群 78.0%（95%CI：73.1，82.8%），48 週時では本剤群 75.7%（95%CI：70.7，80.8%），アフリベルセプト群 65.8%（95%CI：60.4，71.1%）であった。網膜内液が認められなかった患者の割合は，40 週時では本剤群 82.1%（95%CI：77.7，86.5%），アフリベルセプト群 77.2%（95%CI：72.5，81.9%），44 週時では本剤群 75.5%（95%CI：70.6，80.3%），アフリベルセプト群 84.9%（95%CI：80.7，89.1%），48 週時では本剤群 82.1%（95%CI：77.7，86.5%），アフリベルセプト群 74.4%（95%CI：69.4，79.5%）であった。網膜下液及び網膜内液が認められなかった患者の割合は，40 週時では本剤群 64.8%（95%CI：59.3，70.3%），アフリベルセプト群 52.1%（95%CI：46.3，57.9%），44 週時では本剤群 51.4%（95%CI：45.6，57.2%），アフリベルセプト群 65.5%（95%CI：59.8，71.1%），48 週時では本剤群 63.3%（95%CI：57.6，68.9%），アフリベルセプト群 47.1%（95%CI：41.3，52.9%）であった。網膜色素上皮剥離が認められなかった患者の割合は，40 週時では本剤群 7.8%（95%CI：4.7，10.9%），アフリベルセプト群 9.6%（95%CI：6.3，13.0%），44 週時では本剤群 3.6%（95%CI：1.5，5.8%），アフリベルセプト群 8.8%（95%CI：5.5，12.2%），48 週時では本剤群 3.0%（95%CI：1.0，5.1%），アフリベルセプト群 7.7%（95%CI：4.6，10.7%）であった。
- CNV 領域の総面積の変化：ベースライン時の試験眼の CNV 領域の総面積は，本剤群で 4.7 mm^2，アフリベルセプト群で 4.5 mm^2 であった。48 週時点の試験眼の CNV 領域の総面積の変化量は，本剤群で 0.0 mm^2，アフリベルセプト群で 0.4 mm^2 であった。
- 漏出領域の総面積の変化：ベースライン時の試験眼の漏出領域の総面積は，本剤群で 7.0 mm^2，アフリベルセプト群で 7.0 mm^2 であった。48 週時点の試験眼の漏出領域の総面積の変化量は本剤群で−3.8 mm^2，アフリベルセプト群で−3.0 mm^2 であった。

2.7.6.1.5.5 薬物動態

- 房水中ファリシマブ濃度及び血漿中ファリシマブ濃度は高い患者間変動を示した。
- 直近の本剤投与から 4 週後における平均房水中ファリシマブ濃度（SD）は，16 週時で 23.0（16.8）μg/mL，24 週時で 8.05（8.73）μg/mL であった。直近の本剤投与から 8 週後における平均房水中ファリシマブ濃度（SD）は，20 週時で 2.04（2.30）μg/mL，28 週時で 0.871（0.955）μg/mL であった。本剤 4 回目投与 12 週後における平均房水中ファリシマブ濃度（SD）は，24 週時で 1.14（4.49）μg/mL であった。本剤 4 回目投与 16 週後における平均房水中ファリシマブ濃度（SD）は，28 週時で 0.0464（0.0497）μg/mL であった。房水中ファリシマブ濃度について，本剤 4 回目投与 12 週後（24 週時）及び 16 週後（28 週時）には 13.8%及び 27.8%のサンプルが BLQ となった。
- 直近の本剤投与から 4 週後における平均血漿中ファリシマブ濃度（SD）は，4 週時で 0.0288（0.0194）μg/mL，16 週時で 0.0340（0.0265）μg/mL，48 週時で 0.0223（0.0184）μg/mL であった。直近の本剤投与から 8 週後における平均血漿中ファリシマブ濃度（SD）は，20 週時で 0.0044（0.0062）μg/mL，48 週時で 0.0032（0.0033）μg/mL であった。血漿中ファリシマブ濃度について，直近の本剤投与から 8 週後（20 週時及び 48 週時）には 28.7%及び 32.3%のサンプルが BLQ となった。

2.7.6.1.5.6 薬力学

- 房水中遊離 Ang-2 濃度及び房水中遊離 VEGF 濃度は高い患者間変動を示した。

- ベースラインにおける平均房水中遊離 Ang-2 濃度（SD）は 7.17（9.62）pg/mL であった。また，ベースラインにおいて 39.5%のサンプルが BLQ であり，投与後は最大 91.7%（16 週時）が BLQ となった。本剤初回投与 7 日後の平均房水中遊離 Ang-2 濃度（SD）は 3.71（4.92）pg/mL と急激な抑制がみられ，少なくとも疾患活動性を評価する 20 週時まで持続した。また，投与からの期間が長くなるにつれて，BLQ となる割合は減少した。しかし，最長の投与間隔である投与直近の本剤投与から 16 週後においてもベースラインと比較して BLQ となるサンプルの割合は高かった。
- ベースラインにおける平均房水中遊離 VEGF 濃度（SD）は 47.9（25.5）pg/mL であった。本剤初回投与 7 日後から房水中遊離 VEGF 濃度の急激な抑制（平均 VEGF 濃度 2.83 pg/mL）がみられ，少なくとも疾患活動性を評価する 20 週時まで持続した。また，投与からの期間が長くなるにつれて房水中遊離 VEGF 濃度は増加した。
- 本剤群において，血漿中遊離 Ang-2 濃度及び遊離 VEGF 濃度のベースラインからの変化がみられなかった。

2.7.6.1.5.7 免疫原性

- 本剤群において，322 例中 10 例（3.1%）の患者がベースラインから ADA 陽性と判定された。本剤投与後，328 例中 29 例（8.8%）の患者が Treatment induced ADA 又は Treatment boosted ADA と判定された。また，328 例中 28 例（8.5%）が Treatment induced ADA であり，328 例中 1 例（0.3%）が Treatment boosted AD であった。
- ADA による薬物動態への明らかな影響はみられなかった。

2.7.6.1.5.8 安全性

有害事象の概況を表 2.7.6.1.5.8-1に示し，有害事象の集計を試験眼，非試験眼，眼以外についてそれぞれ表 2.7.6.2-12～表 2.7.6.2-14に示した。副作用の集計を試験眼，非試験眼，眼以外についてそれぞれ表 2.7.6.2-15～表 2.7.6.2-17に示した。

本剤の安全性プロファイルはアフリベルセプトと同様であることが示唆された。投与中止に至った有害事象の発現頻度が低く，本剤の忍容性は概して良好であった。有害事象は全般的にコントロール可能であり，想定されない新たな安全性のシグナルは確認されなかった。

48週時までの結果を以下に記載する（2.7.4.1.1.4.1）。

- 有害事象の発現頻度は本剤群及びアフリベルセプト群でそれぞれ 71.5%（238/333 例）及び 69.9%（235/336 例）であり，投与群間で同様であった。
- 試験眼に発現した有害事象の発現頻度は本剤群及びアフリベルセプト群でそれぞれ 36.3%及び 38.1%であり，同様であった。
- 試験眼に発現したいずれかの群で 2%以上の発現頻度の有害事象は，結膜出血，新生血管加齢黄斑変性（医師記載事象名：nAMD の悪化），ドライアイ，硝子体剥離，硝子体浮遊物，眼痛，白内障，眼圧上昇，網膜色素上皮裂孔及び乾性加齢黄斑変性（萎縮型加齢黄斑変性）であった（表 2.7.6.2-12）。硝子体浮遊物（本剤群及びアフリベルセプト群でそれぞれ 3.9%及び 2.1%）の重症度はすべて軽度であり，すべて非重篤であった。網膜色素上皮裂孔（本剤群及びアフリベルセプト群でそれぞれ 2.7%及び 1.8%）の重症度は軽度又は中等度であった。
- 試験眼に発現した副作用の発現頻度は本剤群及びアフリベルセプト群のいずれの群においても 2.7%であった。
- 試験眼においていずれの群においても発現頻度が 2%以上の副作用はなかった（表 2.7.6.2-15）。
- 試験眼に発現した重症度が高度の有害事象の発現頻度は本剤群及びアフリベルセプト群でそれぞれ 1.8%（6 例；白内障，点状角膜炎，核性白内障，ぶどう膜炎，星状硝子体症，処置による疼痛及びウイルス性ぶどう膜炎各 1 例），2.4%［8 例；新生血管加齢黄斑変性（医師

記載事象名：nAMD の悪化）3 例，眼痛，網膜下線維症，複視，硝子体網膜牽引症候群及び眼瞼乳頭腫各 1 例］であり，同様であった。これらの内，副作用は，本剤群のぶどう膜炎及び星状硝子体症各 1 例であった。

- 試験眼に発現した重篤な有害事象の発現頻度は本剤群及びアフリベルセプト群でそれぞれ 1.2%（4 例）及び 1.8%（6 例）であり，低かった。いずれかの群で 2 例以上認められた試験眼における重篤な有害事象は新生血管加齢黄斑変性（医師記載事象名：nAMD の悪化，本剤群及びアフリベルセプト群でそれぞれ 1 例及び 3 例）及び網膜色素上皮裂孔（本剤群で 2 例）であった。
- 試験眼に発現した重篤な副作用はアフリベルセプト群で認められず，本剤群の 3 例（0.9%）に 3 件認められた。その内訳は，網膜色素上皮裂孔（2 例，0.6%）及びぶどう膜炎（1 例，0.3%）であった。
- 試験眼に発現した投与中止に至った有害事象の発現頻度は本剤群で 0.3%（1 例，新生血管加齢黄斑変性）であり，アフリベルセプト群で認められず，低かった。新生血管加齢黄斑変性と治験薬との因果関係は否定された。
- 治験中止に至った有害事象の発現頻度は本剤群及びアフリベルセプト群でいずれも 0.9%（3 例）及び 1.2%（4 例）であり，低かった。試験眼に発現した治験中止に至った有害事象は，いずれの群にも認められなかった。
- 試験眼に発現した特に注目すべき有害事象（AESI）の発現頻度は本剤群及びアフリベルセプト群でそれぞれ 0.9%（3 例）及び 1.8%（6 例）であった。新生血管加齢黄斑変性（医師記載事象名：nAMD の悪化）以外の事象の発現例数はいずれかの群で 1 例であった。試験眼に発現した治験薬との因果関係が否定されなかった AESI は 2 件（網膜色素上皮裂孔及びぶどう膜炎）であり，両事象は 1 時間を超える 30 文字以上の視力低下に至った AESI であった。
- 眼内炎はいずれの群にも認められなかった。
- 試験眼に発現した眼内炎症の発現頻度は本剤群及びアフリベルセプト群でそれぞれ 1.5%（5 例）及び 0.6%（2 例）であり，低かった。網膜血管炎又は網膜血管閉塞事象に関連する眼内炎は認められなかった。30 文字以上の視力低下を伴う眼内炎症（ぶどう膜炎）が本剤群の 1 例に認められた。
- 眼以外に発現した有害事象の発現頻度は本剤群及びアフリベルセプト群でそれぞれ 52.3%及び 51.8%であり，投与群間で同様であった。
- いずれかの群で発現頻度 5%以上の眼以外の有害事象（本剤群及びアフリベルセプト群）は，上咽頭炎（5.4%及び 8.3%），尿路感染（5.1%及び 3.0%）であり，本剤とアフリベルセプトでリスクの違いは認められなかった（表 2.7.6.2-14）。
- 眼以外に発現した重症度が高度の有害事象の発現頻度は，本剤群及びアフリベルセプト群で，それぞれ 5.1%及び 8.3%であった。これらの内，副作用は認められなかった。
- 眼以外に発現した重篤な有害事象の発現頻度は本剤群及びアフリベルセプト群でそれぞれ 9.0%及び 10.1%であり，投与群間で同様であった。
- 死亡に至った有害事象は 6 例で認められ，本剤群及びアフリベルセプト群でそれぞれ 1.5%（5 例）及び 0.3%（1 例）であり，いずれも治験薬投与との関連は否定された。
- 外部判定による APTC 事象の発現頻度はいずれの群においても 0.9%（3 例）であり，低かった。
- 臨床検査項目及びバイタルサインにおいて，投与群間で臨床的に重要な不均衡は認められなかった。
- ADA の発現頻度は全体として低かった。本剤の投与を受けた患者の内，本剤投与後に抗体が検出された（Treatment emergent ADA）患者は 8.8%（29/328 例）であり，この内，28 例は本剤投与後に陽性に転じた（Treatment induced ADA）。ADA 陽性例の数が少なかったため評価に限界があるものの，ADA の安全性及び有効性に対する影響は認められなかった。

表 2.7.6.1.5.8-1 有害事象の概況（GR40306試験）

Protocol: GR40306
Clinical Cutoff Date: 26OCT2020

	Faricimab 6 mg (N=333)	Aflibercept 2 mg (N=336)
Total number of patients with at least one AE	238 (71.5%)	235 (69.9%)
Total number of AEs	858	812
Total number of patients with at least one SAE	34 (10.2%)	44 (13.1%)
Total number of SAEs	47	67
Total number of deaths	5 (1.5%)	1 (0.3%)
Total number of patients withdrawn from study due to an AE	3 (0.9%)	4 (1.2%)
Total number of patients withdrawn from study treatment due to an AE	3 (0.9%)	3 (0.9%)
Total number of patients with at least one AESI	3 (0.9%)	12 (3.6%)
Ocular events: study eye total number of patients with at least one		
AE	121 (36.3%)	128 (38.1%)
SAE	4 (1.2%)	6 (1.8%)
AE leading to withdrawal from study treatment	1 (0.3%)	0
Treatment related AEs	9 (2.7%)	9 (2.7%)
Treatment related SAEs	3 (0.9%)	0
AE of Special Interest	3 (0.9%)	6 (1.8%)
Drop in VA score >=30	3 (0.9%)	4 (1.2%)
Associated with severe IOI	0	1 (0.3%)
Intervention req. to prevent permanent vision loss	0	1 (0.3%)
Suspected transmission of infectious agent by study drug	0	0
Ocular events: fellow eye total number of patients with at least one		
AE	76 (22.8%)	81 (24.1%)
SAE	0	5 (1.5%)
AE of Special Interest	0	5 (1.5%)
Drop in VA score >=30	0	3 (0.9%)
Associated with severe IOI	0	0
Intervention req. to prevent permanent vision loss	0	2 (0.6%)
Suspected transmission of infectious agent by study drug	0	0
Non-ocular events total number of patients with at least one		
AE	174 (52.3%)	174 (51.8%)
SAE	30 (9.0%)	34 (10.1%)
AE leading to withdrawal from study treatment	2 (0.6%)	3 (0.9%)
AE of Special Interest	0	1 (0.3%)
Elevated ALT or AST with either elevated bilirubin or clinical jaundice	0	0
Adjudicated APTC events	3 (0.9%)	3 (0.9%)
Non-fatal MI	1 (0.3%)	1 (0.3%)
Non-fatal Stroke	0	1 (0.3%)
Death	2 (0.6%)	1 (0.3%)

表 2.7.6.1.5.8-1 有害事象の概況（GR40306試験）（続）

AE=Adverse Event; SAE=Serious Adverse Event; AESI=Adverse Event of Special Interest; APTC=Antiplatelet Trialists' Collaboration. IOI=Intraocular Inflammation; SAE=Serious Adverse Event; VA=Visual Acuity.
APTC events are defined as non-fatal strokes or non-fatal myocardial infarctions or vascular deaths (including deaths of unknown cause).
Investigator text for AEs encoded using MedDRA version 23.1.
Drop in VA score >=30 is defined as causing a decrease of >=30 VA score (compared with the last of VA prior to the most recent assessment) lasting more than 1 hour.
Cases of potential drug-induced liver injury that include an elevated ALT or AST with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law.
Intervention req. to prevent permanent vision loss is defined as required surgical or medical intervention to prevent permanent loss of sight.
Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for the "Total number of AEs" row in which multiple occurrences of the same AE are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).

Program: root/clinical_studies/RO6867461/CDPT7716/share/data_analysis/prod/program/t_ae_oview.sas
Output: root/clinical_studies/RO6867461/CDPT7716/GR40306/data_analysis/CSR_Primary/prod/output/t_ae_oview_W48_SE_26OCT2020_40306.out
28JAN2021 0:31

[5.3.5.1-nAMD-3 Table 21を再掲]

2.7.6.1.5.9 その他の結果（COVID-19の影響）

COVID-19のパンデミックは，試験実施中に患者の安全性を監視・管理することに有意な影響を及ぼさなかった。また，COVID-19に関連する一覧を追加した以外に計画された安全性の解析に変更はなかった。

COVID-19の影響を以下に要約した。

- COVID-19 パンデミックによるデータの整合性に対するリスクを軽減するための対策が行われた。
- リスクを軽減するための対策により，安全性データ及び安全性評価における欠落を最小限に抑えることができた。
- 欠測があったものの，本剤の有効性及び安全性データはいずれも解釈可能であり，本剤のベネフィット・リスクプロファイルを明らかにすることができた。

2.7.6.1.5.10 結論

本試験は事前に設定した主要評価項目を満たし，未治療の nAMD 患者を対象に，BCVA におけるベースラインから40/44/48週時点の変化量平均値について，本剤のアフリベルセプトに対する非劣性が検証された。

48週時の本剤群の投与間隔ごとの患者の割合は，Q16W で45.7%，Q12W で34.0%，Q8W で20.3%であった。本剤の Q16W までの投与間隔での有効性は，解剖学的評価によって支持された。

本剤を投与された患者は，アフリベルセプトを投与された患者と比較して，48週時の NEI VFQ-25スコアの平均変化が同様であることが示された。

本剤はアフリベルセプトと同等の安全性プロファイルを有し，投与中止に至った有害事象の発現頻度が低いことから，全般的に忍容性は良好であった。

新たな安全性シグナルは確認されなかった。

ファリシマブに対する ADA の発現頻度は低かった。ADA の全身曝露量，安全性及び有効性に対する明らかな影響は認められなかった。

2.7.6.1.6　海外第 III 相臨床試験（nAMD 患者：GR40844試験）

（評価資料：5.3.5.1- nAMD-4）

2.7.6.1.6.1　概要表

表 2.7.6.1.6.1-1 概要表（GR40844試験）

治験の標題：nAMD 患者を対象としたファリシマブの有効性及び安全性を検討する第 III 相多施設共同，ランダム化，実薬対照，二重遮蔽比較試験	
施設及び国：日本を含まない20カ国（122施設）	
公表文献（引用文献）：なし	
第1症例の登録日：2019年3月11日 データカットオフ日：2020年10月05日	開発のフェーズ：第 III 相
目　　的： 有効性の主要目的 BCVA に対する本剤6.0 mg の硝子体内投与の有効性をアフリベルセプトと比較し評価する 有効性の副次的目的 • 追加の BCVA アウトカムに対する本剤の有効性を評価する • 治験薬の投与頻度を評価する • 光干渉断層撮影（OCT）を用いた解剖学的評価に対する本剤の有効性を評価する • FFA を用いた解剖学的評価に対する本剤の有効性を評価する 安全性の目的 • 本剤の眼及び眼以外の安全性及び忍容性を評価する 探索的有効性の目的 • National Eye Institute 25-Item Visual Function Questionnaire（NEI VFQ-25）を用いて，患者報告による視力関連機能及び生活の質（QOL）に対する本剤の有効性を評価する • OCT を用いた解剖学的評価に対する本剤の有効性を評価する 薬物動態の目的 • ファリシマブの全身薬物動態の特性を明らかにする 主な薬物動態及び薬力学的目的（探索的） • 房水（任意）及び硝子体（任意）におけるファリシマブの薬物動態の特性を明らかにする • 遊離 VEGF-A 及び遊離 Ang-2 の薬物濃度（曝露量）−反応関係を評価する 免疫原性の目的 ファリシマブに対する免疫応答を評価し，ADA の潜在的効果を評価する	
治 験 方 法： 治療歴のない nAMD 患者を対象に，本剤を最長 Q16W で投与したときの有効性，安全性，持続性，薬物動態を検討することを目的とした，第 III 相多施設共同ランダム化実薬（アフリベルセプト）対照二重遮蔽並行群間比較，112週間の試験。 患者は2つの投与群のいずれかに1:1の割合でランダムに割り付けられた。 • 本剤群：本剤群にランダムに割り付けられた患者に，本剤 6.0 mg を 12 週時まで Q4W で 4 回硝子体内投与した。20 週時に治験実施計画書に規定された疾患活動性の評価後，活動性疾患を有する本剤群の患者にはその来院時に本剤を投与し，Q8W の固定投	

与方法で継続した。24 週時に，治験実施計画書に規定された疾患活動性の 2 回目の評価後に，活動性疾患を有する本剤群の患者（20 週時に活動性疾患を有する患者は除く）にはその来院時に本剤を投与し，Q12W の固定投与方法で継続した。治験実施計画書に規定された基準に従い，20 週時及び 24 週時に活動性疾患を有さなかった本剤群の患者には，本剤の Q16W 固定投与方法で治療を行った。これらの固定投与方法による本剤投与は 60 週時まで継続され，補充療法は許容されなかった。

60週時（本剤群のすべての患者に本剤の投与を予定している場合）以降，108週時までは，本剤群のすべての患者に個別化した投与間隔に従って投与した。

- アフリベルセプト群：患者にアフリベルセプト 2 mg を 8 週時まで Q4W で 3 回硝子体内投与した。その後 108 週までアフリベルセプト 2 mg を Q8W で硝子体内投与した。
- 対象眼は片眼のみとした。投与群間の遮蔽を維持するために，該当する来院時に両投与群の患者にシャム注射を行った。
- ランダム化は，ベースライン時における以下の因子により層別化した
  - BCVA スコア（74 文字以上，73～55 文字，54 文字以下）
  - 低輝度条件下での視力低下（LLD，33 文字以上，33 文字未満）
  - 地域（米国及びカナダ，アジア，その他の地域）

主要解析は，グローバル登録期間の全例が48週時まで試験を完了したか又は48週時以前に試験を中止した時点で実施した。

症　例　数：
目標例数：約640例の患者を登録し，2つの投与群のいずれかに1:1の割合でランダムに割り付ける
登録例数：658例；本剤群に331例，アフリベルセプト群に327例

診断及び主要な組入基準：

50歳以上で，以下の試験眼に関する選択基準を満たす患者

- 未治療の CNV を伴う AMD（nAMD）
- FFA 又は OCT により CNV 活動性に関連する中心窩下成分が確認された，中心窩下 CNV 又は傍中心窩/中心窩外 CNV を認める（ここで CNV の活動とは，網膜下液，subretinal hyper-reflective material，もしくは漏出が確認できることと定義する）
- 以下のすべての特徴を示す CNV 病変（すなわち predominantly classic，minimally classic，又は occult）：FFA による病変全体の大きさが乳頭面積の 9 倍以下，FFA による CNV 病巣の面積が病変全体の大きさの 50%以上，FFA による活動性 CNV，及び OCT で確認された CNV からの滲出
- Day 1 に開始距離 4 m で評価する ETDRS 視力検査において，BCVA が 78～24 文字
- 中間透光体が十分にクリアで瞳孔は十分に散大し，確定診断のための良質な網膜画像の撮影が可能

被験薬，用量及び投与方法：
(1) 被験薬：ファリシマブ製剤
　単回使用バイアル製剤
(2) 用量及び投与方法：
　6.0 mg を最長 Q16W で硝子体内投与

対照薬，用量及び投与方法：
(1) 対照薬：アフリベルセプト
　単回使用バイアル製剤
(2) 用量及び投与方法：
　2 mg を Q8W で硝子体内投与

治 療 期 間：
- スクリーニング：最長 28 日間
- ベースライン：Day 1
- 治験薬投与期間：Day 1 から 108 週時まで
- 観察期間：108 週時から 112 週時

評 価 基 準：
(1) 有効性評価項目
- 主要評価項目

BCVA におけるベースラインから40/44/48週時点の変化量平均値（ETDRS 視力表で測定）

- 副次的評価項目
  - BCVA のベースラインからの変化量の推移
  - 40週時，44週時及び48週時の平均並びに経時的な BCVA がベースラインから0，5，10又は15文字以上改善した患者の割合
  - 40週時，44週時及び48週時の平均並びに経時的な BCVA がベースラインから5，10又は15文字以上悪化を回避した患者の割合
  - 40週時，44週時及び48週時の平均並びに経時的な BCVA がベースラインから15文字以上の改善又は84文字以上の BCVA を達成した患者の割合
  - 40週時，44週時及び48週時の平均並びに経時的に Snellen 視標で20/40以上（ETDRS 視力で69文字以上）を達成した患者の割合
  - 40週時，44週時及び48週時の平均並びに経時的に Snellen 視標で20/200以下（ETDRS 視力で38文字以下）となった患者の割合
  - 48週時，60週時及び112週時の本剤群における Q8W，Q12W 及び Q16W 投与の患者の割合
  - 48週時，60週時及び112週時までの治験薬投与回数
  - 40週時，44週時及び48週時の平均並びに経時的な中心領域網膜厚のベースラインからの変化量
  - 経時的な網膜内液が認められなかった患者の割合の変化
  - 経時的な網膜下液が認められなかった患者の割合の変化
  - 経時的な網膜内液及び網膜下液が認められなかった患者の割合の変化
  - 経時的な網膜色素上皮剥離が認められなかった患者の割合の変化
  - 48週時及び112週時における CNV 領域の総面積のベースラインからの変化量
  - 48週時及び112週時の漏出領域の総面積のベースラインからの変化量

- 特定の探索的評価項目
  - NEI VFQ-25スコアのベースラインからの経時変化

(2) 薬物動態学的評価項目
- 血漿中ファリシマブ濃度推移
- ファリシマブの房水濃度（任意）及び硝子体液中濃度（任意）の経時変化（探索的）

(3) 薬力学的評価項目（探索的）
- ファリシマブの薬物動態と房水（任意），血漿中及び/又は硝子体液中（任意）遊離 Ang-2 及び遊離 VEGF-A 濃度との経時的関係

(4) 免疫原性
- ベースライン時における ADA の有無と比較した試験中の ADA の有無
- ADA の有無と有効性，安全性又は薬物動態のエンドポイントとの関係

(5) 安全性評価項目
- 眼の有害事象の発現頻度及び重症度
- 眼以外の有害事象の発現頻度及び重症度

統 計 手 法：
主要な比較は，ITT 集団におけるアフリベルセプトと比較した本剤の非劣性を検証することであった。非劣性試験は，片側有意水準を0.02485，非劣性マージンを4文字とした。
有効性の主要評価項目について，両群の調整済み平均値の差の両側95.03%CI の下限が−4文字（非劣性マージン）を上回った場合，本剤はアフリベルセプトに対して非劣性であるとみなした。
有効性解析は，特に指定のない限り，ITT 集団に基づいて実施した。主要評価項目については，per-protocol 集団に基づく補足的解析も実施した。ベースラインとは，割付け時又はその直前の測定値と定義した。ベースライン時の評価が欠測していた患者は補完されなかった。
特に記載のない限り，有効性評価の解析には，層別因子として投与1日目に測定されたベースラインの BCVA ETDRS 文字スコア（74文字以上，73～55文字，54文字以下），LLD（33文字未満，33文字以上）及び地域（米国及びカナダ，アジア，その他の地域）を用いた。IxRS に記録された層別因子を用いた。
主要な比較は，実対照薬（アフリベルセプト）と本剤との比較とした。連続変数の解析には，MMRM を用いた。二値変数の解析には，二項割合に対する層別解析を用いた。推定値及び CI は，各投与群の平均値（連続変数の場合）又は割合（二値変数の場合）並びに2つの投与群間の平均値又は割合の差を算出した。CI はいずれも両側で95.03%レベルであった。
仮説の頑健性及び新型コロナウイルス感染症（COVID-19）パンデミックの影響を評価するために，異なる中間事象の取扱方法を用いた補足的解析を実施した。

この主要な総括報告書では，主要評価項目に用いた最終時点（48週時）に対応する主要解析の結果を示す。本剤群には，20週時及び24週時の疾患活動性評価による来院後に，Q8W，Q12W 又は Q16W の投与方法が60週時まで固定されている患者が含まれる。

2.7.6.1.6.2 患者の内訳

未治療の nAMD 患者計658例を本試験に1:1の割合でランダムに割り付けた。本剤群に331例，アフリベルセプト群に327例割り付けた。48週時前に治験薬の投与を中止した患者は計6.1%（40例）であり，その内訳は本剤群5.4%（18例），アフリベルセプト群6.7%（22例）であった。

2.7.6.1.6.3 患者背景

ITT 集団では，ベースライン時の人口統計学的患者背景は投与群間で同様であった。年齢の平均値（SD）は本剤群では74.8歳（8.4歳），アフリベルセプト群では76.1歳（8.6歳）であり，全患者の56.4%が75歳以上であった。全患者の59.4%が女性で，主に白人（83.3%），その他の地域（米国及びカナダ地域及びアジア地域以外の地域，49.1%），非ヒスパニック系又は非ラテン系（85.3%）であった。

ITT 集団の試験眼のベースライン時 BCVA の平均値（SD）は，本剤群では58.7文字（14.0文字），アフリベルセプト群では58.9文字（13.3文字）であった。ベースライン時 LLD は，本剤群では25.0文字（12.6文字），アフリベルセプト群では25.8文字（13.5文字）であった。ベースライン時の中心領域網膜厚の平均値（SD）は，本剤群では353.1 μm（120.1 μm），アフリベルセプト群では359.0 μm（131.1 μm）であった。患者報告による nAMD 診断時からの期間の平均値（SD）は，本剤群では3.2カ月（14.5カ月），アフリベルセプト群では1.7カ月（4.5カ月）で

あった。

CNV 領域は，中心窩下が60.8%，傍中心窩が23.9%，中心窩外が13.1%であった。CNV は，Occult Type が47.3%，Classic Type が31.5%，Minimally Classic Type が9.3%であった。CNV 領域の面積の平均値は，本剤群で4.7 mm^2，アフリベルセプト群で4.3 mm^2であった。

2.7.6.1.6.4 有効性

ITT 集団（特に断りのない場合を除く）の主要な有効性の結果は以下のとおりであった（2.7.3.2.1.6.3）。

- ITT 集団において，BCVA におけるベースラインから 40/44/48 週時点の変化量平均値で定義された主要評価項目が達成された。最長 Q16W で本剤を投与した患者群（本剤群）では，Q8W でアフリベルセプトを投与した患者群（アフリベルセプト群）に対して，BCVA におけるベースラインから 40/44/48 週時点の変化量平均値の 95%CI（MMRM method）の下限が非劣性マージンである−4 文字より大きいため，非劣性が確認された。BCVA におけるベースラインから 40/44/48 週時点の変化量平均値は，本剤群では 6.6 文字（95%CI：5.3，7.8 文字），アフリベルセプト群では 6.6 文字（95%CI：5.3，7.8 文字）であった。本剤群及びアフリベルセプト群の差は 0.0 文字（95%CI：−1.7，1.8 文字）であった。
- 主要解析の結果は ITT 集団及び per-protocol 集団の間で一貫しており，感度分析及び補足的解析により裏付けられた。

- BCVA のベースラインからの平均変化量の推移：本剤群はアフリベルセプト群と同様であった。
- ベースライン時から 40/44/48 週時までに BCVA が 15 文字以上改善した患者の割合：本剤群では 20.2%（95%CI：15.9，24.6%），アフリベルセプト群では 22.2%（95%CI：17.7，26.8%）であり，本剤群はアフリベルセプト群と同様であった。
- ベースライン時から 40/44/48 週時までに BCVA の 15 文字以上の悪化を回避した患者の割合：本剤群では 95.8%（95%CI：93.6，98.0%），アフリベルセプト群では 97.3%（95%CI：95.5，99.1%）であり，本剤群はアフリベルセプト群と同様であった。
- 40/44/48 週時点で BCVA の 15 文字以上の改善又は Snellen 視標で 20/20 以上（ETDRS 視力で 84 文字以上）を達成した患者の割合：本剤群では 24.5%（95%CI：19.8，29.2%），アフリベルセプト群では 26.2%（95%CI：21.2，31.1%）であり，本剤群はアフリベルセプト群と同様であった。
- 40/44/48 週時点で Snellen 視標で 20/40 以上（ETDRS 視力で 69 文字以上）を達成した患者の割合：本剤群では 55.2%（95%CI：50.1，60.2%），アフリベルセプト群では 49.4%（95%CI：44.4，54.4%）であり，本剤群はアフリベルセプト群と同様であった。
- 40/44/48 週時点で Snellen 視標で 20/200 以下（ETDRS 視力で 38 文字以下）となった患者の割合：本剤群では 7.9%（95%CI：5.0，10.8%），アフリベルセプト群では 7.5%（95%CI：4.7，10.3%）であり，本剤群はアフリベルセプト群と同様であった。
- ベースライン時から 40/44/48 週時までの中心領域網膜厚の変化量：本剤群では−137.1 μm（95%CI：−143.1，−131.2 μm），アフリベルセプト群では−130.8 μm（95%CI：−136.8，−124.8 μm）であり，本剤群ではアフリベルセプト群と比べて，40/44/48 週時点の中心領域網膜厚の同程度の減少が認められた。
- 本剤群における 48 週に到達した患者の 48 週時点の本剤投与間隔ごとの患者の割合：Q8W が 22.2%，Q12W が 32.9%，Q16W が 44.9%であった。
- 48 週時点までの治験薬の平均投与回数：本剤群では 7.0 回（中央値：7.0 回），アフリベルセプト群では 7.9 回（中央値：8.0 回）であった。
- 40 週，44 週，48 週時点で網膜下液，網膜内液，網膜下液及び網膜内液，又は網膜色素上皮剥離が認められなかった患者の割合：網膜下液が認められなかった患者の割合は，40 週時

では本剤群 77.6%（95%CI：72.9，82.3%），アフリベルセプト群 64.3%（95%CI：58.8，69.8%），44 週時では本剤群 65.8%（95%CI：60.5，71.1%），アフリベルセプト群 76.4%（95%CI：71.4，81.5%），48 週時では本剤群 72.5%（95%CI：67.5，77.5%），アフリベルセプト群 62.1%（95%CI：56.5，67.7%）であった。網膜内液が認められなかった患者の割合は，40 週時では本剤群 84.5%（95%CI：80.3，88.7%），アフリベルセプト群 77.5%（95%CI：72.7，82.3%），44 週時では本剤群 78.2%（95%CI：73.4，82.9%），アフリベルセプト群 84.2%（95%CI：79.9，88.5%），48 週時では本剤群 84.1%（95%CI：79.8，88.4%），アフリベルセプト群 77.7%（95%CI：72.8，82.5%）であった。網膜下液及び網膜内液が認められなかった患者の割合は，40 週時では本剤群 65.8%（95%CI：60.3，71.2%），アフリベルセプト群 49.3%（95%CI：43.6，55.1%），44 週時では本剤群 49.3%（95%CI：43.5，55.1%），アフリベルセプト群 64.5%（95%CI：58.8，70.2%），48 週時では本剤群 62.2%（95%CI：56.6，67.8%），アフリベルセプト群 46.1%（95%CI：40.3，52.0%）であった。網膜色素上皮剥離が認められなかった患者の割合は，40 週時では本剤群 6.3%（95%CI：3.5，9.0%），アフリベルセプト群 7.3%（95%CI：4.4，10.3%），44 週時では本剤群 3.9%（95%CI：1.7，6.1%），アフリベルセプト群 8.9%（95%CI：5.6，12.2%），48 週時では本剤群 3.3%（95%CI：1.2，5.3%），アフリベルセプト群 6.5%（95%CI：3.7，9.3%）であった。

- CNV 領域の総面積の変化：ベースライン時の試験眼の CNV 領域の総面積は，本剤群で 4.7 mm^2，アフリベルセプト群で 4.3 mm^2 であった。48 週時点の試験眼の CNV 領域の総面積の変化量は，本剤群で 0.3 mm^2，アフリベルセプト群で 1.1 mm^2 であった。
- 漏出領域の総面積の変化：ベースライン時の試験眼の漏出領域の総面積は，本剤群で 7.2 mm^2，アフリベルセプト群で 6.4 mm^2 であった。48 週時点の試験眼の漏出領域の総面積の変化量は本剤群で−3.3 mm^2，アフリベルセプト群で−2.1 mm^2 であった。

2.7.6.1.6.5 薬物動態

- 房水中ファリシマブ濃度及び血漿中ファリシマブ濃度は高い患者間変動を示した。
- 直近の本剤投与から 4 週後における平均房水中ファリシマブ濃度（SD）は，16 週時で 19.3（21.6）μg/mL，24 週時で 12.5（7.98）μg/mL であった。直近の本剤投与から 8 週後における平均房水中ファリシマブ濃度（SD）は，20 週時で 1.84（4.21）μg/mL，28 週時で 1.63（1.44）μg/mL であった。本剤 4 回目投与 12 週後における平均房水中ファリシマブ濃度（SD）は，24 週時で 1.28（3.14）μg/mL であった。本剤 4 回目投与 16 週後における平均房水中ファリシマブ濃度（SD）は，28 週時で 0.359（0.790）μg/mL であった。房水中ファリシマブ濃度について，本剤 4 回目投与 12 週後（24 週時）及び 16 週後（28 週時）には 20.0%及び 58.3%のサンプルが BLQ となった。
- 直近の本剤投与から 4 週後における平均血漿中ファリシマブ濃度（SD）は，4 週時で 0.0287（0.0209）μg/mL，16 週時で 0.0337（0.0250）μg/mL，48 週時で 0.0246（0.0187）μg/mL であった。直近の本剤投与から 8 週後における平均血漿中ファリシマブ濃度（SD）は，20 週時で 0.0046（0.0052）μg/mL，48 週時で 0.0049（0.0061）μg/mL であった。血漿中ファリシマブ濃度について，直近の本剤投与から 8 週後（20 週時及び 48 週時）には 26.0%及び 27.2%のサンプルが BLQ となった。

2.7.6.1.6.6 薬力学

- 房水中遊離 Ang-2 濃度及び房水中遊離 VEGF 濃度は高い患者間変動を示した。
- ベースラインにおける平均房水中遊離 Ang-2 濃度（SD）は 5.90（4.13）pg/mL であった。本剤初回投与 7 日後の平均房水中遊離 Ang-2 濃度（SD）は 2.51（1.66）pg/mL と急激な抑制がみられ，少なくとも疾患活動性を評価する 20 週時まで持続した。また，投与からの期間が長くなるにつれて，BLQ となる割合は減少した。しかし，最長の投与間隔である直近の本

剤投与から投与 16 週後においてもベースラインと比較して BLQ となるサンプルの割合は高かった。

- ベースラインにおける平均房水中遊離 VEGF 濃度（SD）は 49.0（20.5）pg/mL であった。本剤初回投与 7 日後の平均房水中遊離 VEGF 濃度（SD）は 1.71（0.93）pg/mL と急激な抑制がみられ，少なくとも疾患活動性を評価する 20 週時まで持続した。また，投与からの期間が長くなるにつれて房水中遊離 VEGF 濃度は増加した。
- 本剤群において，血漿中遊離 Ang-2 濃度及び遊離 VEGF 濃度のベースラインからの変化はみられなかった。

2.7.6.1.6.7 免疫原性

- 本剤群において，318 例中 2 例（0.6%）の患者がベースラインから ADA 陽性と判定された。329 例中 39 例（11.9%）の患者が投与後に Treatment induced ADA と判定された。
- ADA による薬物動態への明らかな影響はみられなかった。

2.7.6.1.6.8 安全性

有害事象の概況を表 2.7.6.1.6.8-1に示し，有害事象の集計を試験眼，非試験眼，眼以外についてそれぞれ表 2.7.6.2-18～表 2.7.6.2-20に示した。試験眼の副作用の集計を表 2.7.6.2-21に示した。

本剤の安全性プロファイルはアフリベルセプトと同様であることが示唆された。治験薬の投与中止に至った有害事象の発現頻度が低く，本剤の忍容性は概して良好であった。有害事象は全般的にコントロール可能であり，想定されない新たな安全性のシグナルは確認されなかった。

48週時までの結果を以下に記載する（2.7.4.1.1.4.2）。

- 有害事象の発現頻度は本剤群及びアフリベルセプト群でそれぞれ 70.4%（233/331 例）及び 76.1%（248/326 例）であり，投与群間で同様であった。
- 試験眼に発現した有害事象の発現頻度は本剤群及びアフリベルセプト群でそれぞれ 40.2%及び 36.2%であり，同様であった。
- 試験眼に発現したいずれかの群で 2%以上の発現頻度の有害事象は，結膜出血，新生血管加齢黄斑変性（医師記載事象名：nAMD の悪化），硝子体剥離，眼痛，白内障，眼圧上昇，ドライアイ，網膜色素上皮裂孔，眼の異物感，点状角膜炎及び硝子体浮遊物であった（表 2.7.6.2-18）。硝子体浮遊物（本剤群及びアフリベルセプト群でそれぞれ 2.1%及び 1.2%）の重症度はいずれも軽度であり，すべて非重篤であった。
- 試験眼に発現した副作用の発現頻度は本剤群及びアフリベルセプト群でそれぞれ 3.0%及び 2.5%であり，同様であった。
- いずれかの群の 2%以上で試験眼に発現した副作用はなかった（表 2.7.6.2-21）。
- 試験眼に発現した重症度が高度の有害事象の発現頻度は本剤群及びアフリベルセプト群でそれぞれ 2.1%［7 例；網膜色素上皮裂孔及び眼圧上昇各 2 例，新生血管加齢黄斑変性（医師記載事象名：nAMD の悪化），眼痛，ぶどう膜炎，脈絡網膜炎及び網膜下線維症各 1 例］及び 0.9%（3 例；ぶどう膜炎，皮質白内障及び眼圧上昇各 1 例）であり，同様であった。これらの内，副作用は，本剤群のぶどう膜炎及び網膜色素上皮裂孔各 1 例，アフリベルセプト群のぶどう膜炎 1 例であった。
- 試験眼に発現した重篤な有害事象の発現頻度は本剤群及びアフリベルセプト群でいずれも 2.1%（7 例）であり，低かった。本剤群又はアフリベルセプト群で 2 例以上に認められた試験眼における重篤な有害事象は網膜色素上皮裂孔及び硝子体炎（いずれも本剤群に 2 例）であった。
- 試験眼に発現した重篤な副作用の発現頻度は本剤群及びアフリベルセプト群でそれぞれ 1.5%（5 例）及び 0.3%（1 例）であった。その内訳は，網膜色素上皮裂孔，硝子体炎（いず

れも本剤群 0.6%，2 例）及びぶどう膜炎（本剤群及びアフリベルセプト群でいずれも 0.3%，1 例）であった。

- 眼に発現した治験薬の投与中止に至った有害事象の発現頻度は本剤群及びアフリベルセプト群でそれぞれ 1.5%（5 例）及び 0.3%（1 例）であり，低かった。その内訳は，本剤群ではぶどう膜炎，虹彩毛様体炎，網膜色素上皮裂孔，硝子体剥離及び硝子体炎（各 0.3%，1 例），アフリベルセプト群ではぶどう膜炎（0.3%，1 例）であった。これらの内，副作用は，本剤群ではぶどう膜炎，虹彩毛様体炎，網膜色素上皮裂孔及び硝子体炎（各 0.3%，1 例），アフリベルセプト群ではぶどう膜炎（0.3%，1 例）であった。
- 治験中止に至った有害事象の発現頻度は本剤群及びアフリベルセプト群でそれぞれ 1.5%（5 例）及び 1.8%（6 例）であり，低かった。眼に発現した治験中止に至った有害事象はいずれの群にも認められなかった。
- 試験眼に発現した AESI の発現頻度は本剤群及びアフリベルセプト群でそれぞれ 1.5%（5 例）及び 1.8%（6 例）であり，低かった。いずれかの群の 2 例以上に認められた試験眼に発現した AESI は認められなかった。試験眼における治験薬との因果関係が否定されなかった AESI は本剤群で 2 件（硝子体炎及び網膜色素上皮裂孔）であり，両事象は 1 時間を超える 30 文字以上の視力低下に至った AESI であった。
- 眼内炎はアフリベルセプト群で 1 例認められた。報告によると，硝子体グラム染色は白血球陽性であり，細菌及び硝子体培養はいずれの増殖に対しても陰性であった。同事象は治療（硝子体穿刺後，シプロフロキサシン及びデキサメサゾンの注射）により回復した。
- 試験眼に発現した眼内炎症の発現頻度は本剤群及びアフリベルセプト群でそれぞれ 2.4%（8 例）及び 1.8%（6 例）であり，低かった。網膜血管炎又は網膜血管閉塞事象を伴う眼内炎症は認められなかった。15 文字以上の視力低下を伴う眼内炎症である脈絡網膜炎（ウイルス性；帯状水痘病原体）が本剤群の 1 例に認められた。
- 眼以外に発現した有害事象の発現頻度は本剤群及びアフリベルセプト群でそれぞれ 52.0%及び 58.0%であり，投与群間で同様であった。
- いずれかの群の 5%以上で眼以外に発現した有害事象（本剤群及びアフリベルセプト群別）は，上咽頭炎（7.3%及び 4.9%）であった（表 2.7.6.2-20）。
- 眼以外に発現した重症度が高度の有害事象の発現頻度は，本剤群及びアフリベルセプト群で，それぞれ 6.0%及び 11.7%であった。これらの内，副作用は本剤群の 2 例（心不全及び血栓性脳梗塞）に認められた。
- 眼以外に発現した重篤な有害事象の発現頻度は本剤群及びアフリベルセプト群でそれぞれ 11.5%及び 14.7%であり，投与群間で同様であった。
- 死亡は 11 例で認められ，本剤群及びアフリベルセプト群でそれぞれ 1.2%（4 例）及び 2.1%（7 例）であり，いずれも治験薬投与との関連は否定された。
- APTC で定義された動脈血栓塞栓事象の発現頻度は本剤群及びアフリベルセプト群でそれぞれ 1.2%（4 例）及び 0.9%（3 例）であり，低かった。
- 臨床検査項目及びバイタルサインにおいて，投与群間で臨床的に重要な不均衡は認められなかった。
- ADA 陽性の発現頻度は全体として低かった。本剤の投与を受け，投与後の評価が可能であった患者の内，本剤投与後に抗体が検出された（Treatment emergent ADA）患者は 11.9%（39/329 例）であり，全例が本剤投与後に陽性に転じた（Treatment emergent ADA）患者であった。ADA 陽性例の数が少なかったため評価に限界があるものの，ADA の安全性及び有効性に対する影響は認められなかった。

表 2.7.6.1.6.8-1 有害事象の概況（GR40844試験）

Protocol: GR40844
Clinical Cutoff Date: 05OCT2020

	Faricimab 6 mg (N=331)	Aflibercept 2 mg (N=326)
Total number of patients with at least one AE	233 (70.4%)	248 (76.1%)
Total number of AEs	812	846
Total number of patients with at least one SAE	49 (14.8%)	57 (17.5%)
Total number of SAEs	68	122
Total number of deaths	4 (1.2%)	7 (2.1%)
Total number of patients withdrawn from study due to an AE	5 (1.5%)	6 (1.8%)
Total number of patients withdrawn from study treatment due to an AE	8 (2.4%)	1 (0.3%)
Total number of patients with at least one AESI	11 (3.3%)	8 (2.5%)
Ocular events: study eye total number of patients with at least one		
AE	133 (40.2%)	118 (36.2%)
SAE	7 (2.1%)	7 (2.1%)
AE leading to withdrawal from study treatment	5 (1.5%)	1 (0.3%)
Treatment related AEs	10 (3.0%)	8 (2.5%)
Treatment related SAEs	5 (1.5%)	1 (0.3%)
AE of Special Interest	5 (1.5%)	6 (1.8%)
Drop in VA score >=30	4 (1.2%)	5 (1.5%)
Associated with severe IOI	1 (0.3%)	1 (0.3%)
Intervention req. to prevent permanent vision loss	0	0
Suspected transmission of infectious agent by study drug	0	0
Ocular events: fellow eye total number of patients with at least one		
AE	93 (28.1%)	81 (24.8%)
SAE	7 (2.1%)	2 (0.6%)
AE of Special Interest	6 (1.8%)	2 (0.6%)
Drop in VA score >=30	5 (1.5%)	1 (0.3%)
Associated with severe IOI	0	0
Intervention req. to prevent permanent vision loss	1 (0.3%)	1 (0.3%)
Suspected transmission of infectious agent by study drug	0	0
Non-ocular events total number of patients with at least one		
AE	172 (52.0%)	189 (58.0%)
SAE	38 (11.5%)	48 (14.7%)
AE leading to withdrawal from study treatment	3 (0.9%)	0
AE of Special Interest	0	0
Elevated ALT or AST with either elevated bilirubin or clinical jaundice	0	0
Adjudicated APTC events	4 (1.2%)	3 (0.9%)
Non-fatal MI	2 (0.6%)	1 (0.3%)
Non-fatal Stroke	2 (0.6%)	0
Death	0	2 (0.6%)

表 2.7.6.1.6.8-1 有害事象の概況（GR40844試験）（続）

AE=Adverse Event; SAE=Serious Adverse Event; AESI=Adverse Event of Special Interest; APTC=Antiplatelet Trialists' Collaboration. IOI=Intraocular Inflammation; SAE=Serious Adverse Event; VA=Visual Acuity.
APTC events are defined as non-fatal strokes or non-fatal myocardial infarctions or vascular deaths (including deaths of unknown cause).
Investigator text for AEs encoded using MedDRA version 23.1.
Drop in VA score >=30 is defined as causing a decrease of >=30 VA score (compared with the last of VA prior to the most recent assessment) lasting more than 1 hour.
Cases of potential drug-induced liver injury that include an elevated ALT or AST with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law.
Intervention req. to prevent permanent vision loss is defined as required surgical or medical intervention to prevent permanent loss of sight.
Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for the "Total number of AEs" row in which multiple occurrences of the same AE are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).

Program: root/clinical_studies/RO6867461/CDPT7716/share/data_analysis/prod/program/t_ae_oview.sas
Output: root/clinical_studies/RO6867461/CDPT7716/GR40844/data_analysis/CSR_Primary/prod/output/t_ae_oview_W48_SE_05OCT2020_40844.out
28JAN2021 16:40

[5.3.5.1-nAMD-4 Table 21を再掲]

2.7.6.1.6.9 その他の結果（COVID-19の影響）

COVID-19のパンデミックは，試験実施中に患者の安全性を監視・管理することに有意な影響を及ぼさなかった。また，COVID-19に関連する一覧を追加した以外に計画された安全性の解析に変更はなかった。

COVID-19の影響を以下に要約した。

- COVID-19 パンデミックによるデータの整合性に対するリスクを軽減するための対策が行われた。
- リスクを軽減するための対策により，安全性データ及び安全性評価における欠落を最小限に抑えることができた。
- 欠測があったものの，本剤の有効性及び安全性データはいずれも解釈可能であり，本剤のベネフィット・リスクプロファイルを明らかにすることができた。

2.7.6.1.6.10 結論

本試験は事前に設定した主要評価項目を満たし，未治療の nAMD 患者を対象に，BCVA におけるベースラインから40/44/48週時点の変化量平均値について，本剤のアフリベルセプトに対する非劣性が検証された。

48週時の本剤群の投与間隔ごとの患者の割合は，Q16W で44.9%，Q12W で32.9%，Q8W で22.2%であった。本剤の Q16W までの投与間隔での有効性は，解剖学的評価によって支持された。

本剤を投与された患者は，アフリベルセプトを投与された患者と比較して，48週時の NEI VFQ-25スコアの平均変化が同様であることが示された。

本剤はアフリベルセプトと同等の安全性プロファイルを有し，投与中止に至った有害事象の発現頻度が低いことから，全般的に忍容性は良好であった。

新たな安全性シグナルは確認されなかった。

ファリシマブに対する ADA の発現頻度は低かった。ADA の全身曝露量，安全性及び有効性に対する明らかな影響は認められなかった。

2.7.6.1.7　海外第 II 相臨床試験（DME 患者：BP30099試験）

（評価資料：5.3.5.1-DME-1）

2.7.6.1.7.1　概要表

表 2.7.6.1.7.1-1 概要表（BP30099試験）

<table>
<tr><td colspan="2">治験の標題：DME 患者にファリシマブを硝子体内投与した際の安全性，忍容性，薬物動態及び有効性を検討する多施設共同，複数用法，ランダム化，実薬対照，二重遮蔽，並行群間比較，36週間の試験</td></tr>
<tr><td colspan="2">施設及び国：米国（77施設）</td></tr>
<tr><td colspan="2">公表文献（引用文献）：なし</td></tr>
<tr><td>第1症例の登録日：2016年4月1日
最終症例の最終来院日：2017年12月14日</td><td>開発のフェーズ：第 II 相</td></tr>
<tr><td colspan="2">目　　的：
主要目的
未治療の中心窩を含む糖尿病黄斑浮腫（CI-DME）患者における本剤の有効性を実対照薬と比較し，評価する。

副次的目的
• 本剤硝子体内反復投与の安全性を評価する。
• 本剤の全身薬物動態を評価する。
• 本剤の作用機序に関する情報を提供する薬力学及び解剖学的アウトカムを検討する。
• 血漿中抗ファリシマブ抗体の発現を検討する。
• 本剤の効果の持続時間を探索する。</td></tr>
<tr><td colspan="2">治 験 方 法：
CI-DME 患者を対象とした多施設共同，複数用法，ランダム化，実薬対照，二重遮蔽，3群並行群間比較試験。
患者を3つの投与群のいずれかにランダムに割り付けた。
• A 群：ラニビズマブ 0.3 mg 硝子体内投与
• B 群：本剤 1.5 mg 硝子体内投与
• C 群：本剤 6.0 mg 硝子体内投与</td></tr>
<tr><td colspan="2">症　例　数：
目標例数：210例；未治療患者約150例（各群に1:1:1の比でランダムに割り付ける）及び抗 VEGF 薬による硝子体内治療歴のある患者（抗 VEGF 薬既治療患者）約60例（A 群及び C 群に1:1の比でランダムに割り付ける）
登録例数：229例；
未治療患者　抗 VEGF 薬既治療患者
• A 群：59 例　31 例
• B 群：54 例　1 例
• C 群：55 例　29 例
抗 VEGF 薬既治療患者1例が B 群に誤ってランダムに割り付けられ，有効性解析対象から除外された。</td></tr>
<tr><td colspan="2">診断及び主要な組入基準：
糖尿病（1型又は2型）の病歴があり，試験眼に，DR に伴う黄斑浮腫，主として DME に起因する視力低下，並びにクリアな中間透光体を有する男女の成人患者</td></tr>
</table>

被験薬，用量及び投与方法：
(1) 被験薬：ファリシマブ製剤
本剤60 mg/0.5 mL（120 mg/mL）を充填した2 mL の単回使用バイアル製剤。
(2) 用量及び投与方法：Day 1に硝子体内投与し，その後 Q4W で最大6回硝子体内投与した。

対照薬，用量及び投与方法：
(1) 対照薬：
- プラセボ（ファリシマブ製剤の適切な用量への希釈にのみ使用）
ファリシマブ製剤と同じ賦形剤組成を含むが本剤を含まない溶液1.0 mL を充填した2 mL の単回使用バイアル。
- ラニビズマブ
ラニビズマブ0.3 mg/0.05 mL（6.0 mg/mL）を充填した2 mL の単回使用バイアル製剤。治験依頼者から提供された。

(2) 用量及び投与方法：Day 1に硝子体内投与し，その後 Q4W で最大6回硝子体内投与した。
観察期間中，患者が事前に規定した基準に該当した場合，ラニビズマブ0.3 mg を単回投与し，試験を終了した。

治 療 期 間：
各患者の治験の総期間は最長40週であり，その内訳は以下のとおりであった。
- スクリーニング：最長 4 週間
- ベースライン：Day 1
- 治験薬投与期間：Day 1 から 20 週時まで
- 観察期間：20 週時から 36 週時又はそれ以前
- 安全性フォローアップの電話：観察期間中及びラニビズマブ投与 7 日後

評 価 基 準：
(1) 有効性評価項目
- 主要評価項目
未治療患者における24週時のベースラインからの BCVA（ETDRS 文字数）の平均変化量

- 副次的評価項目
BCVA
  - 24 週時に BCVA がベースライン時と比較して 15 文字以上改善した患者の割合
  - 24 週時における BCVA が 69 文字以上（20/40 以上）の患者の割合
  - 24 週時における BCVA が 84 文字以上（20/20 以上）の患者の割合

SD-OCT による解剖学的アウトカム指標
  - 24 週時における中心窩厚［FCPT，別名，中心領域網膜厚（CRT）］のベースラインからの平均変化量
  - 24 週時における中心領域網膜厚（直径 1 mm）のベースラインからの平均変化量
  - 24 週時における網膜内滲出液，網膜下液が消失した患者の割合

FFA による解剖学的アウトカム指標
  - 24 週時における黄斑部の漏出が消失した患者の割合
  - 24 週時における中心窩無血管域の大きさのベースラインからの変化量

(2) 薬物動態学的評価項目
主要パラメータ：クリアランス及び分布容積
副次的パラメータ：観察された最高濃度，AUC_{inf}，$AUC_{0\text{-}t}$，T_{max} 及び $t_{1/2}$
必要に応じて，硝子体内濃度を評価するためのコンパートメント解析（探索的）
追加で同意が得られた患者における房水サンプル中のファリシマブ濃度及び適宜，ラニビズマブ濃度（探索的）

(3) 薬力学的評価項目
VEGF 及び Ang-2の血漿中濃度の変化量

(4) 安全性評価項目
- BCVA（ETDRS 文字数），細隙灯顕微鏡検査，散瞳下高倍率の双眼倒像鏡検査，眼圧，眼底写真，SD-OCT，血管造影から得られた関連する安全性所見
- 眼の有害事象の発現頻度及び重症度
- 眼以外の有害事象の発現頻度及び重症度
- 血液学的検査，血液化学的検査及び尿検査の結果に基づく臨床検査値異常の発現頻度
- 抗ファリシマブ抗体
- 心電図
- バイタルサイン

統 計 手 法：
有効性の主要解析及び副次的解析には，割り付けられたすべての未治療患者を含め，割り付けられた投与群に従って解析した。抗 VEGF 薬の硝子体内治療歴のある患者は別に解析した。以前の抗 VEGF 薬の硝子体内投与による本剤の効果に影響があるという強いエビデンスがない場合には，有効性の主要評価項目はランダム化された全患者でも解析した。

有効性の主要評価項目は，24週時のベースラインからの試験眼の BCVA 変化量とした。

有効性の主要解析は，線形 MMRM を用いて行った。このモデルには，未治療患者の3群すべてと抗 VEGF 薬既治療患者の2群（ラニビズマブ0.3 mg 及び本剤6 mg）に対して，応答変数として4～24週時からの BCVA の変化量，カテゴリー共変量として，投与群，来院，及び来院と投与群の交互作用，ランダム化層別因子，連続共変量としてベースラインの BCVA を含めた。患者内相関を説明するために，無構造分散共分散構造を用いた。主要な統計学的検定は以下の帰無仮説を検定することであった。

H_0：24週時の BCVA スコアのベースラインからの平均変化量について，未治療患者集団において対照群（A 群）と本剤群（B 群，C 群）との間にいずれも差はない

H_A： B 群又は C 群と A 群との間に差がある

有効性の主要評価項目として，24週時の各本剤投与群（B 群及び C 群）と対照群（A 群）との差のモデルに基づく推定値を，80%CI 及び対応する P 値とともに示した。各投与群の平均及び80%CI，並びに24週時以外の他の時点における本剤投与群（B 群及び C 群）と対照群（A 群）との差の平均及び80%CI も報告した。多重検定に対する第1種の過誤の正式な調整は行わなかった。B 群対 A 群及び C 群対 A 群の検定では，α は片側10%とした。

2.7.6.1.7.2 患者の内訳

未治療患者168例及び抗 VEGF 薬既治療患者61例の計229例が割り付けられた。未治療患者の投与群別の内訳は A 群に59例，B 群に54例及び C 群に55例であり，抗 VEGF 薬既治療患者の内訳は A 群に31例，誤って B 群に1例及び C 群に29例であった。1施設での GCP 違反により2例（いずれも未治療患者で C 群）が解析から除外された。除外されたことにより結果に大きな影響はなかった。

24週時までに治験薬投与を中止した患者は未治療患者の15例（A 群7例，B 群2例及び C 群6例）及び抗 VEGF 薬既治療患者5例（A 群2例，C 群3例）であった（GCP 違反例2例を除く）。GCP 違反例を除いた未治療患者139/166例（83.7%）及び抗 VEGF 薬既治療患者53/61例（86.9%）が試験を完了した。

2.7.6.1.7.3 患者背景

主な患者背景は未治療患者では投与群間で概して均衡が取れていた。未治療患者全体の年齢

の平均値（標準偏差）は61.2歳（8.8）であった。性別では，男性（53.6%）が全体として多かったが，B 群では女性（64.8%）が多かった。白人（78.3%）が最も多く，次いで黒人又はアフリカ系アメリカ人（18.1%）が多かった。

ベースライン時の試験眼の BCVA の平均値（標準偏差）は，未治療患者全体で60.75文字（10.58）であり，A 群［61.24文字（9.87）］及び B 群［60.94文字（11.11）］に比べて C 群［60.00文字（10.95）］でわずかに低かった。中心領域網膜厚の平均値（標準偏差）は A 群［490.88 μm（139.01）］及び C 群［496.47 μm（134.96）］に比べて B 群［535.44 μm（163.13）］で最も厚かった。

抗 VEGF 薬既治療患者の患者背景は概して未治療患者と同様であった。

2.7.6.1.7.4　有効性

本剤6.0 mg を投与した未治療患者では，0.3 mg のラニビズマブを投与した患者と比較して，24週時の BCVA（ETDRS 文字数）のベースラインからの平均変化量が統計学的に有意に改善し，事前に設定した主要評価項目を達成した。

- 未治療患者では，24 週時の BCVA のベースラインからの平均変化量は，C 群の患者では A 群と比較して有意に大きかった（3.57 文字，80%CI：1.53～5.61；P = 0.03）が，B 群の患者では A 群と比較して有意差は認められなかった（表 2.7.6.1.7.4-1）。
- 既治療患者に対する A 群と C 群との間で，24 週時の BCVA のベースラインからの平均変化量に有意差は認められなかった。
- 全患者（未治療患者及び既治療患者）において，24 週時の BCVA のベースラインからの平均変化量は未治療患者よりも小さかったが，C 群の患者では A 群と比較して統計学的に有意な差を維持していた。
- 他の副次的評価項目では，投与群間で有意差は認められなかったが，ほとんどの評価項目は A 群と比較して数値的に本剤の両投与群の方が優れており，主要評価項目の結果を支持していた。
- 探索的有効性評価項目では，仮説検定は実施されなかったものの，概して，ラニビズマブ 0.3 mg よりも，いずれの用量においても本剤を支持する結果であった。

表 2.7.6.1.7.4-1　24週時における BCVA のベースラインからの平均変化量の概要（BP30099試験，全例）

	A 群 ラニビズマブ 0.3 mg N=90	B 群 本剤 1.5 mg N=55	C 群 本剤 6.0 mg N=82
未治療患者	n=49	n=49	n=44
ラニビズマブとの差（80%CI）	−	1.41 (−0.59，3.41)	3.57 (1.53，5.61)
P 値	−	0.37	0.03
抗 VEGF 薬既治療患者	n=28	n=1	n=23
ラニビズマブとの差（80%CI）	−	−	1.33 (−2.29，4.95)
P 値	−	−	0.63
全患者	n=77	n=50	n=67
ラニビズマブとの差（80%CI）	−	2.27 (0.24，4.30)	2.90 (1.07，4.74)
P 値	−	0.15	0.04

BCVA=最高矯正視力，CI = 信頼区間

[5.3.5.1-DME-1 Table 1を改変]

2.7.6.1.7.5　薬物動態

1週時及びトラフ時の平均ファリシマブ血漿中濃度は，既治療患者及び未治療患者を統合し

た本剤1.5 mg と比較して，本剤6.0 mg で約2～4倍高かった。
1週時の平均ファリシマブ房水中濃度は，本剤1.5 mg と比較して，本剤6.0 mg で約3倍高かった。

2.7.6.1.7.6 薬力学

平均血漿中遊離 VEGF レベルは，いずれの投与群でも投与1週後では，ベースライン値及びその後のトラフ時と比較してわずかに低かった。なお，アッセイの定量下限値未満（BLQ）のサンプルが多数（>50%）であったため，データの解釈は限定的であった。
平均血漿中遊離又は総 Ang-2のベースラインからの明らかな変化は，いずれの投与群でも認められなかった。
VEGF は，本剤1.5又は6.0 mg 投与後に，ラニビズマブ0.3 mg 投与後と比較して強く抑制され，本剤1.5又は6.0 mg 投与1週後にほぼ完全に房水中遊離 VEGF が抑制され，トラフ時でもベースライン値の10%（中央値）未満であった。
房水中遊離 Ang-2濃度はいくつかの検体で BLQ（2.24 pg/mL）であり，Ang-2データの解釈は限定的であった。BLQ の割合又は平均値のいずれかによって評価したところ，遊離 Ang-2の大きな抑制がすべての本剤投与群で観察された。投与終了後，遊離 Ang-2濃度は本剤投与群で上昇し，本剤6.0 mg では最終投与6～8週後から上昇が始まったが，観察期間終了時（最終投与12週後）でもベースライン値に達しなかった。ラニビズマブ0.3 mg での4週時以降の遊離 Ang-2濃度は，ベースライン及び1週時と比較して明らかに低かった。

2.7.6.1.7.7 探索的バイオマーカー

血漿中の血管新生及び炎症の探索的バイオマーカーとして，可溶性血管内皮成長因子受容体，可溶性内皮チロシンキナーゼ（sTEK），インターロイキン−6（IL-6），インターロイキン−7（IL-7），インターロイキン−8（IL-8），単球走化性蛋白質1（MCP-1），及び可溶性細胞間接着分子1（sICAM-1）の解析を行った。いずれの投与群でも，解析されたいずれの探索的バイオマーカーにおいてベースラインからの顕著な変化は認められなかった。

2.7.6.1.7.8 安全性

有害事象の概況を表 2.7.6.1.7.8-1に示し，有害事象の集計を試験眼，非試験眼，眼以外についてそれぞれ表 2.7.6.2-22，表 2.7.6.2-23及び表 2.7.6.2-24に示した。副作用の集計を表 2.7.6.2-25に示した。

安全性解析対象集団は，治験を早期に中止したか否かにかかわらず，治験薬を少なくとも1回投与された全例とされ，224例であった。

- 24 週時までに，有害事象は計 68.3%（153 例）に発現し，有害事象の発現頻度は 3 投与群間で概ね同程度であった（表 2.7.6.1.7.8-1）。
- 24 週時までに発現した眼の有害事象の半数以上は試験眼に発現した。試験眼の有害事象の発現頻度は全体で 26.8%（60 例），A 群 24.7%（22 例），B 群 29.1%（16 例），C 群 27.5%（22 例）であり，3 投与群間で概ね同程度であった（表 2.7.6.2-22）。試験眼の副作用は 3 例に 4 件（A 群：硝子体剥離，C 群：水晶体障害，硝子体浮遊物及び白内障）認められた（表 2.7.6.2-25）。試験眼の重篤な有害事象は全体で 2 件，A 群で 1 件，C 群で 1 件認められたが，いずれも治験薬との因果関係なしと判断された（表 2.7.6.1.7.8-1）。
- 24 週時までに発現した非試験眼の有害事象は，全体で 22.8%（51 例），A 群 21.3%（19 例），B 群 25.5%（14 例），C 群 22.5%（18 例）であった（表 2.7.6.2-23）。非試験眼の副作用は認められなかった。非試験眼の重篤な有害事象は全体で 2 件，B 群で 1 件，C 群で 1 件認められた。

- 24 週時までに眼以外の有害事象は全体で 56.7%（127 例），A 群 57.3%（51 例），B 群 54.5%（30 例），C 群 57.5%（46 例）に発現し，発現頻度は 3 投与群間で概ね同程度であった（表 2.7.6.2-24）。眼以外の副作用は 2 例に 2 件（C 群：血沈亢進，血中クレアチンホスホキナーゼ異常）認められた（表 2.7.6.2-25）。眼以外の重篤な有害事象は A 群 9.0%（8 例），B 群 10.9%（6 例），C 群 8.8%（7 例）に認められた。いずれも治験薬との因果関係なしと判断された（表 2.7.6.1.7.8-1）。
- 24 週時までに，投与中止に至った試験眼の有害事象は A 群の 1 例（重篤な有害事象である糖尿病網膜症）に認められた。投与中止に至った非試験眼の有害事象は認められなかった。投与中止に至った眼以外の有害事象は B 群の 1 例（重篤な有害事象である壊疽）に認められた。投与中止に至った有害事象はいずれも治験薬との因果関係なしと判断された。
- 24 週時までに，死亡に至った有害事象は計 2.2%（5 例）に発現し，その内訳は A 群 2 例，B 群 1 例，C 群 2 例であった。いずれも治験薬との因果関係なしと判断された。

24週以降の観察期間中，有害事象が追加報告され，その大半は，眼以外で重篤ではない重症度が軽度の有害事象であり，治験薬との因果関係なしと判断された。

表 2.7.6.1.7.8-1 24週時までの有害事象の概況（BP30099試験，安全性評価対象例）

Overall Adverse Events Profile up to Week 24, Safety-Evaluable Patients
Protocol: BP30099

	0.3 mg Ranibizumab (N=89)	1.5 mg RO6867461 (N=55)	6 mg RO6867461 (N=80)	All Patients (N=224)
Total number of patients with at least one AE	61 (68.5%)	38 (69.1%)	54 (67.5%)	153 (68.3%)
Total number of events	203	120	190	513
Total number of patients withdrawn due to an AE	1 (1.1%)	0	0	1 (0.4%)
Total number of patients with at least one				
Ocular adverse events on the study eye	22 (24.7%)	16 (29.1%)	22 (27.5%)	60 (26.8%)
Serious Ocular AE on study eye	1 (1.1%)	0	1 (1.3%)	2 (0.9%)
Ocular AE on study eye leading to discontinuation	1 (1.1%)	0	0	1 (0.4%)
Systemic adverse events	51 (57.3%)	30 (54.5%)	46 (57.5%)	127 (56.7%)
Serious Systemic AE	8 (9.0%)	6 (10.9%)	7 (8.8%)	21 (9.4%)
Systemic AE leading to discontinuation	0	1 (1.8%)	0	1 (0.4%)
AE with fatal outcome	2 (2.2%)	1 (1.8%)	2 (2.5%)	5 (2.2%)
Serious AE	9 (10.1%)	7 (12.7%)	8 (10.0%)	24 (10.7%)
Related Serious AE	0	0	0	0
Related AE	1 (1.1%)	0	4 (5.0%)	5 (2.2%)
Related Ocular AE on the study eye	1 (1.1%)	0	2 (2.5%)	3 (1.3%)
Related Systemic AE	0	0	2 (2.5%)	2 (0.9%)
Ocular adverse events	30 (33.7%)	21 (38.2%)	32 (40.0%)	83 (37.1%)
Ocular adverse events on the fellow eye	19 (21.3%)	14 (25.5%)	18 (22.5%)	51 (22.8%)

Percentages are based on N.
Multiple occurences of the same Event in one individual counted only once.
Includes only events within 28 days of the Week 20 visit

Program: /opt/BIOSTAT/prod/ct70122a/i30099c/t_ae_prof_w24p.sas
Output: /opt/BIOSTAT/prod/ct70122a/i30099c/reports/t_ae_prof_w24p_SAF.out
10APR2018 11:59
Page 1 of 1

[5.3.5.1-DME-1 t_ae_prof_w24p_SAF を再掲]

2.7.6.1.7.9　結論

第 II 相 BP30099試験では，本剤6.0 mg を投与した未治療患者では，24週時のベースラインからの BCVA（ETDRS 文字数）の平均変化量がラニビズマブ0.3 mg を投与した未治療患者と比較して統計学的に有意に改善したことが示され，事前に設定した主要評価項目を達成した。

既治療患者の24週時の BCVA の平均変化量及びその他の視力の副次的評価項目に対する本剤の有益な効果が，統計学的に有意ではないものの，観察された。

全体として，本剤2群では，ベースラインから24週時までの DR 重症度スコアが2ステップ以上改善した患者の割合が，ラニビズマブ0.3 mg の群と比較して高かった。

本試験で認められた本剤の眼及び眼以外の安全性所見は，抗 VEGF 薬を硝子体内投与された DME 患者で報告された安全性プロファイルと一致しており，新たな安全性シグナルは確認されなかった。ADA 価と薬物動態/薬力学，安全性アウトカムとの間に明らかな関連性は認められなかった。

全体として，本試験では，未治療の CI-DME 患者における本剤の有効性，安全性及び忍容性が示された。

2.7.6.1.8 国際共同第 III 相臨床試験（DME 患者：GR40349試験）

（評価資料：5.3.5.1-DME-2）

2.7.6.1.8.1 概要表

表 2.7.6.1.8.1-1 概要表（GR40349試験）

<table>
<tr><td colspan="2">治験の標題：DME 患者を対象としたファリシマブの有効性及び安全性を検討する第 III 相多施設共同，ランダム化，実薬対照，二重遮蔽比較試験</td></tr>
<tr><td colspan="2">施設及び国：日本を含む16カ国（179施設）</td></tr>
<tr><td colspan="2">公表文献（引用文献）：なし</td></tr>
<tr><td>第1症例の登録日：2018年9月5日
データカットオフ日：2020年10月20日</td><td>開発のフェーズ：第 III 相</td></tr>
<tr><td colspan="2">目　　的：
有効性の主要目的
BCVA に対する本剤6.0 mg の硝子体内投与の有効性を評価する

有効性の重要な副次的目的
• 糖尿病網膜症重症度に対する本剤の有効性を評価する

有効性の副次的目的
• BCVA に関連した追加の評価項目に対する本剤の有効性を評価する
• 糖尿病網膜症に関連した追加の評価項目に対する本剤の有効性を評価する
• Personalized treatment interval（PTI）群における本剤投与間隔を評価する
• SD-OCT による解剖学的評価に対する本剤の有効性を評価する
• NEI VFQ-25 を用いて，患者報告による視力関連機能及び QOL に対する本剤の有効性を評価する

安全性の目的
• 本剤の眼及び眼以外の安全性及び忍容性を評価する

探索的有効性の目的
本剤の有効性を更に評価する
• 追加の糖尿病網膜症評価
• FFA 及び/又は光干渉断層撮影-angiography（OCT−A）を用いた解剖学的評価
• SD-OCT を用いた解剖学的評価
• NEI VFQ-25 を用いた患者報告による視力関連機能及び QOL

薬物動態の目的
• ファリシマブの全身薬物動態の特性を明らかにする

免疫原性の目的
ファリシマブに対する免疫応答を評価し，ADA の潜在的効果を評価する

主な薬物動態及び薬力学的目的（探索的）
• 房水（任意）及び硝子体（任意）におけるファリシマブの薬物動態の特性を明らかにする
• 遊離 VEGF-A 及び遊離 Ang-2 の薬物濃度（曝露量）−反応関係を評価する</td></tr>
</table>

治 験 方 法：

DME 患者を対象としたランダム化二重遮蔽実薬対照3並行群間比較，100週間の試験。

試験では，試験眼に対する抗 VEGF 薬未治療 DME 患者と，試験眼に対する抗 VEGF 薬治療歴があり，最後の投与が Day1の来院（初回治験治療）から3カ月以上前である患者を登録の対象とした。抗 VEGF 薬治療歴がある患者の目標例数は，登録の最低10%，最大25%とした。

治験薬の投与群：

- 本剤 Q8W 群：患者にファリシマブ 6.0 mg を 20 週時まで Q4W で硝子体内投与した後，本剤 6.0 mg を 96 週時まで Q8W で硝子体内投与し，100 週時に最終来院した。
- 本剤 PTI 群：患者には本剤 6.0 mg を 12 週時まで Q4W で硝子体内投与し，続いて本剤 6.0 mg を 96 週時まで最長 Q16W で硝子体内投与し，続いて 100 週時に最終来院した。
- アフリベルセプト Q8W 群：患者にアフリベルセプト 2.0 mg を 16 週時まで Q4W で硝子体内投与した後，アフリベルセプト 2.0 mg を 96 週時まで Q8W で硝子体内投与し，100 週時に最終来院した。
- 割付けは，ベースライン時における以下の因子により層別化した。
  - BCVA ETDRS スコア（64 文字以上，64 文字未満）
  - 抗 VEGF 薬硝子体内治療歴（あり，なし）
  - 地域（米国及びカナダ，アジア，その他の地域）

投与群間の遮蔽を維持するために，該当する来院時に投与群すべての患者にシャム注射を行った。

主要解析は，全例が56週時まで試験を完了したか又は56週時以前に試験を中止した場合に実施した。

症 例 数：

目標例数：約900例の患者を登録し，3つの投与群のいずれかに1:1:1の割合でランダムに割り付ける

登録例数：940例；本剤 Q8W 群に315例，本剤 PTI 群に313例，アフリベルセプト Q8W 群に312例

診断及び主要な組入基準：

糖尿病（1型又は2型）と確定診断された18歳以上の患者。現在，糖尿病の治療にインスリン又は他の注射剤を常用している，及び/又は現在，糖尿病の治療に経口高血糖治療薬を常用している。Day 1来院日前2カ月以内に HbA1c が10%以下であった患者。試験への組み入れに際して，以下の試験眼の選択基準を満たしている。

- スクリーニング時の Spectralis SD-OCT で 325 µm 以上，又は Cirrus SD-OCT 又は Topcon SD-OCT で 315 µm 以上の中心窩を含む黄斑の肥厚
- Day 1 に開始距離 4 m で評価する ETDRS 視力検査において，BCVA が 73～25 文字（Snellen 式では 20/40～20/320 に相当）
- 中間透光体が十分にクリアで瞳孔は十分に散大し，良質な CFP（糖尿病網膜症の重症度判定及び網膜の評価が可能な ETDRS 改変 7 方向又は広角 4 方向）の撮影及び他の画像検査が可能

被験薬，用量及び投与方法：

(1) 被験薬：ファリシマブ製剤
単回使用バイアル製剤

(2) 用量及び投与方法：

本剤 Q8W 群：本剤6.0 mg を20週時まで Q4W で硝子体内投与，以降は96週時まで Q8W で硝子体内投与

本剤 PTI 群：本剤6.0 mg を12週時まで Q4W で硝子体内投与，以降は96週時まで PTI で硝子体内投与。PTI を受けている患者は，患者の参照中心領域網膜厚及び参照 BCVA と比較し

た中心領域網膜厚の相対的変化及び BCVA の絶対変化に基づいて，最長 Q16W 又は最短 Q4W まで4週間単位で，治験薬投与来院時に延長，短縮又は維持された。

対照薬，用量及び投与方法：
(1) 対照薬：アフリベルセプト
単回使用バイアル製剤
(2) 用量及び投与方法：
アフリベルセプト Q8W 群：アフリベルセプト2.0 mg を16週時まで Q4W で硝子体内投与，その後96週時まで Q8W で硝子体内投与。

治 療 期 間：
- スクリーニング：最長 28 日間
- ベースライン：Day 1
- 治験薬投与期間：Day 1 から 96 週時まで
- 観察期間：96 週時から 100 週時

評 価 基 準：
(1) 有効性評価項目
- 主要評価項目

BCVA におけるベースライン値から1年後（48，52，56週時）の各時点の平均変化量の平均値（ETDRS 視力表で開始距離4 m から測定する，以降，BCVA におけるベースラインから48/52/56週時点の変化量平均値）

- 重要な副次的評価項目

ETDRS diabetic retinopathy severity scale（DRSS）において，ベースラインから52週時までに2段階以上の改善が認められた患者の割合

- 副次的評価項目及び探索的評価項目
  - 1年後及び経時的な BCVA がベースラインから0，5，10又は15文字以上改善した患者の割合
  - 1年後及び経時的な BCVA がベースラインから5，10又は15文字以上悪化を回避した患者の割合
  - 1年後の中心領域網膜厚のベースラインからの変化量
  - 1年後及び経時的な DME が認められない（Spectralis SD-OCT で中心領域網膜厚が325 μm 未満）患者の割合
  - 52週時及び経時的な網膜内液が認められなかった患者の割合
  - 52週時及び経時的な網膜下液が認められなかった患者の割合
  - 本剤 PTI 群における52週時の Q4W，Q8W，Q12W 又は Q16W 投与の患者の割合
  - 52週時及び経時的な NEI VFQ-25スコアのベースラインからの変化量
  - 経時的な NEI VFQ-25 Near Activities，Distance Activities，Driving Subscale のベースラインからの変化
  - 経時的な NEI VFQ-25スコアのベースラインからの改善が4ポイント以上であった患者の割合の変化

(2) 薬物動態学的評価項目
- 血漿中ファリシマブ濃度推移
- ファリシマブの房水濃度（任意）及び硝子体液中濃度（任意）の経時変化（探索的）

(3) 薬力学的評価項目（探索的）
- ファリシマブの薬物動態と房水（任意），血漿中及び/又は硝子体液中（任意）遊離

Ang-2 及び遊離 VEGF-A 濃度との経時的関係

(4) 免疫原性
- ベースライン時における ADA の有無と比較した試験中の ADA の有無
- ADA の有無と有効性，安全性又は薬物動態のエンドポイントとの関係

(5) 安全性評価項目
- 眼の有害事象の発現頻度及び重症度
- 眼以外の有害事象の発現頻度及び重症度

統 計 手 法：
有効性解析は，特に明記しない限り，ITT 集団及び未治療の患者集団について行った。主要評価項目及び重要な副次的評価項目については，per-protocol 集団に基づく補足的解析も実施した。ベースラインとは，割付け時又はその直前の測定値と定義した。ベースライン時の評価が欠測していた患者は補完されなかった。

特に記載のない限り，有効性評価の解析は，割付けの層別因子で調整した：ベースライン（Day 1）の BCVA ETDRS 文字スコア（64文字以上，64文字未満），抗 VEGF 薬の硝子体内治療歴（あり，なし），地域（米国及びカナダ，アジア，その他の地域）。IxRS に記録された層別因子を用いた。

主要な比較は，実対照薬（アフリベルセプト Q8W 群）と各本剤群（Q8W 群と PTI 群）との比較とした。連続変数の解析には，MMRM を用いた。二値変数の解析には，二項割合に対する層別解析を用いた。推定値及び CI は，3つの投与群のそれぞれについての平均値（連続変数の場合）又は割合（二値変数の場合）並びに実対照薬（アフリベルセプト Q8W 群）と本剤の各群（Q8W 群及び PTI 群）の平均値又は割合の差を算出した。

仮説の頑健性及び COVID-19パンデミックの影響を評価するために，異なる中間事象の取扱方法を用いて，有効性の主要評価項目及び重要な副次的評価項目の補足的解析を実施した。

この主要な総括報告書は，主要評価項目の最終時点（56週時）に対応する主要解析の結果を示す。以降，48週時，52週時，56週時で平均したエンドポイントを「48/52/56週時」のエンドポイントと呼ぶ。

2.7.6.1.8.2 患者の内訳

本試験に登録された940例の DME 患者を，ベースライン時 BCVA ETDRS スコア，抗 VEGF 薬硝子体内治療歴，及び地域を層別因子として，層別置換ブロック法により1:1:1の比でランダムに，本剤 Q8W 群に315例，本剤 PTI 群に313例及びアフリベルセプト Q8W 群に312例割り付けた。

2.7.6.1.8.3 患者背景

ITT 集団では，ベースライン時の人口統計学的患者背景は投与群間で同様であった。年齢の平均値（SD）は本剤 Q8W 群では61.6歳（9.5歳），本剤 PTI 群では62.8歳（10.0歳），アフリベルセプト Q8W 群では62.2歳（9.6歳）であり，全患者の57.1%が65歳未満であった。全患者の59.8%が男性で，主に白人（78.1%），米国及びカナダ地域（53.5%），非ヒスパニック系又は非ラテン系（86.5%）であった。アジア人の割合は本剤 Q8W 群では315例中31例（9.8%），本剤 PTI 群では313例中26例（8.3%），アフリベルセプト Q8W 群では312例中27例（8.7%），日本人は本剤 Q8W 群の24例，本剤 PTI 群の19例，及びアフリベルセプト Q8W 群の21例であった。

ITT 集団の試験眼のベースライン時 BCVA の平均値（SD）は，本剤 Q8W 群では62.0文字（9.9文字），本剤 PTI 群では61.9文字（10.2文字），アフリベルセプト Q8W 群では62.2文字

（9.5文字）であった。ベースライン時の中心領域網膜厚の平均値（SD）は，本剤 Q8W 群では492.3 μm（135.8 μm），本剤 PTI 群では485.8 μm（130.8 μm），アフリベルセプト Q8W 群では484.5 μm（131.1 μm）であった。患者報告による DME 診断時からの期間の平均値（SD）は，本剤 Q8W 群では14.0カ月（21.7カ月），本剤 PTI 群では17.6カ月（36.2カ月），アフリベルセプト Q8W 群では17.5カ月（27.6カ月）であった。

試験眼の77.1%が過去に抗 VEGF 治療を受けていなかった。過去に抗 VEGF 治療を受けた患者における最後の抗 VEGF 薬投与からの期間の平均値（SD）は，本剤 Q8W 群では20.5カ月（20.5カ月），本剤 PTI 群では17.6カ月（17.2カ月），アフリベルセプト Q8W 群では16.6カ月（12.6カ月）であった。ベースライン時の糖尿病網膜症の特性は概して均衡がとれていた。全体では，中等度から重度の非増殖性糖尿病網膜症（non-proliferative diabetic retinopathy，NPDR）患者（DRSS 43/47/53）は60.6%，軽度の NPDR 患者（DRSS <43）は27.6%，PDR 患者（DRSS >53）は6.4%であった。

ITT 集団の77.1%が治療歴のない患者であったため，DME 診断からの期間に影響が認められた。未治療の患者集団における DME 診断時からの期間の平均値（SD）は9.7カ月（23.4カ月）であったが，中央値は1.6カ月（範囲：0～304カ月）であった。この他の未治療の患者集団におけるベースライン時の眼の疾患特性は ITT 集団と類似していた。

2.7.6.1.8.4 有効性

ITT 集団（特に断りのない場合を除く）の主要な有効性の結果は以下のとおりであった（2.7.3.2.2.7.3）。

- ITT 集団では，BCVA におけるベースラインから 48/52/56 週時点の変化量平均値は，本剤 Q8W 群では 10.7 文字（97.5%CI：9.4，12.0 文字），本剤 PTI 群では 11.6 文字（97.5%CI：10.3，12.9 文字），アフリベルセプト Q8W 群では 10.9 文字（97.5%CI：9.6，12.2 文字）であった。本剤 Q8W 群及び本剤 PTI 群では，アフリベルセプト Q8W 群に対して，BCVA におけるベースラインから 48/52/56 週時点の変化量平均値の差の 97.5%CI の下限が−4 文字より大きいため，非劣性が示された。48/52/56 週時点の変化量平均値における本剤 Q8W 群及び本剤 PTI 群のアフリベルセプト Q8W 群との差は，それぞれ−0.2 文字（97.5%CI：−2.0，1.6 文字）及び 0.7 文字（97.5%CI：−1.1，2.5 文字）であった。
- 未治療の患者集団では，本剤 Q8W 群及び本剤 PTI 群の BCVA におけるベースラインから 48/52/56 週時点の変化量平均値は，アフリベルセプト Q8W 群に対して非劣性が検証され，優越性は示されなかった。48/52/56 週時点の変化量平均値における本剤 Q8W 群及び本剤 PTI 群のアフリベルセプト Q8W 群との差は，それぞれ−0.7 文字（97.5%CI：−2.8，1.4 文字）及び 0.0 文字（97.5%CI：−2.1，2.2 文字）であった。
- 主要評価項目では ITT 集団及び per-protocol 集団の間で一貫しており，感度分析及び補足的解析により裏付けられた。補足的解析の結果は，中間事象に対する処理方法間及び患者集団間で一貫していた。
- ITT 集団では，ETDRS DRSS においてベースライン時から 52 週時までに 2 段階以上の改善が認められた患者の割合は，本剤 Q8W 群とアフリベルセプト Q8W 群では本剤 Q8W 群は 46.0%（97.5%CI：38.8，53.1%），アフリベルセプト Q8W 群は 35.8%（97.5%CI：29.1，42.5%）であり，本剤 PTI 群とアフリベルセプト Q8W 群の間では本剤 PTI 群は 42.5%（97.5%CI：35.5，49.5%），アフリベルセプト Q8W 群は 36.4%（97.5%CI：29.6，43.1%）であった。
- ETDRS DRSS においてベースライン時から 52 週時までに 2 段階以上の改善が認められた患者の割合の差は，本剤 Q8W 群及びアフリベルセプト Q8W 群の間では 10.2%（97.5%CI：0.3，20.0%），本剤 PTI 群及びアフリベルセプト Q8W 群の間では 6.1%（97.5%CI：−3.6，15.8%）であった。これらの結果は ITT 集団及び per-protocol 集団で一貫しており，補足的解析により裏付けられた。

- BCVA のベースラインからの平均変化量の推移：本剤 Q8W 群及び本剤 PTI 群は，アフリベルセプト Q8W 群と同様であった。
- ベースライン時から 48/52/56 週時までに BCVA が 15 文字以上改善した患者の割合：本剤 Q8W 群とアフリベルセプト Q8W 群の間では本剤 Q8W 群は 29.2%（95%CI：23.9，34.5%），アフリベルセプト Q8W 群は 31.8%（95%CI：26.6，37.0%）であり，本剤 PTI 群とアフリベルセプト Q8W 群の間では本剤 PTI 群は 35.5%（95%CI：30.1，40.9%），アフリベルセプト Q8W 群は 32.0%（95%CI：26.7，37.2%）であり，本剤 Q8W 群及び本剤 PTI 群は，アフリベルセプト Q8W 群と同様であった。
- ベースライン時から 48/52/56 週時までに BCVA の 15 文字以上の悪化を回避した患者の割合：本剤 Q8W 群とアフリベルセプト Q8W 群の間では本剤 Q8W 群は 98.1%（95%CI：96.5，99.7%），アフリベルセプト Q8W 群は 98.9%（95%CI：97.6，100.0%）であり，本剤 PTI 群とアフリベルセプト Q8W 群の間では本剤 PTI 群は 98.6%（95%CI：97.2，100.0%），アフリベルセプト Q8W 群は 98.9%（95%CI：97.7，100.0%）であり，本剤 Q8W 群及び本剤 PTI 群は，アフリベルセプト Q8W 群と同様であった。
- ベースライン時から 48/52/56 週時までの中心領域網膜厚の変化量：本剤 Q8W 群では−206.6 μm（95%CI：−214.7，−198.4 μm），本剤 PTI 群では−196.5 μm（95%CI：−204.7，−188.4 μm），アフリベルセプト Q8W 群では−170.3 μm（95%CI：−178.5，−162.2 μm）であり，本剤 Q8W 群及び本剤 PTI 群は，アフリベルセプト Q8W 群と比べて，同程度の減少であった。
- 52 週時の本剤 PTI 群における本剤の硝子体内投与が Q4W，Q8W，Q12W，Q16W であった患者の割合：それぞれ 10.8%，15.4%，21.0%，52.8%であった。なお，本剤 PTI 群における 52 週時の本剤の硝子体内投与が，Q12W 未満に短縮することなく Q12W 以上を達成した患者の割合は 67.8%であった。
- ベースライン時から 52 週時までの NEI VFQ-25 スコアの変化量：本剤 Q8W 群では 7.6（95%CI：6.3，9.0），本剤 PTI 群では 7.9（95%CI：6.6，9.3），アフリベルセプト Q8W 群では 7.8（95%CI：6.4，9.2）であり，本剤 Q8W 群及び本剤 PTI 群は，アフリベルセプト Q8W 群と同様であった。
- 16 週時及び 52 週時に新たに PDR となった患者の割合：16 週時は本剤 Q8W 群では 1.9%（95%CI：0.2，3.6%），本剤 PTI 群では 0.4%（95%CI：0.0，1.1%），アフリベルセプト Q8W 群では 0.0%（95%CI：0.0，0.0%），52 週時は本剤 Q8W 群では 0.9%（95%CI：0.0，2.2%），本剤 PTI 群では 0.9%（95%CI：0.0，2.1%），アフリベルセプト Q8W 群では 0.5%（95%CI：0.0，1.4%）であり，いずれも 3%未満であった。
- 48/52/56 週時に DME が認められなかった患者の割合：DME の消失を中心領域網膜厚が Spectralis の SD-OCT で 325 μm 未満，Cirrus 又は Topcon の SD-OCT で 315 μm 未満と定義した。本剤 Q8W 群では 81.3%（95%CI：76.6，85.9%），本剤 PTI 群では 77.9%（95%CI：73.0，82.8%），アフリベルセプト Q8W 群では 65.1%（95%CI：59.4，70.7%）であり，本剤 Q8W 群及び本剤 PTI 群ではアフリベルセプト Q8W 群と比べて高かった。
- 48 週，52 週，56 週時点で網膜内液及び網膜下液が認められなかった患者の割合：48 週時に網膜内液及び網膜下液が認められなかった患者の割合は，本剤 Q8W 群 45.8%（95%CI：39.7，52.0%），本剤 PTI 群 32.8%（95%CI：27.1，38.5%），アフリベルセプト Q8W 群 21.7%（95%CI：16.7，26.7%），52 週時では本剤 Q8W 群 42.1%（95%CI：36.0，48.2%），本剤 PTI 群 38.5%（95%CI：32.5，44.5%），アフリベルセプト Q8W 群 24.8%（95%CI：19.4，30.2%），56 週時では本剤 Q8W 群 46.6%（95%CI：40.2，53.0%），本剤 PTI 群 42.0%（95%CI：35.8，48.2%），アフリベルセプト Q8W 群 22.9%（95%CI：17.6，28.1%）であった。本剤 Q8W 群及び本剤 PTI 群ではアフリベルセプト Q8W 群と比べて，網膜内液及び網膜下液が認められなかった患者の割合は，48 週時，52 週時，56 週時で一貫して高かった。

- 52 週時の NEI VFQ-25 スコアがベースラインから 4 以上改善した患者の割合は，アフリベルセプト Q8W 群と比べて，本剤 Q8W 群又は本剤 PTI 群で同等であった（本剤 Q8W 群，本剤 PTI 群及びアフリベルセプト Q8W 群でそれぞれ 57.3%，59.4%及び 57.3%）。

2.7.6.1.8.5 薬物動態

- 房水中ファリシマブ濃度は両本剤群ともに試験期間を通じて測定可能であった。また，房水中ファリシマブ濃度及び血漿中ファリシマブ濃度は高い患者間変動を示した。
- 直近の本剤投与から 4 週後における平均房水中ファリシマブ濃度（SD）は，本剤 Q8W 群において 16 週時で 12.2（10.4）μg/mL，20 週時で 18.8（16.1）μg/mL，32 週時で 8.07（7.91）μg/mL であり，本剤 PTI 群において 16 週時で 15.7（12.4）μg/mL，20 週時で 15.7（12.9）μg/mL，32 週時で 16.0（19.5）μg/mL であった。直近の本剤投与から 8 週後における平均房水中ファリシマブ濃度（SD）は，本剤 PTI 群において 20 週時で 2.12（2.49）μg/mL であった。本剤 PTI 群において直近の本剤投与から 12 週後（32 週時）には 33.3%のサンプルが BLQ となった。
- 各投与 4 週後における平均血漿中ファリシマブ濃度（SD）は，本剤 Q8W 群において 4 週時で 0.0193（0.0160）μg/mL であり，本剤 PTI 群において 4 週時で 0.0181（0.0139）μg/mL，52 週時で 0.0176（0.0142）μg/mL であった。各投与 8 週後における平均血漿中ファリシマブ濃度（SD）は，本剤 Q8W 群において 28 週時で 0.0029（0.0039）μg/mL，52 週時で 0.0025（0.0038）μg/mL であり，本剤 PTI 群において 28 週時で 0.0028（0.0037）μg/mL，52 週時で 0.0024（0.0035）μg/mL であった。直近の本剤投与から 8 週後（28 週時及び 52 週時）において，本剤 Q8W 群では 42.0%及び 48.8%,本剤 PTI 群では 33.1%及び 41.1%のサンプルが BLQ となった。

2.7.6.1.8.6 薬力学

- 房水中遊離 Ang-2 濃度及び房水中遊離 VEGF 濃度は高い患者間変動を示した。
- ベースライン時における平均房水中遊離 Ang-2 濃度（SD）は本剤 Q8W 群で 12.6（11.2）pg/mL，本剤 PTI 群で 13.3（12.8）pg/mL であった。また，ベースライン時において本剤 Q8W 投与群で 20.6%，本剤 PTI 群で 18.8%のサンプルが BLQ であり，投与後は最大でそれぞれ 88.5%（20 週時），93.1%（16 週時）が BLQ となった。両本剤投与群において，本剤初回投与 7 日後の平均房水中遊離 Ang-2 濃度は 3.2 pg/mL 以下と急激な抑制がみられ，抑制は試験期間を通じて持続した。
- ベースライン時における平均房水中遊離 VEGF 濃度（SD）は本剤 Q8W 群で 149（185）pg/mL，本剤 PTI 群で 102（72.7）pg/mL であった。両本剤群において，本剤初回投与 7 日後の平均房水中遊離 VEGF 濃度は 5 pg/mL 未満と急激な抑制がみられ，その後持続した。本剤 Q8W 群における平均房水中遊離 VEGF 濃度は投与後から 32 週時まで 18.7 pg/mL 以下であった。本剤 PTI 群における平均房水中遊離 VEGF 濃度（SD）は 32 週時に最も高く，44.0（36.1）pg/mL であった。また，投与からの期間が長くなるにつれて房水中遊離 VEGF 濃度は増加する傾向がみられた。
- 両本剤群において，血漿中遊離 Ang-2 濃度及び遊離 VEGF 濃度のベースライン時からの変化はみられなかった。

2.7.6.1.8.7 免疫原性

- 本剤投与群において，603 例中 6 例（1.0%）の患者がベースライン時から ADA 陽性と判定された。本剤投与後，619 例中 62 例（10.0%）の患者が Treatment induced ADA 又は Treatment boosted ADA と判定された。この内，619 例中 61 例（Q8W 群：31 例，PTI 群：30 例）が Treatment induced ADA であり，PTI 群の 1 例が Treatment boosted ADA であった。

- ADA による薬物動態への明らかな影響はみられなかった。

2.7.6.1.8.8 安全性

有害事象の概況を表 2.7.6.1.8.8-1に示し，有害事象の集計を試験眼，非試験眼，眼以外についてそれぞれ表 2.7.6.2-26～表 2.7.6.2-28に示した。副作用の集計を試験眼，非試験眼，眼以外についてそれぞれ表 2.7.6.2-29～表 2.7.6.2-31に示した。

本剤の安全性プロファイルはアフリベルセプトと同様であることが示唆された。中止に至った有害事象の発現頻度が低く，本剤は概して忍容性は良好であった。有害事象は概してコントロール可能であり，新たな安全性のシグナルは確認されなかった。

56週時までの結果を以下に記載する（2.7.4.1.1.4.6）。

- 有害事象の発現頻度は本剤 Q8W 群，本剤 PTI 群及びアフリベルセプト Q8W 群でそれぞれ 82.1%（257/313 例），80.8%（253/313 例）及び 78.5%（244/311 例）であり，投与群間で同様であった。
- 試験眼に発現した有害事象の発現頻度は本剤 Q8W 群，本剤 PTI 群及びアフリベルセプト Q8W 群でそれぞれ 31.3%，33.9%及び 32.8%であり，同様であった。
- いずれかの群の 2%以上で試験眼に発現した有害事象は，結膜出血，白内障，硝子体剥離，眼痛，硝子体浮遊物，眼圧上昇，ドライアイ及び皮質白内障であった（表 2.7.6.2-26）。硝子体浮遊物（本剤 Q8W 群，本剤 PTI 群及びアフリベルセプト Q8W 群でそれぞれ 4.8%，1.9%及び 0.6%）の発現頻度はアフリベルセプト Q8W 群に比べて両本剤群で高かったが，重症度は軽度が主であり，すべて非重篤であった。
- 試験眼に発現した副作用の発現頻度は本剤 Q8W 群，本剤 PTI 群及びアフリベルセプト Q8W 群でそれぞれ 3.5%，2.6%及び 1.6%であった。
- いずれかの群の 2%以上で試験眼に発現した副作用はなかった（表 2.7.6.2-29）。
- 試験眼に発現した重症度が高度の有害事象の発現頻度は本剤 Q8W 群，本剤 PTI 群及びアフリベルセプト Q8W 群でそれぞれ 1.0%（3 例；糖尿病性網膜浮腫，硝子体炎，裂孔原性網膜剥離及び眼圧上昇各 1 例），1.6%（5 例；ぶどう膜炎 2 例，眼窩周囲痛，ぶどう膜炎性緑内障，眼内炎及びウイルス性角膜炎各 1 例）及び 1.6%（5 例；白内障，眼痛，流涙増加，網膜動脈閉塞及び結膜炎各 1 例）であり，同様であった。これらの内，副作用は，本剤 Q8W 群の 1 例（眼圧上昇及び硝子体炎），本剤 PTI 群の 2 例（ぶどう膜炎 2 例）であった。
- 試験眼に発現した重篤な有害事象の発現頻度は本剤 Q8W 群，本剤 PTI 群及びアフリベルセプト Q8W 群でそれぞれ 1.9%（6 例），2.9%（9 例）及び 0.6%（2 例）であり，アフリベルセプト Q8W 群に比較して両本剤群で高かった。両本剤群又はアフリベルセプト Q8W 群で 2 例以上に認められた試験眼における重篤な有害事象はぶどう膜炎（本剤 PTI 群に 3 例），次いで糖尿病性網膜浮腫（本剤 Q8W 群及び本剤 PTI 群に各 1 例）及び眼内炎（本剤 PTI 群に 2 例）であった。本剤 Q8W 群と本剤 PTI 群との間で一貫した傾向は認められなかった。
- 試験眼に発現した重篤な副作用は本剤 Q8W 群及びアフリベルセプト Q8W 群では認められず，本剤 PTI 群の 4 例（1.3%）に 5 件認められた。その内訳は，ぶどう膜炎（3 例，1.0%），脈絡網膜炎，角膜ぶどう膜炎（各 0.3%，1 例）であった。
- 治験薬の投与中止に至った有害事象の発現頻度は本剤 Q8W 群，本剤 PTI 群及びアフリベルセプト Q8W 群でそれぞれ 1.9%（6 例），2.6%（8 例）及び 1.0%（3 例）であり，投与群間で同様に低かった（表 2.7.6.1.8.8-1）。眼に発現した治験薬の投与中止に至った有害事象の発現頻度は本剤 Q8W 群，本剤 PTI 群及びアフリベルセプト Q8W 群でそれぞれ 0.6%（2 例），1.6%（5 例）及び 0.3%（1 例）であり，すべての群で低かった。その内訳は，本剤 Q8W 群では眼圧上昇，裂孔原性網膜剥離，硝子体炎（各 0.3%，1 例），本剤 PTI 群では眼内炎，ぶどう膜炎（各 0.6%，2 例），化学物質アレルギー（0.3%，1 例），アフリベルセプト Q8W 群では網膜動脈閉塞（0.3%，1 例）であった。これらの内，副作用は，本剤 Q8W

群では眼圧上昇，硝子体炎（各 0.3%，1 例），本剤 PTI 群ではぶどう膜炎（0.6%，2 例）であった。

- 治験中止に至った有害事象の発現頻度は本剤 Q8W 群，本剤 PTI 群及びアフリベルセプト Q8W 群でそれぞれ 3.2%（10 例），3.5%（11 例）及び 1.9%（6 例）であり，投与群間で同様に低かった。眼に発現した治験中止に至った有害事象の発現頻度は本剤 Q8W 群，本剤 PTI 群及びアフリベルセプト Q8W 群でそれぞれ 0.6%（2 例），0.6%（2 例）及び 0.3%（1 例）であり，低く，投与群間で同様であった。眼に発現した治験中止に至った有害事象は，本剤 Q8W 群で眼圧上昇，裂孔原性網膜剥離，硝子体炎（各 0.3%，1 例），本剤 PTI 群で化学物質アレルギー，眼内炎（各 0.3%，1 例），アフリベルセプト Q8W 群で網膜動脈閉塞（0.3%，1 例）であった。これらの内，副作用は，本剤 Q8W 群の 1 例（眼圧上昇及び硝子体炎）であった。
- 試験眼に発現した AESI の発現頻度は本剤 Q8W 群，本剤 PTI 群及びアフリベルセプト Q8W 群でそれぞれ 1.9%（6 例），2.6%（8 例）及び 0.3%（1 例）であり，アフリベルセプト Q8W 群に比べて両本剤群で高かった。ぶどう膜炎以外の事象の発現例数はいずれかの群で 1 例であり，本剤 Q8W 群と本剤 PTI 群との間で一貫した傾向は認められなかった。本剤 Q8W 群及び本剤 PTI 群の各 0.6%（2 例）及びアフリベルセプト Q8W 群の 0.3%（1 例）では 1 時間を超える 30 文字以上の視力低下に至った AESI（AESI 基準）が認められた。
- 試験眼に発現した眼内炎は本剤 PTI 群で 2 例に認められた。両事象は重篤と判断され，重症度は中等度及び高度が各 1 例であった。いずれも治験薬との因果関係は否定され，治験薬投与中止後，56 週時までに回復した。
- 試験眼に発現した眼内炎症の発現頻度は本剤 Q8W 群，本剤 PTI 群及びアフリベルセプト Q8W 群でそれぞれ 1.6%（5 例），2.2%（7 例）及び 1.0%（3 例）であり，低かった。網膜血管炎又は網膜血管閉塞事象を伴う眼内炎症は認められなかった。30 文字以上の視力低下を伴う眼内炎症（角膜後面沈着物及びぶどう膜炎）が本剤 PTI 群の 1 例に認められた。
- 眼以外に発現した有害事象の発現頻度は本剤 Q8W 群，本剤 PTI 群及びアフリベルセプト Q8W 群でそれぞれ 65.2%，67.1%及び 65.3%であり，投与群間で同様であった。
- いずれかの群の 5%以上で眼以外に発現した有害事象（本剤 Q8W 群，本剤 PTI 群及びアフリベルセプト Q8W 群別）は，上咽頭炎（6.7%，4.8%及び 7.1%），高血圧（5.4%，5.8%及び 8.0%）であった（表 2.7.6.2-28）。
- 眼以外に発現した重症度が高度の有害事象の発現頻度は，本剤 Q8W 群，本剤 PTI 群及びアフリベルセプト Q8W 群で，それぞれ 15.7%，13.4%及び 12.9%であった。これらの内，副作用は，本剤 Q8W 群の 1 例（高血圧）で認められた。
- 眼以外に発現した重篤な有害事象の発現頻度は本剤 Q8W 群，本剤 PTI 群及びアフリベルセプト Q8W 群でそれぞれ 24.0%，20.4%及び 16.1%であり，アフリベルセプト Q8W 群に比べて両本剤群で高かった。投与群間で一貫した傾向は認められなかった。
- 死亡は 21 例で認められ，本剤 Q8W 群，本剤 PTI 群及びアフリベルセプト Q8W 群でそれぞれ 2.6%（8 例），2.9%（9 例）及び 1.3%（4 例）であり，いずれも治験薬投与との関連は否定された。
- APTC で定義された動脈血栓塞栓事象の発現頻度は本剤 Q8W 群，本剤 PTI 群及びアフリベルセプト Q8W 群でそれぞれ 2.9%（9 例），3.2%（10 例）及び 2.9%（9 例）であり，投与群間で同様に低かった。
- 臨床検査項目において，投与群間で臨床的に重要な不均衡は認められなかった。
- ADA 陽性の発現頻度は全体として低かった。本剤の投与を受け，投与後の評価が可能であった患者の内，本剤投与後に抗体が検出された（Treatment emergent ADA）患者は 10.0%（62/619 例）であり，この内，61 例（本剤 Q8W 群及び本剤 PTI 群でそれぞれ 31 例及び 30 例）は本剤投与後に陽性に転じ（Treatment emergent ADA），1 例（本剤 PTI 群）は本剤投与後に抗体価が 4 倍以上，上昇した（treatment boosted ADA）。ADA 陽性例の数が少なかっ

たため評価に限界があるものの，ADA の安全性及び有効性に対する影響は認められなかった。

表 2.7.6.1.8.8-1 有害事象の概況（GR40349試験）

	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Faricimab 6 mg All (N=626)	Aflibercept 2 mg Q8W (N=311)
Total number of patients with at least one AE	257 (82.1%)	253 (80.8%)	510 (81.5%)	244 (78.5%)
Total number of AEs	1062	1016	2078	938
Total number of patients with at least one SAE	82 (26.2%)	77 (24.6%)	159 (25.4%)	56 (18.0%)
Total number of SAEs	171	114	285	96
Total number of deaths	8 (2.6%)	9 (2.9%)	17 (2.7%)	4 (1.3%)
Total number of patients withdrawn from study due to an AE	10 (3.2%)	11 (3.5%)	21 (3.4%)	6 (1.9%)
Total number of patients withdrawn from study treatment due to an AE	6 (1.9%)	8 (2.6%)	14 (2.2%)	3 (1.0%)
Total number of patients with at least one AESI	12 (3.8%)	15 (4.8%)	27 (4.3%)	6 (1.9%)
Ocular events: study eye total number of patients with at least one				
AE	98 (31.3%)	106 (33.9%)	204 (32.6%)	102 (32.8%)
SAE	6 (1.9%)	9 (2.9%)	15 (2.4%)	2 (0.6%)
AE leading to withdrawal from study treatment	2 (0.6%)	5 (1.6%)	7 (1.1%)	1 (0.3%)
Treatment related AEs	11 (3.5%)	8 (2.6%)	19 (3.0%)	5 (1.6%)
Treatment related SAEs	0	4 (1.3%)	4 (0.6%)	0
AE of Special Interest	6 (1.9%)	8 (2.6%)	14 (2.2%)	1 (0.3%)
Drop in VA score >=30	2 (0.6%)	2 (0.6%)	4 (0.6%)	1 (0.3%)
Associated with severe IOI	2 (0.6%)	5 (1.6%)	7 (1.1%)	0
Intervention req. to prevent permanent vision loss	3 (1.0%)	2 (0.6%)	5 (0.8%)	0
Suspected transmission of infectious agent by study drug	0	0	0	0
Ocular events: fellow eye total number of patients with at least one				
AE	89 (28.4%)	104 (33.2%)	193 (30.8%)	106 (34.1%)
SAE	7 (2.2%)	7 (2.2%)	14 (2.2%)	5 (1.6%)
AE of Special Interest	7 (2.2%)	7 (2.2%)	14 (2.2%)	4 (1.3%)
Drop in VA score >=30	6 (1.9%)	4 (1.3%)	10 (1.6%)	2 (0.6%)
Associated with severe IOI	0	1 (0.3%)	1 (0.2%)	0
Intervention req. to prevent permanent vision loss	1 (0.3%)	3 (1.0%)	4 (0.6%)	2 (0.6%)
Suspected transmission of infectious agent by study drug	0	0	0	0
Non-ocular events total number of patients with at least one				
AE	204 (65.2%)	210 (67.1%)	414 (66.1%)	203 (65.3%)
SAE	75 (24.0%)	64 (20.4%)	139 (22.2%)	50 (16.1%)
AE leading to withdrawal from study treatment	4 (1.3%)	3 (1.0%)	7 (1.1%)	2 (0.6%)
AE of Special Interest	0	0	0	1 (0.3%)
Elevated ALT or AST with either elevated bilirubin or clinical jaundice	0	0	0	1 (0.3%)
Adjudicated APTC events	9 (2.9%)	10 (3.2%)	19 (3.0%)	9 (2.9%)
Non-fatal MI	4 (1.3%)	2 (0.6%)	6 (1.0%)	4 (1.3%)
Non-fatal Stroke	3 (1.0%)	2 (0.6%)	5 (0.8%)	3 (1.0%)
Death	2 (0.6%)	6 (1.9%)	8 (1.3%)	2 (0.6%)

表 2.7.6.1.8.8-1 有害事象の概況（GR40349試験）（続）

AESI=Adverse Event of Special Interest; APTC = Antiplatelet Trialists' Collaboration; IOI=Intraocular Inflammation; MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W); SAE=Serious Adverse Event; VA = Visual Acuity; MedDRA = Medical Dictionary for Regulatory Activities.
APTC events are defined as non-fatal strokes or non-fatal myocardial infarctions or vascular deaths (including deaths of unknown cause). Investigator text for AEs encoded using MedDRA version 23.1.
Drop in VA score >=30 is defined as causing a decrease of >=30 VA score lasting more than 1 hour.
Intervention req. to prevent permanent vision loss is defined as required surgical or medical intervention to prevent permanent loss of sight.
Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for the "Total number of AEs" row in which multiple occurrences of the same AE are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

Program: root/clinical_studies/RO6867461/CDT70122/share/data_analysis/prod/program/t_ae_oview.sas
Output: root/clinical_studies/RO6867461/CDT70122/GR40349/data_analysis/CSR_Primary/prod/output/t_ae_oview_W56_SE_20OCT2020_40349.out
22JAN2021 6:00

[5.3.5.1-DME-2 Table 21を再掲]

2.7.6.1.8.9 その他の結果（COVID-19の影響）

COVID-19のパンデミックは，試験実施中に患者の安全性を監視・管理することに有意な影響を及ぼさなかった。また，COVID-19に関連する一覧を追加した以外に計画された安全性の解析に変更はなかった。

COVID-19の影響を以下に要約した。

- COVID-19 パンデミックによるデータの整合性に対するリスクを軽減するための対策が行われた。
- リスクを軽減するための対策により，安全性データ及び安全性評価における欠落を最小限に抑えることができた。
- 欠測があったものの，本剤の有効性及び安全性データはいずれも解釈可能であり，本剤のベネフィット・リスクプロファイルを明らかにすることができた。

2.7.6.1.8.10 結論

DME 患者を対象とした GR40349試験では，事前に規定した主要評価項目を満たし，BCVA におけるベースラインから48/52/56週時点の変化量平均値について，両本剤投与レジメンのアフリベルセプトに対する非劣性が検証された。

本剤群及びアフリベルセプト群において，ETDRS DRSS がベースラインから52週時に臨床的に意味のある，2段階以上及び3段階以上の改善を達成した患者の割合は同様であった。

PTI 投与レジメンによる治療を受けた患者において，本剤の投与間隔を Q16W まで延長できる可能性が示された。主要評価項目について，本剤 PTI 群（最長 Q16W 投与レジメン）はアフリベルセプト Q8W 群に対して非劣性であることが示され，52週時の本剤 PTI 群における本剤の硝子体内投与が Q4W，Q8W，Q12W，Q16W であった患者の割合はそれぞれ10.8%，15.4%，21.0%，52.8%であった。解剖学的評価を追加することにより，Q16W までの投与間隔で本剤の有効性を更に裏付けることができる。

本剤を Q8W 及び PTI で投与された患者は，アフリベルセプト Q8W を投与された患者と比較して，52週時の NEI VFQ-25スコア，近距離活動スコア，遠距離活動スコア，及び運転スコアの平均改善が同程度であることが示された。NEI VFQ-25スコアの臨床的に意味のある変化の閾値を超える改善が認められた患者の割合は，投与群間で同様であった。

投与中止に至った有害事象の発現頻度が低いことから，本剤はアフリベルセプトと同等の安全性プロファイルであり，全般的に忍容性は良好であった。新たな安全性シグナルは確認されなかった。

ファリシマブに対する ADA の発現頻度は低かった。ADA の全身曝露量，安全性及び有効性に対する明らかな影響は認められなかった。

2.7.6.1.9　海外第 III 相臨床試験（DME 患者：GR40398試験）

（評価資料：5.3.5.1-DME-3）

2.7.6.1.9.1　概要表

表 2.7.6.1.9.1-1 概要表（GR40398試験）

<table>
<tr><td colspan="2">治験の標題：DME 患者を対象としたファリシマブの有効性及び安全性を検討する第 III 相多施設共同，ランダム化，実薬対照，二重遮蔽比較試験</td></tr>
<tr><td colspan="2">施設及び国：日本を含まない24カ国（174施設）</td></tr>
<tr><td colspan="2">公表文献（引用文献）：なし</td></tr>
<tr><td>第1症例の登録日：2018年10月9日
データカットオフ日：2020年10月19日</td><td>開発のフェーズ：第 III 相</td></tr>
<tr><td colspan="2">目　　的：
有効性の主要目的
BCVA に対する本剤6.0 mg の硝子体内投与の有効性を評価する

有効性の重要な副次的目的
• 糖尿病網膜症重症度に対する本剤の有効性を評価する

有効性の副次的目的
• BCVA に関連した追加の評価項目に対する本剤の有効性を評価する
• 糖尿病網膜症に関連した追加の評価項目に対する本剤の有効性を評価する
• Personalized treatment interval（PTI）群における本剤投与間隔を評価する
• SD-OCT による解剖学的評価に対する本剤の有効性を評価する
• NEI VFQ-25 を用いて，患者報告による視力関連機能及び QOL に対する本剤の有効性を評価する

安全性の目的
• 本剤の眼及び眼以外の安全性及び忍容性を評価する

探索的有効性の目的
本剤の有効性を更に評価する
• 追加の糖尿病網膜症評価
• FFA 及び/又は光干渉断層撮影-angiography（OCT−A）を用いた解剖学的評価
• SD-OCT を用いた解剖学的評価
• NEI VFQ-25 を用いた患者報告による視力関連機能及び QOL

薬物動態の目的
• ファリシマブの全身薬物動態の特性を明らかにする

免疫原性の目的
ファリシマブに対する免疫応答を評価し，ADA の潜在的効果を評価する

主な薬物動態及び薬力学的目的（探索的）
• 房水（任意）及び硝子体（任意）におけるファリシマブの薬物動態の特性を明らかにする
• 遊離 VEGF-A 及び遊離 Ang-2 の薬物濃度（曝露量）−反応関係を評価する</td></tr>
</table>

治 験 方 法：

DME 患者を対象としたランダム化二重遮蔽実薬対照3並行群間比較，100週間の試験。

試験では，試験眼に対する抗 VEGF 薬未治療 DME 患者と，試験眼に対する抗 VEGF 薬治療歴があり，最後の投与が Day1の来院（初回治験治療）から3カ月以上前である患者を登録の対象とした。抗 VEGF 薬治療歴がある患者の目標例数は，登録の最低10%，最大25%とした。

治験薬の投与群：

- 本剤 Q8W 群：患者に本剤 6.0 mg を 20 週時まで Q4W で硝子体内投与した後，本剤 6.0 mg を 96 週時まで Q8W で硝子体内投与し，100 週時に最終来院した。
- 本剤 PTI 群：患者には本剤 6.0 mg を 12 週時まで Q4W で硝子体内投与し，続いて本剤 6.0 mg を 96 週時まで最長 Q16W で硝子体内投与し，続いて 100 週時に最終来院した。
- アフリベルセプト Q8W 群：患者にアフリベルセプト 2.0 mg を 16 週時まで Q4W で硝子体内投与した後，アフリベルセプト 2.0 mg を 96 週時まで Q8W で硝子体内投与し，100 週時に最終来院した。
- 割付けは，ベースライン時における以下の因子により層別化した。
  - BCVA スコア（64 文字以上，64 文字未満）
  - 抗 VEGF 薬硝子体内治療歴（あり，なし）
  - 地域（米国及びカナダ，アジア，その他の地域）

投与群間の遮蔽を維持するために，該当する来院時に投与群すべての患者にシャム注射を行った。

主要解析は，全例が56週時まで試験を完了したか又は56週時以前に試験を中止した場合に実施した。

症 例 数：

目標例数：約900例の患者を登録し，3つの投与群のいずれかに1:1:1の割合でランダムに割り付ける

登録例数：951例；本剤 Q8W 群に317例，本剤 PTI 群に319例，アフリベルセプト Q8W 群に315例

診断及び主要な組入基準：

糖尿病（1型又は2型）と確定診断された18歳以上の患者。現在，糖尿病の治療にインスリン又は他の注射剤を常用している，及び/又は現在，糖尿病の治療に経口高血糖治療薬を常用している。Day 1来院日前2カ月以内に HbA1c が10%以下であった患者。試験への組み入れに際して，以下の試験眼の選択基準を満たしている。

- スクリーニング時の Spectralis SD-OCT で 325 µm 以上，又は Cirrus SD-OCT 又は Topcon SD-OCT で 315 µm 以上の中心窩を含む黄斑の肥厚
- Day 1 に開始距離 4 m で評価する ETDRS 視力検査において，BCVA が 73～25 文字（Snellen 式では 20/40～20/320 に相当）
- 中間透光体が十分にクリアで瞳孔は十分に散大し，良質な CFP（糖尿病網膜症の重症度判定及び網膜の評価が可能な ETDRS 改変 7 方向又は広角 4 方向）の撮影及び他の画像検査が可能

被験薬，用量及び投与方法：

(1) 被験薬：ファリシマブ製剤
単回使用バイアル製剤

(2) 用量及び投与方法：

本剤 Q8W 群：本剤6.0 mg を20週時まで Q4W で硝子体内投与，以降は96週時まで Q8W で硝子体内投与

本剤 PTI 群：本剤6.0 mg を12週時まで Q4W で硝子体内投与，以降は96週時まで PTI で硝子体内投与。PTI を受けている患者は，患者の参照中心領域網膜厚及び参照 BCVA と比較し

た中心領域網膜厚の相対的変化及び BCVA の絶対変化に基づいて，最長 Q16W 又は最短 Q4W まで4週間単位で，治験薬投与来院時に延長，短縮又は維持された。

対照薬，用量及び投与方法：
(1) 対照薬：アフリベルセプト
単回使用バイアル製剤
(2) 用量及び投与方法：
アフリベルセプト Q8W 群：アフリベルセプト2.0 mg を16週時まで Q4W で硝子体内投与，その後96週時まで Q8W で硝子体内投与。

治 療 期 間：
- スクリーニング：最長 28 日間
- ベースライン：Day 1
- 治験薬投与期間：Day 1 から 96 週時まで
- 観察期間：96 週時から 100 週時

評 価 基 準：
(1) 有効性評価項目
- 主要評価項目

BCVA におけるベースライン値から1年後（48，52，56週時）の各時点の平均変化量の平均値（ETDRS 視力表で開始距離4 m から測定する，以降，BCVA におけるベースラインから48/52/56週時点の変化量平均値）

- 重要な副次的評価項目

ETDRS diabetic retinopathy severity scale（DRSS）において，ベースラインから52週時までに2段階以上の改善が認められた患者の割合

- 副次的評価項目及び探索的評価項目
  - 1年後及び経時的な BCVA がベースラインから0，5，10又は15文字以上改善した患者の割合
  - 1年後及び経時的な BCVA がベースラインから5，10又は15文字以上悪化を回避した患者の割合
  - 1年後の中心領域網膜厚のベースラインからの変化量
  - 1年後及び経時的な DME が認められない（Spectralis SD-OCT で中心領域網膜厚が325 μm 未満）患者の割合
  - 52週時及び経時的な網膜内液が認められなかった患者の割合
  - 52週時及び経時的な網膜下液が認められなかった患者の割合
  - 本剤 PTI 群における52週時の Q4W，Q8W，Q12W 又は Q16W 投与の患者の割合
  - 52週時及び経時的な NEI VFQ-25スコアのベースラインからの変化量
  - 経時的な NEI VFQ-25 Near Activities，Distance Activities，Driving Subscale のベースラインからの変化
  - 経時的な NEI VFQ-25スコアのベースラインからの改善が4ポイント以上であった患者の割合の変化

(2) 薬物動態学的評価項目
- 血漿中ファリシマブ濃度推移
- ファリシマブの房水濃度（任意）及び硝子体液中濃度（任意）の経時変化（探索的）

(3) 薬力学的評価項目（探索的）
- ファリシマブの薬物動態と房水（任意），血漿中及び/又は硝子体液中（任意）遊離

Ang-2 及び遊離 VEGF-A 濃度との経時的関係 (4) 免疫原性 • ベースライン時における ADA の有無と比較した試験中の ADA の有無 • ADA の有無と有効性，安全性又は薬物動態のエンドポイントとの関係 (5) 安全性評価項目 • 眼の有害事象の発現頻度及び重症度 • 眼以外の有害事象の発現頻度及び重症度
統 計 手 法： 有効性解析は，特に明記しない限り，ITT 集団及び未治療の患者集集団について行った。主要解析及び重要な副次的非劣性解析のために，per-protocol 集団に基づく補足的解析も実施した。ベースラインとは，割付け時又はその直前の測定値と定義した。ベースライン時の評価が欠測していた患者は補完されなかった。 特に記載のない限り，有効性評価の解析は，割付けの層別因子で調整した：ベースライン（Day 1）の BCVA ETDRS 文字スコア（64文字以上，64文字未満），抗 VEGF 薬の硝子体内治療歴（あり，なし），地域（米国及びカナダ，アジア，その他の地域）。IxRS に記録された層別因子を用いた。 主要な比較は，実対照薬（アフリベルセプト Q8W 群）と各本剤群（Q8W 群と PTI 群）との比較とした。連続変数の解析には，MMRM を用いた。二値変数の解析には，二項割合に対する層別解析を用いた。推定値及び CI は，3つの投与群のそれぞれについての平均値（連続変数の場合）又は割合（二値変数の場合）並びに実対照薬（アフリベルセプト Q8W 群）と本剤の各群（Q8W 群及び PTI 群）の平均値又は割合の差を算出した。 仮説の頑健性及び COVID-19パンデミックの影響を評価するために，異なる中間事象の取扱方法を用いて，有効性の主要評価項目及び重要な副次的評価項目の補足的解析を実施した。

この主要な総括報告書は，主要評価項目の最終時点（56週時）に対応する主要解析の結果を提供するものである。48週時，52週時，56週時で平均したエンドポイントを「48/52/56週時」のエンドポイントと呼ぶ。

2.7.6.1.9.2 患者の内訳

本試験に登録された951例の DME 患者を，ベースライン時 BCVA ETDRS スコア，抗 VEGF 薬硝子体内治療歴，及び地域を層別因子として，層別置換ブロック法により1:1:1の比でランダムに，本剤 Q8W 群に317例，本剤 PTI 群に319例及びアフリベルセプト Q8W 群に315例割り付けた。

2.7.6.1.9.3 患者背景

ITT 集団では，ベースライン時の人口統計学的患者背景は投与群間で同様であった（表 2.7.4.1.3.2.4-1，表 2.7.4.1.3.2.4-2）。年齢の平均値（SD）は本剤 Q8W 群では62.5歳（10.1歳），本剤 PTI 群では61.6歳（10.1歳），アフリベルセプト Q8W 群では62.3歳（10.1歳）であり，全患者の57.0%が65歳未満であった。全患者の60.9%が男性で，主に白人（79.1%），その他の地域（米国及びカナダ地域及びアジア地域以外の地域，56.5%），非ヒスパニック系又は非ラテン系（76.1%）であった。

ITT 集団の試験眼のベースライン時 BCVA の平均値（SD）は，本剤 Q8W 群では61.9文字（10.1文字），本剤 PTI 群では62.5文字（9.3文字），アフリベルセプト Q8W 群では62.1文字（9.4文字）であった。ベースライン時の中心領域網膜厚の平均値（SD）は，本剤 Q8W 群では466.2 μm（119.4 μm），本剤 PTI 群では471.3 μm（127.0 μm），アフリベルセプト Q8W 群で

は477.3 μm（129.4 μm）であった。患者報告による DME 診断時からの期間の平均値（SD）は，本剤 Q8W 群では18.9カ月（32.2カ月），本剤 PTI 群では20.7カ月（33.0カ月），アフリベルセプト Q8W 群では20.3カ月（37.1カ月）であった。

試験眼の79.6%が過去に抗 VEGF 治療を受けていなかった。過去に抗 VEGF 治療を受けた患者における最後の抗 VEGF 薬投与からの期間の平均値（SD）は，本剤 Q8W 群では20.7カ月（20.8カ月），本剤 PTI 群では15.5カ月（19.5カ月），アフリベルセプト Q8W 群では19.9カ月（17.4カ月）であった。ベースライン時の糖尿病網膜症の特性は概して均衡がとれていた。全体では，中等度から重度の NPDR 患者（DRSS 43/47/53）は58.0%，軽度の NPDR 患者（DRSS <43）は29.0%，PDR 患者（DRSS >53）は8.1%であった。

試験眼の79.6%が過去に抗 VEGF 治療を受けていなかった。

2.7.6.1.9.4 有効性

ITT 集団（特に断りのない場合を除く）の主要な有効性の結果は以下のとおりであった（2.7.3.2.2.8.3）。

- ITT 集団では，BCVA におけるベースラインから 48/52/56 週時点の変化量平均値は，本剤 Q8W 群では 11.8 文字（97.5%CI：10.6，13.0 文字），本剤 PTI 群では 10.8 文字（97.5%CI：9.6，11.9 文字），アフリベルセプト Q8W 群では 10.3 文字（97.5%CI：9.1，11.4 文字）であった。本剤 Q8W 群及び本剤 PTI 群では，アフリベルセプト Q8W 群に対して，BCVA におけるベースラインから 48/52/56 週時点の変化量平均値の差の 97.5%CI の下限が−4 文字より大きいため，非劣性が示された。48/52/56 週時点の変化量平均値における本剤 Q8W 群及び本剤 PTI 群のアフリベルセプト Q8W 群との差は，それぞれ 1.5 文字（97.5%CI：−0.1，3.2 文字）及び 0.5 文字（97.5%CI：−1.1，2.1 文字）であった。
- 未治療の患者集団では，本剤 Q8W 群及び本剤 PTI 群の BCVA におけるベースラインから 48/52/56 週時点の変化量平均値は，アフリベルセプト Q8W 群に対して，優越性は示されなかった。未治療の患者集団における結果は，ITT 集団における結果と同様であり，48/52/56 週時点の変化量平均値における本剤 Q8W 群及び本剤 PTI 群のアフリベルセプト Q8W 群との差は，それぞれ 1.1 文字（97.5%CI：−0.7，3.0 文字）及び 0.6 文字（97.5%CI：−1.2，2.4 文字）であった。
- 主要評価項目では ITT 集団及び per-protocol 集団の間で一貫しており，感度分析及び補足的解析により裏付けられた。補足的解析の結果は，中間事象に対する処理方法間及び患者集団間で一貫していた。
- ITT 集団では，ETDRS DRSS においてベースライン時から 52 週時までに 2 段階以上の改善が認められた患者の割合は，本剤 Q8W 群とアフリベルセプト Q8W 群の間では本剤 Q8W 群は 44.2%（97.5%CI：37.1，51.4%），フリベルセプト Q8W 群は 46.8%（97.5%CI：39.8，53.8%）であり，本剤 PTI 群とアフリベルセプト Q8W 群では本剤 PTI 群は 43.7%（97.5%CI：36.8，50.7%），アフリベルセプト Q8W 群は 47.3%（97.5%CI：40.2，54.3%）であった。
- ETDRS DRSS においてベースライン時から 52 週時までに 2 段階以上の改善が認められた患者の割合の差は，本剤 Q8W 群及びアフリベルセプト Q8W 群の間では−2.6%（97.5%CI：−12.6，7.4%），本剤 PTI 群及びアフリベルセプト Q8W 群の間では−3.5%（97.5%CI：−13.4，6.3%）であった。これらの結果は ITT 集団及び per-protocol 集団で一貫しており，補足的解析により裏付けられた。
- BCVA のベースラインからの平均変化量の推移：本剤 Q8W 群及び本剤 PTI 群は，アフリベルセプト Q8W 群と同様であった。
- ベースライン時から 48/52/56 週時までに BCVA が 15 文字以上改善した患者の割合：本剤 Q8W 群とアフリベルセプト Q8W 群の間では本剤 Q8W 群は 33.8%（95%CI：28.4，39.2%），アフリベルセプト Q8W 群では 30.3%（95%CI：25.0，35.5%）であり，本剤 PTI 群とアフリ

ベルセプト Q8W 群の間では本剤 PTI 群は 28.5%（95%CI：23.6，33.3%），アフリベルセプト Q8W 群は 30.4%（95%CI：25.2，35.7%）であり，本剤 Q8W 群及び本剤 PTI 群は，アフリベルセプト Q8W 群と同様であった。

- ベースライン時から 48/52/56 週時までに BCVA の 15 文字以上の悪化を回避した患者の割合：本剤 Q8W 群とアフリベルセプト Q8W 群の間では本剤 Q8W 群は 98.9%（95%CI：97.6，100.0%），アフリベルセプト Q8W 群は 98.6%（95%CI：97.2，99.9%）であり，剤 PTI 群とアフリベルセプト Q8W 群の間では本剤 PTI 群は 98.7%（95%CI：97.4，100.0%），アフリベルセプト Q8W 群は 98.6%（95%CI：97.3，99.9%）であり，本剤 Q8W 群及び本剤 PTI 群は，アフリベルセプト Q8W 群と同様であった。
- ベースライン時から 48/52/56 週時までの中心領域網膜厚の変化量：本剤 Q8W 群では−195.8 μm（95%CI：−204.1，−187.5 μm），本剤 PTI 群では−187.6 μm（95%CI：−195.8，−179.5 μm），アフリベルセプト Q8W 群では−170.1 μm（95%CI：−178.3，−161.8 μm）であり，本剤 Q8W 群及び本剤 PTI 群は，アフリベルセプト Q8W 群と比べて，同程度の減少であった。
- 52 週時の本剤 PTI 群における本剤の硝子体内投与が Q4W，Q8W，Q12W，Q16W であった患者の割合：それぞれ 13.3%，15.6%，20.1%，51.0%であった。なお，本剤 PTI 群における 52 週時の本剤の硝子体内投与が，Q12W 未満に短縮することなく Q12W 以上を達成した患者の割合は 64.3%であった。
- ベースライン時から 52 週時までの NEI VFQ-25 スコアの変化量：本剤 Q8W 群では 6.9（95%CI：5.5，8.2），本剤 PTI 群では 7.0（95%CI：5.7，8.2），アフリベルセプト Q8W 群では 7.6（95%CI：6.3，8.9）であり，本剤 Q8W 群及び本剤 PTI 群は，アフリベルセプト Q8W 群と同様であった。
- 16 週時及び 52 週時に新たに PDR となった患者の割合：16 週時は本剤 Q8W 群では 1.1%（95%CI：0.0，2.4%），本剤 PTI 群では 0.4%（95%CI：0.0，1.2%），アフリベルセプト Q8W 群では 0.8%（95%CI：0.0，1.9%），52 週時は本剤 Q8W 群では 0.9%（95%CI：0.0，2.2%），本剤 PTI 群では 0.9%（95%CI：0.0，2.2%），アフリベルセプト Q8W 群では 0.5%（95%CI：0.0，1.3%）であった。
- 48/52/56 週時に DME が認められなかった患者の割合：DME の消失を中心領域網膜厚が Spectralis の SD-OCT で 325 μm 未満，Cirrus 又は Topcon の SD-OCT で 315 μm 未満と定義した。本剤 Q8W 群では 85.4%（95%CI：81.2，89.7%），本剤 PTI 群では 81.6%（95%CI：77.2，86.1%），アフリベルセプト Q8W 群では 73.1%（95%CI：67.9，78.3%）であり，本剤 Q8W 群及び本剤 PTI 群ではアフリベルセプト Q8W 群と比べて高かった。
- 48 週，52 週，56 週時点で網膜内液及び網膜下液が認められなかった患者の割合：48 週時に網膜内液及び網膜下液が認められなかった患者の割合は，本剤 Q8W 群 40.4%（95%CI：34.2，46.6%），本剤 PTI 群 31.9%（95%CI：26.3，37.4%），アフリベルセプト Q8W 群 22.9%（95%CI：17.9，28.0%），52 週時では本剤 Q8W 群 39.3%（95%CI：33.2，45.4%），本剤 PTI 群 36.2%（95%CI：30.4，41.9%），アフリベルセプト Q8W 群 29.1%（95%CI：23.6，34.6%），56 週時では本剤 Q8W 群 42.6%（95%CI：36.3，48.8%），本剤 PTI 群 40.3%（95%CI：34.4，46.2%），アフリベルセプト Q8W 群 27.1%（95%CI：21.6，32.7%）であった。本剤 Q8W 群及び本剤 PTI 群ではアフリベルセプト Q8W 群と比べて，網膜内液及び網膜下液が認められなかった患者の割合は，48 週時，52 週時，56 週時で一貫して高かった。
- ベースライン時から 52 週時までに NEI VFQ-25 スコアが 4 以上改善した患者の割合：本剤 Q8W 群，本剤 PTI 群のベースライン時から 52 週時までに NEI VFQ-25 スコアが 4 以上改善した患者の割合はアフリベルセプト Q8W 群と同様であった。ベースライン時から 52 週時までに NEI VFQ-25 スコアが 4 以上改善した患者の割合は，本剤 Q8W 群では 53.0%（95%CI：46.8，59.2%），本剤 PTI 群では 52.6%（95%CI：46.6，58.5%），アフリベルセプト Q8W 群では 49.8%（95%CI：43.7，55.9%）であった。

2.7.6.1.9.5 薬物動態

- 房水中ファリシマブ濃度は両本剤群ともに試験期間を通じて測定可能であった。また，房水中ファリシマブ濃度及び血漿中ファリシマブ濃度は高い患者間変動を示した。
- 各投与 4 週後における平均房水中ファリシマブ濃度（SD）は，本剤 Q8W 群において 16 週時で 14.8（12.8）μg/mL，20 週時で 13.7（12.7）μg/mL，32 週時で 9.42（8.33）μg/mL であり，本剤 PTI 群において 16 週時で 11.5（10.9）μg/mL，20 週時で 16.3（15.9）μg/mL，32 週時で 11.2（12.9）μg/mL であった。各投与 8 週後における平均房水中ファリシマブ濃度（SD）は，本剤 PTI 群において 20 週時で 0.444（0.564）μg/mL であった。本剤 PTI 群において直近の本剤投与から 12 週後（32 週時）には 42.9%のサンプルが BLQ となった。
- 各投与 4 週後における平均血漿中ファリシマブ濃度（SD）は，本剤 Q8W 群において 4 週時で 0.0193（0.0163）μg/mL であり，本剤 PTI 群において 4 週時で 0.0197（0.0151）μg/mL，52 週時で 0.0191（0.0144）μg/mL であった。各投与 8 週後における平均血漿中ファリシマブ濃度（SD）は，本剤 Q8W 群において 28 週時で 0.0027（0.0035）μg/mL，52 週時で 0.0023（0.0032）μg/mL であり，本剤 PTI 群において 28 週時で 0.0032（0.0040）μg/mL，52 週時で 0.0021（0.0028）μg/mL であった。直近の本剤投与から 8 週後（28 週時及び 52 週時）には本剤 Q8W 群において 37.4%及び 41.8%，本剤 PTI 群において 38.0%及び 38.5%のサンプルが BLQ となった。

2.7.6.1.9.6 薬力学

- 房水中遊離 Ang-2 濃度及び房水中遊離 VEGF 濃度は高い患者間変動を示した。
- ベースライン時における平均房水中遊離 Ang-2 濃度（SD）は本剤 Q8W 群で 12.5（8.9）pg/mL，本剤 PTI 群で 9.1（7.4）pg/mL であった。また，ベースラインにおいて本剤 Q8W 投与群で 15.0%，本剤 PTI 群で 30.4%のサンプルが BLQ であり，投与後は最大でそれぞれ 86.7%（20 週時），100%（16 週時）が BLQ となった。両本剤群において，本剤初回投与 7 日後から房水中遊離 Ang-2 濃度の急激な抑制（平均 Ang-2 濃度 3.2 pg/mL 以下）がみられ，抑制は試験期間を通じて持続した。
- ベースライン時における平均房水中遊離 VEGF 濃度（SD）は本剤 Q8W 群で 176（160）pg/mL，本剤 PTI 群で 96.3（60.9）pg/mL であった。両本剤群において，本剤初回投与 7 日後の平均房水中遊離 VEGF 濃度は 7.1 pg/mL 以下と急激な抑制がみられ，その後持続した。本剤 Q8W 群における平均房水中遊離 VEGF 濃度（SD）は投与後から 32 週時まで 31 pg/mL 以下であった。本剤 PTI 群における平均房水中遊離 VEGF 濃度（SD）は 32 週時で 59.0（55.9）pg/mL であった。また，投与からの期間が長くなるにつれて房水中遊離 VEGF 濃度は増加する傾向がみられた。
- 本剤投与群において，血漿中遊離 Ang-2 濃度及び遊離 VEGF 濃度のベースライン時からの変化はみられなかった。

2.7.6.1.9.7 免疫原性

- 本剤投与群において，604 例中 4 例（0.6%）の患者がベースライン時から ADA 陽性と判定された。本剤投与後，624 例中 43 例（6.9%）の患者が Treatment induced ADA と判定された（本剤 Q8W 群：20 例，本剤 PTI 群：23 例）。
- ADA による薬物動態への明らかな影響はみられなかった。

2.7.6.1.9.8 安全性

有害事象の概況を表 2.7.6.1.9.8-1に示し，有害事象の集計を試験眼，非試験眼，眼以外についてそれぞれ表 2.7.6.2-32～表 2.7.6.2-34に示した。副作用の集計を試験眼及び非試験眼につい

てそれぞれ表 2.7.6.2-35及び表 2.7.6.2-36に示した。

本剤の安全性プロファイルはアフリベルセプトと同様であることが示唆された。中止に至った有害事象の発現頻度が低く，本剤は概して忍容性は良好であった。有害事象は概してコントロール可能であり，新たな安全性のシグナルは確認されなかった。

56週時までの結果を以下に記載する（2.7.4.1.1.4.7）。

- 有害事象の発現頻度は本剤 Q8W 群，本剤 PTI 群及びアフリベルセプト Q8W 群でそれぞれ 80.8%（256/317 例），73.0%（233/319 例）及び 77.7%（244/314 例）であり，投与群間で同様であった。
- 試験眼に発現した有害事象の発現頻度は本剤 Q8W 群，本剤 PTI 群及びアフリベルセプト Q8W 群でそれぞれ 43.2%，37.3%及び 36.0%であり，本剤 PTI 群及びアフリベルセプト Q8W 群に比べて本剤 Q8W 群で高かった。
- いずれかの群の 2%以上で試験眼に発現した有害事象は，結膜出血，白内障，ドライアイ，硝子体剥離，眼圧上昇，硝子体浮遊物，眼痛，投薬過誤（いずれの投薬過誤も有害事象との関連なし），眼瞼炎及び皮質白内障であった（表 2.7.6.2-32）。硝子体浮遊物の発現頻度は本剤 PTI 群及びアフリベルセプト Q8W 群に比べて本剤 Q8W 群で高かった（本剤 Q8W 群，本剤 PTI 群及びアフリベルセプト Q8W 群でそれぞれ 4.7%，2.2%及び 2.5%）が，重症度は軽度が主であり，すべて非重篤であった。
- 試験眼に発現した副作用の発現頻度は本剤 Q8W 群，本剤 PTI 群及びアフリベルセプト Q8W 群でそれぞれ 2.5%，2.5%及び 4.5%であった。
- いずれかの群の 2%以上で試験眼に発現した副作用はなかった（表 2.7.6.2-35）。
- 試験眼に発現した重症度が高度の有害事象の発現頻度は本剤 Q8W 群，本剤 PTI 群及びアフリベルセプト Q8W 群でそれぞれ 2.5%（8 例；白内障，ドライアイ，眼そう痒症，硝子体出血，視力障害，眼内炎，インフルエンザ及び異物感各 1 例），1.6%（5 例；点状角膜炎，高眼圧症，糖尿病性眼病変，網膜静脈閉塞及び角膜擦過傷各 1 例）及び 1.3%（4 例；黄斑線維症，一過性視力低下，緑内障及び眼内炎各 1 例）であり，同様であった。これらの内，副作用は，本剤 PTI 群の 1 例（高眼圧症）であった。
- 試験眼に発現した重篤な有害事象の発現頻度は本剤 Q8W 群，本剤 PTI 群及びアフリベルセプト Q8W 群でそれぞれ 2.8%（9 例），3.1%（10 例）及び 1.9%（6 例）であり，投与群間で同様であった。いずれかの群で 2 例以上に認められた試験眼に発現した重篤な有害事象は白内障，糖尿病性網膜浮腫（医師記載事象名：糖尿病性網膜浮腫の悪化）及び眼内炎であった。試験眼に発現した重篤な有害事象のほとんどは 1 例の患者に発現し，本剤 Q8W 群と本剤 PTI 群との間で一貫した傾向は認められなかった。
- 試験眼に発現した重篤な副作用は本剤 Q8W 群及びアフリベルセプト Q8W 群では認められず，本剤 PTI 群の 1 例（0.3%）に 1 件（高眼圧症）認められた。
- 治験薬の投与中止に至った有害事象の発現頻度はいずれの群においても 1.3%（4 例）であり，投与群間で同様に低かった（表 2.7.6.1.9.8-1）。眼に発現した治験薬の投与中止に至った有害事象は，本剤 Q8W 群では認められず，本剤 PTI 群 0.9%（3 例），アフリベルセプト Q8W 群 0.3%（1 例）であり，すべての群で低かった。その内訳は，本剤 PTI 群では糖尿病性眼病変，高眼圧症，潰瘍性角膜炎（各 0.3%，1 例），アフリベルセプト Q8W 群では眼内炎（0.3%，1 例）であった。これらの内，副作用は，本剤 PTI 群の高眼圧症（0.3%，1 例）であった。
- 治験中止に至った有害事象の発現頻度は本剤 Q8W 群，本剤 PTI 群及びアフリベルセプト Q8W 群でそれぞれ 1.9%（6 例），0.3%（1 例）及び 1.0%（3 例）であり，投与群間で同様に低かった。眼に発現した治験中止に至った有害事象はいずれの群にも認められなかった。
- 試験眼に発現した AESI の発現頻度は，本剤 Q8W 群，本剤 PTI 群及びアフリベルセプト Q8W 群でそれぞれ 2.8%（9 例），2.8%（9 例）及び 1.6%（5 例）であり，概して投与群間で同様であった。白内障及び糖尿病性網膜浮腫（医師記載事象名：糖尿病性網膜浮腫の悪化）

以外の事象の発現例数はいずれかの群で 1 例であり，本剤 Q8W 群と本剤 PTI 群との間で一貫した傾向は認められなかった。本剤 Q8W 群及び本剤 PTI 群の各 1.9%（6 例）及びアフリベルセプト Q8W 群の 0.6%（2 例）では 1 時間を超える 30 文字以上の視力低下に至った AESI が認められた。

- 眼内炎が計 3 例（本剤 Q8W 群 2 例及びアフリベルセプト Q8W 群 1 例）に 3 件認められた。すべて重篤と判断され，重症度は中等度又は高度であった。いずれも治験薬との因果関係は否定され，56 週時までに軽快，回復又は回復したが後遺症ありとなった。内，1 例では治験薬の投与中止に至った。
- 試験眼に発現した眼内炎症の発現頻度は本剤 Q8W 群，本剤 PTI 群及びアフリベルセプト Q8W 群でそれぞれ 0.9%（3 例），0.6%（2 例）及び 0.3%（1 例）であり，発現頻度は低かった。いずれの群にも網膜血管炎又は網膜血管閉塞事象を伴う眼内炎症は認められなかった。30 文字以上の視力低下に関連した眼内炎症は両本剤群で認められなかった。
- 眼以外に発現した有害事象の発現頻度は本剤 Q8W 群，本剤 PTI 群及びアフリベルセプト Q8W 群でそれぞれ 59.6%，54.9%及び 59.6%であり，投与群間で同様であった。
- いずれかの群の 5%以上で眼以外に発現した有害事象（本剤 Q8W 群，本剤 PTI 群及びアフリベルセプト Q8W 群別）は，上咽頭炎（7.3%，6.9%及び 9.9%），尿路感染（2.2%，3.4%及び 6.7%），頭痛（5.0%，2.8%及び 1.6%）及び高血圧（4.7%，6.0%及び 3.8%）であった（表 2.7.6.2-34）。
- 眼以外に発現した重症度が高度の有害事象の発現頻度は，本剤 Q8W 群，本剤 PTI 群及びアフリベルセプト Q8W 群で，それぞれ 10.4%，9.4%及び 12.4%であった。
- 眼以外に発現した重篤な有害事象の発現頻度は，本剤 Q8W 群，本剤 PTI 群及びアフリベルセプト Q8W 群でそれぞれ 16.4%，12.2%及び 16.6%であり，投与群間で同様であった。一定の傾向は認められなかった。
- 死亡は 10 例で認められ，本剤 Q8W 群及びアフリベルセプト Q8W 群で各 1.6%（5 例）であり，いずれも治験薬投与との関連は否定された。
- APTC で定義された動脈血栓塞栓事象の発現頻度は本剤 Q8W 群，本剤 PTI 群及びアフリベルセプト Q8W 群でそれぞれ 1.3%（4 例），0.6%（2 例）及び 1.6%（5 例）であり，発現頻度は投与群間で同様に低かった。
- 臨床検査値において，投与群間で臨床的に重要な不均衡は認められなかった。
- ADA 陽性の発現頻度は全体として低かった。本剤の投与を受け，投与後の評価が可能であった患者の内，本剤投与後に抗体が検出された（Treatment emergent ADA）患者は 6.9%（43/624 例，本剤 Q8W 群及び本剤 PTI 群でそれぞれ 20 例及び 23 例）であり，本剤投与後に抗体価が 4 倍以上，上昇した（treatment boosted ADA）患者はいなかった。ADA 陽性例の数が少なかったため評価に限界があるものの，ADA の安全性及び有効性に対する影響は認められなかった。

表 2.7.6.1.9.8-1 有害事象の概況（GR40398試験）

	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Faricimab 6 mg All (N=636)	Aflibercept 2 mg Q8W (N=314)
Total number of patients with at least one AE	256 (80.8%)	233 (73.0%)	489 (76.9%)	244 (77.7%)
Total number of AEs	1107	875	1982	914
Total number of patients with at least one SAE	67 (21.1%)	49 (15.4%)	116 (18.2%)	58 (18.5%)
Total number of SAEs	101	79	180	95
Total number of deaths	5 (1.6%)	0	5 (0.8%)	5 (1.6%)
Total number of patients withdrawn from study due to an AE	6 (1.9%)	1 (0.3%)	7 (1.1%)	3 (1.0%)
Total number of patients withdrawn from study treatment due to an AE	4 (1.3%)	4 (1.3%)	8 (1.3%)	4 (1.3%)
Total number of patients with at least one AESI	15 (4.7%)	11 (3.4%)	26 (4.1%)	7 (2.2%)
Ocular events: study eye total number of patients with at least one				
AE	137 (43.2%)	119 (37.3%)	256 (40.3%)	113 (36.0%)
SAE	9 (2.8%)	10 (3.1%)	19 (3.0%)	6 (1.9%)
AE leading to withdrawal from study treatment	0	3 (0.9%)	3 (0.5%)	1 (0.3%)
Treatment related AEs	8 (2.5%)	8 (2.5%)	16 (2.5%)	14 (4.5%)
Treatment related SAEs	0	1 (0.3%)	1 (0.2%)	0
AE of Special Interest	9 (2.8%)	9 (2.8%)	18 (2.8%)	5 (1.6%)
Drop in VA score >=30	6 (1.9%)	6 (1.9%)	12 (1.9%)	2 (0.6%)
Associated with severe IOI	1 (0.3%)	0	1 (0.2%)	1 (0.3%)
Intervention req. to prevent permanent vision loss	2 (0.6%)	3 (0.9%)	5 (0.8%)	2 (0.6%)
Suspected transmission of infectious agent by study drug	0	0	0	0
Ocular events: fellow eye total number of patients with at least one				
AE	128 (40.4%)	91 (28.5%)	219 (34.4%)	105 (33.4%)
SAE	6 (1.9%)	4 (1.3%)	10 (1.6%)	3 (1.0%)
AE of Special Interest	6 (1.9%)	2 (0.6%)	8 (1.3%)	2 (0.6%)
Drop in VA score >=30	6 (1.9%)	2 (0.6%)	8 (1.3%)	2 (0.6%)
Associated with severe IOI	0	0	0	0
Intervention req. to prevent permanent vision loss	0	0	0	0
Suspected transmission of infectious agent by study drug	0	0	0	0
Non-ocular events total number of patients with at least one				
AE	189 (59.6%)	175 (54.9%)	364 (57.2%)	187 (59.6%)
SAE	52 (16.4%)	39 (12.2%)	91 (14.3%)	52 (16.6%)
AE leading to withdrawal from study treatment	4 (1.3%)	1 (0.3%)	5 (0.8%)	3 (1.0%)
AE of Special Interest	0	0	0	0
Elevated ALT or AST with either elevated bilirubin or clinical jaundice	0	0	0	0
Adjudicated APTC events	4 (1.3%)	2 (0.6%)	6 (0.9%)	5 (1.6%)
Non-fatal MI	0	0	0	2 (0.6%)
Non-fatal Stroke	1 (0.3%)	2 (0.6%)	3 (0.5%)	1 (0.3%)
Death	3 (0.9%)	0	3 (0.5%)	2 (0.6%)

表 2.7.6.1.9.8-1 有害事象の概況（GR40398試験）（続）

AESI=Adverse Event of Special Interest; APTC = Antiplatelet Trialists' Collaboration; IOI=Intraocular Inflammation; MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W); SAE=Serious Adverse Event; VA = Visual Acuity; MedDRA = Medical Dictionary for Regulatory Activities.
APTC events are defined as non-fatal strokes or non-fatal myocardial infarctions or vascular deaths (including deaths of unknown cause). Investigator text for AEs encoded using MedDRA version 23.1.
Drop in VA score >=30 is defined as causing a decrease of >=30 VA score lasting more than 1 hour.
Intervention req. to prevent permanent vision loss is defined as required surgical or medical intervention to prevent permanent loss of sight.
Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for the "Total number of AEs" row in which multiple occurrences of the same AE are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

Program: root/clinical_studies/RO6867461/CDT70122/share/data_analysis/prod/program/t_ae_oview.sas
Output: root/clinical_studies/RO6867461/CDT70122/GR40398/data_analysis/CSR_Primary/prod/output/t_ae_oview_W56_SE_19OCT2020_40398.out
22JAN2021 6:00

[5.3.5.1-DME-3 Table 21を再掲]

2.7.6.1.9.9 その他の結果（COVID-19の影響）

COVID-19のパンデミックは，試験実施中に患者の安全性を監視・管理することに有意な影響を及ぼさなかった。また，COVID-19に関連する一覧を追加した以外に計画された安全性の解析に変更はなかった。

COVID-19の影響を以下に要約した。

- COVID-19 パンデミックによるデータの整合性に対するリスクを軽減するための対策が行われた。
- リスクを軽減するための対策により，安全性データ及び安全性評価における欠落を最小限に抑えることができた。
- 欠測があったものの，本剤の有効性及び安全性データはいずれも解釈可能であり，本剤のベネフィット・リスクプロファイルを明らかにすることができた。

2.7.6.1.9.10 結論

DME 患者を対象とした GR40398試験では，事前に設定した主要評価項目を満たし，BCVAにおけるベースラインから48/52/56週時点の変化量平均値について，両本剤投与レジメンのアフリベルセプトに対する非劣性が検証された。

52週時に ETDRS DRSS のベースラインからの臨床的に意味のある2段階以上及び3段階以上の改善を達成した患者の割合は，本剤群とアフリベルセプト群で同様であった。52週時にETDRS DRSS の2段階以上の改善が認められた患者の割合は，アフリベルセプト群と比較して，本剤 Q8W 群と PTI 群のいずれについても非劣性を示さなかった。

52週時の最長 Q16W で本剤を投与した患者群における本剤の硝子体内投与が Q4W，Q8W，Q12W，Q16W であった患者の割合はそれぞれ13.3%，15.6%，20.1%，51.0%であった。解剖学的評価を追加することにより，Q16W までの投与間隔で本剤の有効性を更に裏付けることができる。

本剤を Q8W 及び PTI で投与された患者は，アフリベルセプト Q8W を投与された患者と比較して，52週時の NEI VFQ-25スコア，近距離活動スコア，遠距離活動スコア，及び運転スコアの平均改善が同程度であることが示された。NEI VFQ-25スコアの臨床的に意味のある変化の閾値を超える改善が認められた患者の割合は，各群で同等であった。

投与中止に至った有害事象の発現頻度が低いことから，本剤はアフリベルセプトと同等の安全性プロファイルであり，全般的に忍容性は良好であった。新たな安全性シグナルは確認されなかった。

ファリシマブに対する ADA の発現頻度は低かった。ADA の全身曝露量，安全性及び有効性に対する明らかな影響は認められなかった。

2.7.6.2 付録

表 2.7.6.2-1 有害事象の集計（BP28936試験—パート A）

Summary of Adverse Events by System Organ Class and Preferred Term
Protocol: BP28936
Study Part: Single Ascending Dose
Population: All Patients

Category of Adverse Events MedDRA System Organ Class MedDRA Preferred Term	RO6867461 0.5 mg (SD) (N=3)	RO6867461 1.5 mg (SD) (N=3)	RO6867461 3.0 mg (SD) (N=3)	RO6867461 6.0 mg (SD) (N=3)	All Patients (N=12)
Overall total number of events	0	5	12	10	27
Total number of patients with at least one adverse event	0	2 (66.7%)	3 (100.0%)	2 (66.7%)	7 (58.3%)
Ocular (Study Eye)					
Total number of patients with at least one adverse event	0	0	2 (66.7%)	2 (66.7%)	4 (33.3%)
Total number of events	0	0	4	3	7
眼障害					
Total number of patients with at least one adverse event	0	0	2 (66.7%)	2 (66.7%)	4 (33.3%)
Total number of events	0	0	4	3	7
眼瞼炎	0	0	2 (66.7%)	0	2 (16.7%)
結膜出血	0	0	0	1 (33.3%)	1 (8.3%)
眼痛	0	0	0	1 (33.3%)	1 (8.3%)
眼部腫脹	0	0	0	1 (33.3%)	1 (8.3%)
虹彩毛様体炎	0	0	1 (33.3%)	0	1 (8.3%)
霧視	0	0	1 (33.3%)	0	1 (8.3%)
Ocular (Non-Study Eye)					
Total number of patients with at least one adverse event	0	1 (33.3%)	2 (66.7%)	0	3 (25.0%)
Total number of events	0	2	6	0	8
眼障害					
Total number of patients with at least one adverse event	0	1 (33.3%)	2 (66.7%)	0	3 (25.0%)
Total number of events	0	1	6	0	7
眼瞼炎	0	0	2 (66.7%)	0	2 (16.7%)
結膜出血	0	0	1 (33.3%)	0	1 (8.3%)
眼乾燥	0	0	1 (33.3%)	0	1 (8.3%)
網膜出血	0	1 (33.3%)	0	0	1 (8.3%)
霧視	0	0	1 (33.3%)	0	1 (8.3%)
硝子体浮遊物	0	0	1 (33.3%)	0	1 (8.3%)

Percentages are based on N.
Multiple occurences of the same AE in one individual counted only once except for "total number of events" where all events are being counted.
Investigator text for Adverse Events encoded using MedDRA Version 18.0.

表 2.7.6.2-1 有害事象の集計（BP28936試験—パート A）（続）

Summary of Adverse Events by System Organ Class and Preferred Term
Protocol: BP28936
Study Part: Single Ascending Dose
Population: All Patients

Category of Adverse Events MedDRA System Organ Class MedDRA Preferred Term	RO6867461 0.5 mg (SD) (N=3)	RO6867461 1.5 mg (SD) (N=3)	RO6867461 3.0 mg (SD) (N=3)	RO6867461 6.0 mg (SD) (N=3)	All Patients (N=12)
感染症および寄生虫症					
Total number of patients with at least one adverse event	0	1 (33.3%)	0	0	1 (8.3%)
Total number of events	0	1	0	0	1
結膜炎	0	1 (33.3%)	0	0	1 (8.3%)
Systemic					
Total number of patients with at least one adverse event	0	1 (33.3%)	2 (66.7%)	2 (66.7%)	5 (41.7%)
Total number of events	0	3	2	7	12
感染症および寄生虫症					
Total number of patients with at least one adverse event	0	0	0	1 (33.3%)	1 (8.3%)
Total number of events	0	0	0	1	1
副鼻腔炎	0	0	0	1 (33.3%)	1 (8.3%)
神経系障害					
Total number of patients with at least one adverse event	0	0	0	2 (66.7%)	2 (16.7%)
Total number of events	0	0	0	3	3
浮動性めまい	0	0	0	1 (33.3%)	1 (8.3%)
頭痛	0	0	0	1 (33.3%)	1 (8.3%)
呼吸器、胸郭および縦隔障害					
Total number of patients with at least one adverse event	0	1 (33.3%)	0	1 (33.3%)	2 (16.7%)
Total number of events	0	1	0	1	2
誤嚥性肺炎	0	1 (33.3%)	0	0	1 (8.3%)
気道うっ血	0	0	0	1 (33.3%)	1 (8.3%)
心臓障害					
Total number of patients with at least one adverse event	0	0	1 (33.3%)	0	1 (8.3%)
Total number of events	0	0	1	0	1
冠動脈疾患	0	0	1 (33.3%)	0	1 (8.3%)
胃腸障害					
Total number of patients with at least one adverse event	0	1 (33.3%)	0	0	1 (8.3%)
Total number of events	0	1	0	0	1
胃腸出血	0	1 (33.3%)	0	0	1 (8.3%)

Percentages are based on N.
Multiple occurences of the same AE in one individual counted only once except for "total number of events" where all events are being counted.
Investigator text for Adverse Events encoded using MedDRA Version 18.0.

表 2.7.6.2-1 有害事象の集計（BP28936試験—パート A）（続）

Summary of Adverse Events by System Organ Class and Preferred Term
Protocol: BP28936
Study Part: Single Ascending Dose
Population: All Patients

Category of Adverse Events MedDRA System Organ Class MedDRA Preferred Term	RO6867461 0.5 mg (SD) (N=3)	RO6867461 1.5 mg (SD) (N=3)	RO6867461 3.0 mg (SD) (N=3)	RO6867461 6.0 mg (SD) (N=3)	All Patients (N=12)
一般・全身障害および投与部位の状態					
Total number of patients with at least one adverse event	0	0	1 (33.3%)	0	1 (8.3%)
Total number of events	0	0	1	0	1
疲労	0	0	1 (33.3%)	0	1 (8.3%)
筋骨格系および結合組織障害					
Total number of patients with at least one adverse event	0	0	0	1 (33.3%)	1 (8.3%)
Total number of events	0	0	0	1	1
背部痛	0	0	0	1 (33.3%)	1 (8.3%)
精神障害					
Total number of patients with at least one adverse event	0	1 (33.3%)	0	0	1 (8.3%)
Total number of events	0	1	0	0	1
アルコール離脱症候群	0	1 (33.3%)	0	0	1 (8.3%)
血管障害					
Total number of patients with at least one adverse event	0	0	0	1 (33.3%)	1 (8.3%)
Total number of events	0	0	0	1	1
高血圧	0	0	0	1 (33.3%)	1 (8.3%)

Percentages are based on N.
Multiple occurences of the same AE in one individual counted only once except for "total number of events" where all events are being counted.
Investigator text for Adverse Events encoded using MedDRA Version 18.0.

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[5.3.3.2-1 Table 11を改変]

表 2.7.6.2-2 有害事象の集計（BP28936試験—パート B）

Summary of Adverse Events by System Organ Class and Preferred Term
Protocol: BP28936
Study Part: Multiple Ascending Dose
Population: All Patients

Category of Adverse Events MedDRA System Organ Class MedDRA Preferred Term	RO6867461 3.0 mg (MD) (N=6)	RO6867461 6.0 mg (MD) (N=6)	All Patients (N=12)
Overall total number of events	20	4	24
Total number of patients with at least one adverse event	5 (83.3%)	2 (33.3%)	7 (58.3%)
Ocular (Study Eye)			
Total number of patients with at least one adverse event	4 (66.7%)	1 (16.7%)	5 (41.7%)
Total number of events	6	1	7
感染症および寄生虫症			
Total number of patients with at least one adverse event	1 (16.7%)	0	1 (8.3%)
Total number of events	1	0	1
結膜炎	1 (16.7%)	0	1 (8.3%)
眼障害			
Total number of patients with at least one adverse event	3 (50.0%)	0	3 (25.0%)
Total number of events	4	0	4
眼痛	1 (16.7%)	0	1 (8.3%)
眼充血	1 (16.7%)	0	1 (8.3%)
羞明	1 (16.7%)	0	1 (8.3%)
霧視	1 (16.7%)	0	1 (8.3%)
傷害、中毒および処置合併症			
Total number of patients with at least one adverse event	1 (16.7%)	0	1 (8.3%)
Total number of events	1	0	1
角膜擦過傷	1 (16.7%)	0	1 (8.3%)
臨床検査			
Total number of patients with at least one adverse event	0	1 (16.7%)	1 (8.3%)
Total number of events	0	1	1
眼圧上昇	0	1 (16.7%)	1 (8.3%)
Ocular (Non-Study Eye)			
Total number of patients with at least one adverse event	1 (16.7%)	1 (16.7%)	2 (16.7%)
Total number of events	1	1	2

Percentages are based on N.
Multiple occurences of the same AE in one individual counted only once except for "total number of events" where all events are being counted.
Investigator text for Adverse Events encoded using MedDRA Version 18.0.

表 2.7.6.2-2 有害事象の集計（BP28936試験—パート B）（続）

Summary of Adverse Events by System Organ Class and Preferred Term
Protocol: BP28936
Study Part: Multiple Ascending Dose
Population: All Patients

Category of Adverse Events MedDRA System Organ Class MedDRA Preferred Term	RO6867461 3.0 mg (MD) (N=6)	RO6867461 6.0 mg (MD) (N=6)	All Patients (N=12)
感染症および寄生虫症			
Total number of patients with at least one adverse event	1 (16.7%)	0	1 (8.3%)
Total number of events	1	0	1
結膜炎	1 (16.7%)	0	1 (8.3%)
眼障害			
Total number of patients with at least one adverse event	0	1 (16.7%)	1 (8.3%)
Total number of events	0	1	1
結膜出血	0	1 (16.7%)	1 (8.3%)
Systemic			
Total number of patients with at least one adverse event	3 (50.0%)	1 (16.7%)	4 (33.3%)
Total number of events	13	2	15
感染症および寄生虫症			
Total number of patients with at least one adverse event	3 (50.0%)	0	3 (25.0%)
Total number of events	5	0	5
耳感染	1 (16.7%)	0	1 (8.3%)
歯感染	1 (16.7%)	0	1 (8.3%)
上気道感染	1 (16.7%)	0	1 (8.3%)
尿路感染	1 (16.7%)	0	1 (8.3%)
傷害、中毒および処置合併症			
Total number of patients with at least one adverse event	0	1 (16.7%)	1 (8.3%)
Total number of events	0	1	1
靭帯断裂	0	1 (16.7%)	1 (8.3%)
臨床検査			
Total number of patients with at least one adverse event	1 (16.7%)	0	1 (8.3%)
Total number of events	3	0	3
ヘマトクリット減少	1 (16.7%)	0	1 (8.3%)
ヘモグロビン減少	1 (16.7%)	0	1 (8.3%)
血沈亢進	1 (16.7%)	0	1 (8.3%)

Percentages are based on N.
Multiple occurences of the same AE in one individual counted only once except for "total number of events" where all events are being counted.
Investigator text for Adverse Events encoded using MedDRA Version 18.0.

表 2.7.6.2-2 有害事象の集計（BP28936試験—パート B）（続）

Summary of Adverse Events by System Organ Class and Preferred Term
Protocol: BP28936
Study Part: Multiple Ascending Dose
Population: All Patients

Category of Adverse Events MedDRA System Organ Class MedDRA Preferred Term	RO6867461 3.0 mg (MD) (N=6)	RO6867461 6.0 mg (MD) (N=6)	All Patients (N=12)
胃腸障害			
Total number of patients with at least one adverse event	1 (16.7%)	0	1 (8.3%)
Total number of events	1	0	1
悪心	1 (16.7%)	0	1 (8.3%)
免疫系障害			
Total number of patients with at least one adverse event	1 (16.7%)	0	1 (8.3%)
Total number of events	1	0	1
薬物過敏症	1 (16.7%)	0	1 (8.3%)
筋骨格系および結合組織障害			
Total number of patients with at least one adverse event	1 (16.7%)	0	1 (8.3%)
Total number of events	1	0	1
背部痛	1 (16.7%)	0	1 (8.3%)
神経系障害			
Total number of patients with at least one adverse event	1 (16.7%)	0	1 (8.3%)
Total number of events	1	0	1
嗜眠	1 (16.7%)	0	1 (8.3%)
精神障害			
Total number of patients with at least one adverse event	1 (16.7%)	0	1 (8.3%)
Total number of events	1	0	1
不眠症	1 (16.7%)	0	1 (8.3%)
生殖系および乳房障害			
Total number of patients with at least one adverse event	0	1 (16.7%)	1 (8.3%)
Total number of events	0	1	1
前立腺腫大	0	1 (16.7%)	1 (8.3%)

Percentages are based on N.
Multiple occurences of the same AE in one individual counted only once except for "total number of events" where all events are being counted.
Investigator text for Adverse Events encoded using MedDRA Version 18.0.

[5.3.3.2-1 Table 12を改変]

表 2.7.6.2-3 有害事象の集計（BP29647試験）

Summary of Adverse Events by System Organ Class and Preferred Term, Safety-Evaluable Patients
Protocol: BP29647

MedDRA System Organ Class MedDRA Preferred Term	0.5 mg ranibizumab Monthly (N=67)	1.5 mg RO6867461 Monthly (N=46)	6 mg RO6867461 Monthly (N=39)	6 mg RO6867461 Monthly(Wk12), Bi-Monthly (Wk28) (N=46)	0.5 mg ranibizumab Monthly(Wk8), 6 mg RO6867461 Monthly (Wk32) (N=64)
Total number of patients with at least one AE	51 (76.1%)	39 (84.8%)	31 (79.5%)	39 (84.8%)	54 (84.4%)
Overall total number of events	191	187	131	150	193
眼障害					
Total number of patients with at least one AE	39 (58.2%)	25 (54.3%)	21 (53.8%)	27 (58.7%)	34 (53.1%)
Total number of events	75	51	51	66	65
結膜出血	14 (20.9%)	4 (8.7%)	6 (15.4%)	6 (13.0%)	6 (9.4%)
新生血管加齢黄斑変性	7 (10.4%)	4 (8.7%)	3 (7.7%)	3 (6.5%)	5 (7.8%)
硝子体剥離	3 (4.5%)	5 (10.9%)	3 (7.7%)	5 (10.9%)	4 (6.3%)
眼痛	2 (3.0%)	4 (8.7%)	2 (5.1%)	5 (10.9%)	3 (4.7%)
硝子体浮遊物	2 (3.0%)	3 (6.5%)	4 (10.3%)	3 (6.5%)	1 (1.6%)
白内障	2 (3.0%)	2 (4.3%)	2 (5.1%)	2 (4.3%)	2 (3.1%)
眼刺激	0	1 (2.2%)	4 (10.3%)	4 (8.7%)	1 (1.6%)
網膜出血	3 (4.5%)	2 (4.3%)	1 (2.6%)	1 (2.2%)	3 (4.7%)
霧視	2 (3.0%)	1 (2.2%)	3 (7.7%)	2 (4.3%)	2 (3.1%)
後嚢部混濁	2 (3.0%)	1 (2.2%)	3 (7.7%)	0	1 (1.6%)
網膜色素上皮裂孔	3 (4.5%)	0	2 (5.1%)	2 (4.3%)	0
眼瞼炎	0	1 (2.2%)	2 (5.1%)	1 (2.2%)	2 (3.1%)
乾性加齢黄斑変性	4 (6.0%)	0	1 (2.6%)	0	1 (1.6%)
視力障害	1 (1.5%)	1 (2.2%)	1 (2.6%)	2 (4.3%)	1 (1.6%)
前房のフレア	3 (4.5%)	1 (2.2%)	0	0	1 (1.6%)
流涙増加	1 (1.5%)	0	1 (2.6%)	3 (6.5%)	0
点状角膜炎	0	0	0	0	5 (7.8%)
視力低下	1 (1.5%)	2 (4.3%)	0	2 (4.3%)	0
前房内細胞	2 (3.0%)	0	2 (5.1%)	0	0
核性白内障	2 (3.0%)	0	0	0	2 (3.1%)
眼乾燥	1 (1.5%)	0	0	2 (4.3%)	1 (1.6%)
眼そう痒症	2 (3.0%)	1 (2.2%)	0	1 (2.2%)	0
硝子体出血	2 (3.0%)	1 (2.2%)	0	1 (2.2%)	0

Percentages are based on N.
Multiple occurences of the same AE in one individual counted only once except for "total number of events" where all events are being counted.
Investigator text for Adverse Events encoded using MedDRA Version 20.1.

表 2.7.6.2-3 有害事象の集計（BP29647試験）（続）

Summary of Adverse Events by System Organ Class and Preferred Term, Safety-Evaluable Patients
Protocol: BP29647

MedDRA System Organ Class MedDRA Preferred Term	0.5 mg ranibizumab Monthly (N=67)	1.5 mg RO6867461 Monthly (N=46)	6 mg RO6867461 Monthly (N=39)	6 mg RO6867461 Monthly(Wk12), Bi-Monthly (Wk28) (N=46)	0.5 mg ranibizumab Monthly(Wk8), 6 mg RO6867461 Monthly (Wk32) (N=64)
光視症	1 (1.5%)	0	1 (2.6%)	1 (2.2%)	0
網膜滲出物	0	2 (4.3%)	0	0	1 (1.6%)
加齢黄斑変性	2 (3.0%)	0	0	0	0
嚢下白内障	0	0	1 (2.6%)	0	1 (1.6%)
複視	2 (3.0%)	0	0	0	0
黄斑線維症	1 (1.5%)	0	0	1 (2.2%)	0
黄斑円孔	0	1 (2.2%)	0	0	1 (1.6%)
眼部不快感	0	0	1 (2.6%)	0	1 (1.6%)
羞明	1 (1.5%)	0	0	1 (2.2%)	0
網膜下液	2 (3.0%)	0	0	0	0
閉塞隅角緑内障	0	1 (2.2%)	0	0	0
皮質白内障	0	0	0	0	1 (1.6%)
霰粒腫	0	0	0	0	1 (1.6%)
結膜充血	0	0	0	1 (2.2%)	0
結膜浮腫	0	1 (2.2%)	0	0	0
角膜障害	0	1 (2.2%)	0	0	0
角膜混濁	1 (1.5%)	0	0	0	0
角膜色素沈着	0	0	0	1 (2.2%)	0
角膜瘢痕	0	0	0	1 (2.2%)	0
嚢胞様黄斑浮腫	0	0	0	1 (2.2%)	0
網膜色素上皮剥離	0	0	1 (2.6%)	0	0
異常３色覚	0	0	0	1 (2.2%)	0
眼脂	0	0	0	0	1 (1.6%)
眼出血	0	1 (2.2%)	0	0	0
眼の炎症	0	1 (2.2%)	0	0	0
眼瞼刺激	0	0	0	0	1 (1.6%)
眼瞼浮腫	0	0	0	1 (2.2%)	0
眼の異物感	0	0	0	0	1 (1.6%)
緑内障	0	0	0	0	1 (1.6%)
虹彩炎	0	0	0	0	1 (1.6%)

Percentages are based on N.
Multiple occurences of the same AE in one individual counted only once except for "total number of events" where all events are being counted.
Investigator text for Adverse Events encoded using MedDRA Version 20.1.

表 2.7.6.2-3 有害事象の集計（BP29647試験）（続）

Summary of Adverse Events by System Organ Class and Preferred Term, Safety-Evaluable Patients
Protocol: BP29647

MedDRA System Organ Class MedDRA Preferred Term	0.5 mg ranibizumab Monthly (N=67)	1.5 mg RO6867461 Monthly (N=46)	6 mg RO6867461 Monthly (N=39)	6 mg RO6867461 Monthly(Wk12), Bi-Monthly (Wk28) (N=46)	0.5 mg ranibizumab Monthly(Wk8), 6 mg RO6867461 Monthly (Wk32) (N=64)
角膜後面沈着物	0	1 (2.2%)	0	0	0
黄斑症	0	0	0	0	1 (1.6%)
マイボーム腺機能不全	0	0	0	1 (2.2%)	0
変視症	0	0	0	1 (2.2%)	0
開放隅角緑内障	1 (1.5%)	0	0	0	0
網膜血管瘤	1 (1.5%)	0	0	0	0
網膜動脈塞栓症	0	0	1 (2.6%)	0	0
網膜変性	0	0	0	1 (2.2%)	0
網膜色素脱失	0	0	0	0	1 (1.6%)
網膜ドルーゼン	0	1 (2.2%)	0	0	0
網膜梗塞	0	0	1 (2.6%)	0	0
網膜瘢痕	0	0	0	0	1 (1.6%)
網膜静脈閉塞	0	0	0	0	1 (1.6%)
網膜分離症	0	0	0	1 (2.2%)	0
網膜下線維症	0	1 (2.2%)	0	0	0
硝子体混濁	0	1 (2.2%)	0	0	0
感染症および寄生虫症					
Total number of patients with at least one AE	21 (31.3%)	21 (45.7%)	8 (20.5%)	15 (32.6%)	22 (34.4%)
Total number of events	33	34	13	18	35
尿路感染	6 (9.0%)	11 (23.9%)	2 (5.1%)	0	3 (4.7%)
上咽頭炎	9 (13.4%)	4 (8.7%)	1 (2.6%)	1 (2.2%)	5 (7.8%)
インフルエンザ	3 (4.5%)	3 (6.5%)	1 (2.6%)	0	1 (1.6%)
副鼻腔炎	2 (3.0%)	1 (2.2%)	0	1 (2.2%)	2 (3.1%)
上気道感染	1 (1.5%)	1 (2.2%)	0	2 (4.3%)	2 (3.1%)
気管支炎	0	2 (4.3%)	2 (5.1%)	0	1 (1.6%)
膀胱炎	1 (1.5%)	1 (2.2%)	0	0	3 (4.7%)
肺炎	0	1 (2.2%)	1 (2.6%)	3 (6.5%)	0
歯膿瘍	1 (1.5%)	2 (4.3%)	1 (2.6%)	0	1 (1.6%)
ウイルス性胃腸炎	3 (4.5%)	0	0	1 (2.2%)	0

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Investigator text for Adverse Events encoded using MedDRA Version 20.1.

表 2.7.6.2-3 有害事象の集計（BP29647試験）（続）

Summary of Adverse Events by System Organ Class and Preferred Term, Safety-Evaluable Patients
Protocol: BP29647

MedDRA System Organ Class MedDRA Preferred Term	0.5 mg ranibizumab Monthly (N=67)	1.5 mg RO6867461 Monthly (N=46)	6 mg RO6867461 Monthly (N=39)	6 mg RO6867461 Monthly(Wk12), Bi-Monthly (Wk28) (N=46)	0.5 mg ranibizumab Monthly(Wk8), 6 mg RO6867461 Monthly (Wk32) (N=64)
急性副鼻腔炎	0	0	0	1 (2.2%)	1 (1.6%)
蜂巣炎	1 (1.5%)	0	0	0	1 (1.6%)
眼内炎	0	1 (2.2%)	0	0	1 (1.6%)
帯状疱疹	0	0	0	1 (2.2%)	1 (1.6%)
喉頭炎	0	0	0	2 (4.3%)	0
歯感染	0	0	0	1 (2.2%)	1 (1.6%)
感染性関節炎	0	0	0	1 (2.2%)	0
結膜炎	0	0	0	1 (2.2%)	0
角膜感染	0	0	0	0	1 (1.6%)
憩室炎	0	0	1 (2.6%)	0	0
真菌性耳感染	0	1 (2.2%)	0	0	0
大腸菌性尿路感染	0	0	0	0	1 (1.6%)
真菌感染	0	0	1 (2.6%)	0	0
せつ	0	0	0	0	1 (1.6%)
ガードネレラ感染	0	0	0	1 (2.2%)	0
胃腸炎	0	0	0	0	1 (1.6%)
感染性大腸炎	0	1 (2.2%)	0	0	0
腎感染	0	0	0	0	1 (1.6%)
限局性感染	1 (1.5%)	0	0	0	0
口腔ヘルペス	0	0	0	1 (2.2%)	0
急性中耳炎	0	0	0	1 (2.2%)	0
細菌性中耳炎	0	0	0	0	1 (1.6%)
レンサ球菌性咽頭炎	0	1 (2.2%)	0	0	0
気道感染	0	0	1 (2.6%)	0	0
鼻炎	1 (1.5%)	0	0	0	0
ウイルス感染	1 (1.5%)	0	0	0	0

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表 2.7.6.2-3 有害事象の集計（BP29647試験）（続）

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Protocol: BP29647

MedDRA System Organ Class MedDRA Preferred Term	0.5 mg ranibizumab Monthly (N=67)	1.5 mg RO6867461 Monthly (N=46)	6 mg RO6867461 Monthly (N=39)	6 mg RO6867461 Monthly(Wk12), Bi-Monthly (Wk28) (N=46)	0.5 mg ranibizumab Monthly(Wk8), 6 mg RO6867461 Monthly (Wk32) (N=64)
筋骨格系および結合組織障害					
Total number of patients with at least one AE	9 (13.4%)	6 (13.0%)	3 (7.7%)	4 (8.7%)	11 (17.2%)
Total number of events	10	8	7	7	20
背部痛	1 (1.5%)	2 (4.3%)	1 (2.6%)	0	3 (4.7%)
四肢痛	2 (3.0%)	0	0	2 (4.3%)	1 (1.6%)
筋骨格痛	0	0	1 (2.6%)	1 (2.2%)	2 (3.1%)
関節炎	0	0	1 (2.6%)	0	2 (3.1%)
変形性関節症	1 (1.5%)	0	0	1 (2.2%)	1 (1.6%)
リウマチ性多発筋痛	1 (1.5%)	1 (2.2%)	0	0	1 (1.6%)
変形性脊椎症	1 (1.5%)	0	0	0	2 (3.1%)
関節痛	0	1 (2.2%)	1 (2.6%)	0	0
関節腫脹	0	2 (4.3%)	0	0	0
筋痙縮	1 (1.5%)	1 (2.2%)	0	0	0
筋骨格硬直	0	0	0	0	2 (3.1%)
頚部痛	0	0	1 (2.6%)	1 (2.2%)	0
脊柱管狭窄症	0	0	0	1 (2.2%)	1 (1.6%)
滑液包炎	1 (1.5%)	0	0	0	0
胤径部痛	0	0	0	0	1 (1.6%)
椎間板突出	0	0	1 (2.6%)	0	0
筋攣縮	0	0	0	0	1 (1.6%)
筋肉痛	0	1 (2.2%)	0	0	0
骨壊死	0	0	1 (2.6%)	0	0
顎痛	1 (1.5%)	0	0	0	0
関節リウマチ	1 (1.5%)	0	0	0	0
脊椎炎	0	0	0	0	1 (1.6%)

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Investigator text for Adverse Events encoded using MedDRA Version 20.1.

表 2.7.6.2-3 有害事象の集計（BP29647試験）（続）

Summary of Adverse Events by System Organ Class and Preferred Term, Safety-Evaluable Patients
Protocol: BP29647

MedDRA System Organ Class MedDRA Preferred Term	0.5 mg ranibizumab Monthly (N=67)	1.5 mg RO6867461 Monthly (N=46)	6 mg RO6867461 Monthly (N=39)	6 mg RO6867461 Monthly(Wk12), Bi-Monthly (Wk28) (N=46)	0.5 mg ranibizumab Monthly(Wk8), 6 mg RO6867461 Monthly (Wk32) (N=64)
傷害、中毒および処置合併症					
Total number of patients with at least one AE	4 (6.0%)	8 (17.4%)	4 (10.3%)	5 (10.9%)	7 (10.9%)
Total number of events	6	11	10	6	12
転倒	2 (3.0%)	2 (4.3%)	1 (2.6%)	3 (6.5%)	3 (4.7%)
挫傷	0	1 (2.2%)	1 (2.6%)	1 (2.2%)	1 (1.6%)
角膜擦過傷	0	0	1 (2.6%)	0	2 (3.1%)
節足動物咬傷	0	1 (2.2%)	0	0	1 (1.6%)
足骨折	0	1 (2.2%)	0	0	1 (1.6%)
裂傷	0	1 (2.2%)	0	0	1 (1.6%)
処置による疼痛	1 (1.5%)	1 (2.2%)	0	0	0
手首関節骨折	0	1 (2.2%)	1 (2.6%)	0	0
骨挫傷	0	0	1 (2.6%)	0	0
顔面骨骨折	1 (1.5%)	0	0	0	0
手骨折	0	0	1 (2.6%)	0	0
頭部損傷	0	0	0	0	1 (1.6%)
前房出血	0	0	1 (2.6%)	0	0
切開部位痛	1 (1.5%)	0	0	0	0
下肢骨折	0	0	0	1 (2.2%)	0
多発骨折	0	1 (2.2%)	0	0	0
過量投与	0	1 (2.2%)	0	0	0
交通事故	1 (1.5%)	0	0	0	0
各種物質毒性	0	0	0	1 (2.2%)	0
上肢骨折	0	1 (2.2%)	0	0	0

Percentages are based on N.
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Investigator text for Adverse Events encoded using MedDRA Version 20.1.

表 2.7.6.2-3 有害事象の集計（BP29647試験）（続）

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Protocol: BP29647

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呼吸器、胸郭および縦隔障害					
Total number of patients with at least one AE	8 (11.9%)	8 (17.4%)	2 (5.1%)	3 (6.5%)	7 (10.9%)
Total number of events	14	16	3	3	7
副鼻腔うっ血	2 (3.0%)	1 (2.2%)	0	2 (4.3%)	2 (3.1%)
慢性閉塞性肺疾患	1 (1.5%)	1 (2.2%)	1 (2.6%)	0	1 (1.6%)
咳嗽	2 (3.0%)	1 (2.2%)	0	0	0
呼吸困難	1 (1.5%)	1 (2.2%)	0	0	0
鼻出血	0	1 (2.2%)	0	0	1 (1.6%)
胸水	1 (1.5%)	1 (2.2%)	0	0	0
胸膜炎	0	1 (2.2%)	0	1 (2.2%)	0
肺高血圧症	1 (1.5%)	1 (2.2%)	0	0	0
急性呼吸不全	0	1 (2.2%)	0	0	0
アレルギー性副鼻腔炎	0	1 (2.2%)	0	0	0
無気肺	1 (1.5%)	0	0	0	0
肺気腫	1 (1.5%)	0	0	0	0
低酸素症	0	1 (2.2%)	0	0	0
鼻閉	1 (1.5%)	0	0	0	0
副鼻腔分泌過多	0	1 (2.2%)	0	0	0
胸膜線維症	0	1 (2.2%)	0	0	0
誤嚥性肺炎	1 (1.5%)	0	0	0	0
肺うっ血	1 (1.5%)	0	0	0	0
肺線維症	0	0	0	0	1 (1.6%)
肺水腫	0	1 (2.2%)	0	0	0
気道うっ血	0	0	0	0	1 (1.6%)
副鼻腔障害	0	0	1 (2.6%)	0	0
睡眠時無呼吸症候群	0	0	1 (2.6%)	0	0
くしゃみ	0	1 (2.2%)	0	0	0
喘鳴	0	0	0	0	1 (1.6%)

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表 2.7.6.2-3 有害事象の集計（BP29647試験）（続）

Summary of Adverse Events by System Organ Class and Preferred Term, Safety-Evaluable Patients
Protocol: BP29647

MedDRA System Organ Class MedDRA Preferred Term	0.5 mg ranibizumab Monthly (N=67)	1.5 mg RO6867461 Monthly (N=46)	6 mg RO6867461 Monthly (N=39)	6 mg RO6867461 Monthly(Wk12), Bi-Monthly (Wk28) (N=46)	0.5 mg ranibizumab Monthly(Wk8), 6 mg RO6867461 Monthly (Wk32) (N=64)
神経系障害					
Total number of patients with at least one AE	4 (6.0%)	8 (17.4%)	3 (7.7%)	5 (10.9%)	7 (10.9%)
Total number of events	4	9	3	8	9
浮動性めまい	1 (1.5%)	1 (2.2%)	0	2 (4.3%)	2 (3.1%)
頭痛	0	2 (4.3%)	0	2 (4.3%)	2 (3.1%)
認知症	0	0	0	1 (2.2%)	1 (1.6%)
片頭痛	0	2 (4.3%)	0	0	0
パーキンソン病	1 (1.5%)	1 (2.2%)	0	0	0
一過性脳虚血発作	1 (1.5%)	1 (2.2%)	0	0	0
視野欠損	1 (1.5%)	0	0	1 (2.2%)	0
健忘	0	1 (2.2%)	0	0	0
平衡障害	0	0	0	0	1 (1.6%)
大脳基底核梗塞	0	0	0	1 (2.2%)	0
手根管症候群	0	0	1 (2.6%)	0	0
脳血管発作	0	0	0	0	1 (1.6%)
糖尿病性ニューロパチー	0	0	0	0	1 (1.6%)
構語障害	0	0	0	1 (2.2%)	0
神経圧迫	0	0	1 (2.6%)	0	0
末梢性ニューロパチー	0	0	0	0	1 (1.6%)
坐骨神経痛	0	1 (2.2%)	0	0	0
失神	0	0	1 (2.6%)	0	0

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表 2.7.6.2-3 有害事象の集計（BP29647試験）（続）

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臨床検査					
Total number of patients with at least one AE	4 (6.0%)	5 (10.9%)	5 (12.8%)	5 (10.9%)	6 (9.4%)
Total number of events	5	5	7	10	11
眼圧上昇	0	3 (6.5%)	0	0	1 (1.6%)
体重減少	0	0	2 (5.1%)	2 (4.3%)	0
血沈亢進	0	0	1 (2.6%)	0	2 (3.1%)
体重増加	0	0	2 (5.1%)	0	1 (1.6%)
血中リン増加	0	1 (2.2%)	0	0	1 (1.6%)
Ｃ－反応性蛋白増加	0	0	1 (2.6%)	0	1 (1.6%)
肝機能検査値上昇	0	0	0	1 (2.2%)	1 (1.6%)
冠血管造影	0	0	1 (2.6%)	0	0
血中重炭酸塩増加	1 (1.5%)	0	0	0	0
血球数異常	0	0	0	1 (2.2%)	0
血中クレアチニン増加	0	0	0	1 (2.2%)	0
血中ブドウ糖増加	1 (1.5%)	0	0	0	0
血中カリウム増加	1 (1.5%)	0	0	0	0
血圧上昇	0	1 (2.2%)	0	0	0
血中尿素窒素／クレアチニン比増加	0	0	0	0	1 (1.6%)
骨密度減少	0	0	0	1 (2.2%)	0
胸部Ｘ線異常	1 (1.5%)	0	0	0	0
心電図ＱＴ延長	0	0	0	1 (2.2%)	0
γ－グルタミルトランスフェラーゼ増加	0	0	0	0	1 (1.6%)
糸球体濾過率減少	0	0	0	1 (2.2%)	0
グリコヘモグロビン増加	1 (1.5%)	0	0	0	0
ヘマトクリット減少	0	0	0	1 (2.2%)	0
リンパ球数減少	0	0	0	0	1 (1.6%)
血小板数増加	0	0	0	1 (2.2%)	0
尿検査異常	0	0	0	0	1 (1.6%)

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表 2.7.6.2-3 有害事象の集計（BP29647試験）（続）

Summary of Adverse Events by System Organ Class and Preferred Term, Safety-Evaluable Patients
Protocol: BP29647

MedDRA System Organ Class MedDRA Preferred Term	0.5 mg ranibizumab Monthly (N=67)	1.5 mg RO6867461 Monthly (N=46)	6 mg RO6867461 Monthly (N=39)	6 mg RO6867461 Monthly(Wk12), Bi-Monthly (Wk28) (N=46)	0.5 mg ranibizumab Monthly(Wk8), 6 mg RO6867461 Monthly (Wk32) (N=64)
胃腸障害					
Total number of patients with at least one AE	4 (6.0%)	4 (8.7%)	5 (12.8%)	6 (13.0%)	3 (4.7%)
Total number of events	7	6	5	6	4
下痢	1 (1.5%)	2 (4.3%)	1 (2.6%)	2 (4.3%)	1 (1.6%)
便秘	0	2 (4.3%)	2 (5.1%)	0	0
悪心	1 (1.5%)	1 (2.2%)	1 (2.6%)	0	1 (1.6%)
胃食道逆流性疾患	1 (1.5%)	0	1 (2.6%)	0	1 (1.6%)
腹痛	0	1 (2.2%)	0	0	0
上腹部痛	1 (1.5%)	0	0	0	0
齲歯	0	0	0	1 (2.2%)	0
歯組織の壊死	0	0	0	1 (2.2%)	0
食中毒	0	0	0	1 (2.2%)	0
胃障害	1 (1.5%)	0	0	0	0
鼠径ヘルニア	0	0	0	1 (2.2%)	0
膵臓障害	1 (1.5%)	0	0	0	0
小腸閉塞	1 (1.5%)	0	0	0	0
嘔吐	0	0	0	0	1 (1.6%)

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表 2.7.6.2-3 有害事象の集計（BP29647試験）（続）

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一般・全身障害および投与部位の状態					
Total number of patients with at least one AE	2 (3.0%)	5 (10.9%)	2 (5.1%)	4 (8.7%)	4 (6.3%)
Total number of events	2	6	2	4	4
胸痛	2 (3.0%)	0	1 (2.6%)	0	0
異物感	0	1 (2.2%)	0	2 (4.3%)	0
線維症	0	1 (2.2%)	0	0	1 (1.6%)
発熱	0	2 (4.3%)	0	0	0
無力症	0	1 (2.2%)	0	0	0
石灰沈着症	0	0	0	0	1 (1.6%)
嚢胞	0	0	0	0	1 (1.6%)
滲出液	0	1 (2.2%)	0	0	0
顔面痛	0	0	0	1 (2.2%)	0
炎症	0	0	0	0	1 (1.6%)
インフルエンザ様疾患	0	0	1 (2.6%)	0	0
非心臓性胸痛	0	0	0	1 (2.2%)	0
血管障害					
Total number of patients with at least one AE	4 (6.0%)	1 (2.2%)	4 (10.3%)	4 (8.7%)	4 (6.3%)
Total number of events	4	2	4	4	4
高血圧	2 (3.0%)	1 (2.2%)	2 (5.1%)	3 (6.5%)	3 (4.7%)
大動脈瘤	1 (1.5%)	0	0	0	0
大動脈硬化症	0	0	0	0	1 (1.6%)
本態性高血圧症	0	1 (2.2%)	0	0	0
低血圧	0	0	1 (2.6%)	0	0
リンパ管障害	1 (1.5%)	0	0	0	0
リンパ浮腫	0	0	0	1 (2.2%)	0
ショック	0	0	1 (2.6%)	0	0

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表 2.7.6.2-3 有害事象の集計（BP29647試験）（続）

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心臓障害					
Total number of patients with at least one AE	4 (6.0%)	1 (2.2%)	4 (10.3%)	2 (4.3%)	3 (4.7%)
Total number of events	4	1	11	4	3
心房細動	0	0	1 (2.6%)	1 (2.2%)	0
冠動脈疾患	0	0	1 (2.6%)	0	1 (1.6%)
心嚢液貯留	1 (1.5%)	1 (2.2%)	0	0	0
急性心筋梗塞	0	0	1 (2.6%)	0	0
心房粗動	0	0	0	1 (2.2%)	0
房室ブロック	0	0	1 (2.6%)	0	0
完全房室ブロック	0	0	1 (2.6%)	0	0
第一度房室ブロック	0	0	0	1 (2.2%)	0
徐脈	0	0	1 (2.6%)	0	0
心停止	1 (1.5%)	0	0	0	0
心障害	1 (1.5%)	0	0	0	0
うっ血性心不全	0	0	1 (2.6%)	0	0
心肺停止	0	0	0	0	1 (1.6%)
心拡大	1 (1.5%)	0	0	0	0
心筋症	0	0	0	1 (2.2%)	0
伝導障害	0	0	1 (2.6%)	0	0
心室内伝導障害	0	0	1 (2.6%)	0	0
変性僧帽弁疾患	0	0	0	0	1 (1.6%)
洞結節機能不全	0	0	1 (2.6%)	0	0

Percentages are based on N.
Multiple occurences of the same AE in one individual counted only once except for "total number of events" where all events are being counted.
Investigator text for Adverse Events encoded using MedDRA Version 20.1.

表 2.7.6.2-3 有害事象の集計（BP29647試験）（続）

Summary of Adverse Events by System Organ Class and Preferred Term, Safety-Evaluable Patients
Protocol: BP29647

MedDRA System Organ Class MedDRA Preferred Term	0.5 mg ranibizumab Monthly (N=67)	1.5 mg RO6867461 Monthly (N=46)	6 mg RO6867461 Monthly (N=39)	6 mg RO6867461 Monthly(Wk12), Bi-Monthly (Wk28) (N=46)	0.5 mg ranibizumab Monthly(Wk8), 6 mg RO6867461 Monthly (Wk32) (N=64)
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）					
Total number of patients with at least one AE	4 (6.0%)	3 (6.5%)	2 (5.1%)	2 (4.3%)	3 (4.7%)
Total number of events	6	5	2	2	3
基底細胞癌	1 (1.5%)	1 (2.2%)	0	0	0
メラノサイト性母斑	0	0	1 (2.6%)	0	1 (1.6%)
再発膀胱癌	0	0	0	0	1 (1.6%)
眼の母斑	0	0	1 (2.6%)	0	0
浸潤性乳管癌	0	0	0	1 (2.2%)	0
乳腺浸潤性小葉癌	0	0	0	0	1 (1.6%)
Ｌ鎖病	0	1 (2.2%)	0	0	0
肺腺癌	1 (1.5%)	0	0	0	0
皮膚の新生物	0	0	0	1 (2.2%)	0
膵癌	0	1 (2.2%)	0	0	0
形質細胞性骨髄腫	0	1 (2.2%)	0	0	0
腎癌	0	1 (2.2%)	0	0	0
脂漏性角化症	1 (1.5%)	0	0	0	0
紡錘細胞肉腫	1 (1.5%)	0	0	0	0
扁平上皮癌	1 (1.5%)	0	0	0	0
精神障害					
Total number of patients with at least one AE	3 (4.5%)	3 (6.5%)	2 (5.1%)	2 (4.3%)	4 (6.3%)
Total number of events	3	5	3	2	4
不安	2 (3.0%)	1 (2.2%)	1 (2.6%)	1 (2.2%)	4 (6.3%)
うつ病	0	2 (4.3%)	0	1 (2.2%)	0
不眠症	1 (1.5%)	0	2 (5.1%)	0	0
幻視	0	1 (2.2%)	0	0	0

Percentages are based on N.
Multiple occurences of the same AE in one individual counted only once except for "total number of events" where all events are being counted.
Investigator text for Adverse Events encoded using MedDRA Version 20.1.

表 2.7.6.2-3 有害事象の集計（BP29647試験）（続）

Summary of Adverse Events by System Organ Class and Preferred Term, Safety-Evaluable Patients
Protocol: BP29647

MedDRA System Organ Class MedDRA Preferred Term	0.5 mg ranibizumab Monthly (N=67)	1.5 mg RO6867461 Monthly (N=46)	6 mg RO6867461 Monthly (N=39)	6 mg RO6867461 Monthly(Wk12), Bi-Monthly (Wk28) (N=46)	0.5 mg ranibizumab Monthly(Wk8), 6 mg RO6867461 Monthly (Wk32) (N=64)
皮膚および皮下組織障害					
Total number of patients with at least one AE	5 (7.5%)	4 (8.7%)	0	3 (6.5%)	2 (3.1%)
Total number of events	5	4	0	3	2
発疹	1 (1.5%)	1 (2.2%)	0	1 (2.2%)	1 (1.6%)
乾癬	1 (1.5%)	1 (2.2%)	0	0	0
光線角化症	1 (1.5%)	0	0	0	0
皮膚嚢腫	0	1 (2.2%)	0	0	0
接触皮膚炎	0	0	0	1 (2.2%)	0
湿疹	1 (1.5%)	0	0	0	0
紅斑	0	1 (2.2%)	0	0	0
点状出血	0	0	0	0	1 (1.6%)
そう痒症	0	0	0	1 (2.2%)	0
黄色板腫	1 (1.5%)	0	0	0	0
代謝および栄養障害					
Total number of patients with at least one AE	2 (3.0%)	4 (8.7%)	3 (7.7%)	2 (4.3%)	2 (3.1%)
Total number of events	4	8	3	2	2
脱水	1 (1.5%)	2 (4.3%)	0	0	0
痛風	0	0	1 (2.6%)	0	2 (3.1%)
高血糖	1 (1.5%)	1 (2.2%)	0	0	0
高脂血症	0	1 (2.2%)	0	1 (2.2%)	0
低カリウム血症	0	0	1 (2.6%)	1 (2.2%)	0
食欲減退	0	1 (2.2%)	0	0	0
体液貯留	0	0	1 (2.6%)	0	0
高カリウム血症	0	1 (2.2%)	0	0	0
高マグネシウム血症	0	1 (2.2%)	0	0	0
低ナトリウム血症	0	1 (2.2%)	0	0	0
栄養障害	1 (1.5%)	0	0	0	0
ビタミンＤ欠乏	1 (1.5%)	0	0	0	0

Percentages are based on N.
Multiple occurences of the same AE in one individual counted only once except for "total number of events" where all events are being counted.
Investigator text for Adverse Events encoded using MedDRA Version 20.1.

表 2.7.6.2-3 有害事象の集計（BP29647試験）（続）

Summary of Adverse Events by System Organ Class and Preferred Term, Safety-Evaluable Patients
Protocol: BP29647

MedDRA System Organ Class MedDRA Preferred Term	0.5 mg ranibizumab Monthly (N=67)	1.5 mg RO6867461 Monthly (N=46)	6 mg RO6867461 Monthly (N=39)	6 mg RO6867461 Monthly(Wk12), Bi-Monthly (Wk28) (N=46)	0.5 mg ranibizumab Monthly(Wk8), 6 mg RO6867461 Monthly (Wk32) (N=64)
腎および尿路障害					
Total number of patients with at least one AE	1 (1.5%)	4 (8.7%)	2 (5.1%)	3 (6.5%)	1 (1.6%)
Total number of events	1	9	2	3	1
腎結石症	0	1 (2.2%)	1 (2.6%)	1 (2.2%)	0
腎嚢胞	0	1 (2.2%)	0	0	1 (1.6%)
急性腎障害	0	1 (2.2%)	0	0	0
糖尿病性腎症	0	1 (2.2%)	0	0	0
排尿困難	0	1 (2.2%)	0	0	0
血尿	1 (1.5%)	0	0	0	0
水腎症	0	1 (2.2%)	0	0	0
腎不全	0	1 (2.2%)	0	0	0
腎性高血圧	0	0	0	1 (2.2%)	0
腎機能障害	0	0	1 (2.6%)	0	0
尿失禁	0	1 (2.2%)	0	0	0
尿閉	0	0	0	1 (2.2%)	0
外科および内科処置					
Total number of patients with at least one AE	2 (3.0%)	4 (8.7%)	0	0	2 (3.1%)
Total number of events	2	4	0	0	2
副鼻腔手術	0	1 (2.2%)	0	0	1 (1.6%)
抜歯	0	1 (2.2%)	0	0	1 (1.6%)
歯内療法	1 (1.5%)	0	0	0	0
肺切除	1 (1.5%)	0	0	0	0
皮膚新生物切除	0	1 (2.2%)	0	0	0
甲状腺摘除	0	1 (2.2%)	0	0	0

Percentages are based on N.
Multiple occurences of the same AE in one individual counted only once except for "total number of events" where all events are being counted.
Investigator text for Adverse Events encoded using MedDRA Version 20.1.

表 2.7.6.2-3 有害事象の集計（BP29647試験）（続）

Summary of Adverse Events by System Organ Class and Preferred Term, Safety-Evaluable Patients
Protocol: BP29647

MedDRA System Organ Class MedDRA Preferred Term	0.5 mg ranibizumab Monthly (N=67)	1.5 mg RO6867461 Monthly (N=46)	6 mg RO6867461 Monthly (N=39)	6 mg RO6867461 Monthly(Wk12), Bi-Monthly (Wk28) (N=46)	0.5 mg ranibizumab Monthly(Wk8), 6 mg RO6867461 Monthly (Wk32) (N=64)
血液およびリンパ系障害					
Total number of patients with at least one AE	2 (3.0%)	1 (2.2%)	1 (2.6%)	0	0
Total number of events	2	1	1	0	0
貧血	1 (1.5%)	1 (2.2%)	1 (2.6%)	0	0
リンパ節症	1 (1.5%)	0	0	0	0
免疫系障害					
Total number of patients with at least one AE	1 (1.5%)	0	1 (2.6%)	1 (2.2%)	1 (1.6%)
Total number of events	1	0	2	1	1
造影剤アレルギー	1 (1.5%)	0	0	1 (2.2%)	0
ワクチンアレルギー	0	0	0	0	1 (1.6%)
過敏症	0	0	1 (2.6%)	0	0
耳および迷路障害					
Total number of patients with at least one AE	0	0	0	1 (2.2%)	2 (3.1%)
Total number of events	0	0	0	1	3
回転性めまい	0	0	0	1 (2.2%)	2 (3.1%)
耳鳴	0	0	0	0	1 (1.6%)
内分泌障害					
Total number of patients with at least one AE	1 (1.5%)	1 (2.2%)	0	0	1 (1.6%)
Total number of events	1	1	0	0	1
副腎障害	1 (1.5%)	0	0	0	0
甲状腺機能低下症	0	0	0	0	1 (1.6%)
甲状腺腫瘤	0	1 (2.2%)	0	0	0

Percentages are based on N.
Multiple occurences of the same AE in one individual counted only once except for "total number of events" where all events are being counted.
Investigator text for Adverse Events encoded using MedDRA Version 20.1.

表 2.7.6.2-3 有害事象の集計（BP29647試験）（続）

Summary of Adverse Events by System Organ Class and Preferred Term, Safety-Evaluable Patients
Protocol: BP29647

MedDRA System Organ Class MedDRA Preferred Term	0.5 mg ranibizumab Monthly (N=67)	1.5 mg RO6867461 Monthly (N=46)	6 mg RO6867461 Monthly (N=39)	6 mg RO6867461 Monthly(Wk12), Bi-Monthly (Wk28) (N=46)	0.5 mg ranibizumab Monthly(Wk8), 6 mg RO6867461 Monthly (Wk32) (N=64)
生殖系および乳房障害					
Total number of patients with at least one AE	0	1 (2.2%)	2 (5.1%)	0	0
Total number of events	0	1	2	0	0
良性前立腺肥大症	0	0	1 (2.6%)	0	0
乳房痛	0	1 (2.2%)	0	0	0
閉経後出血	0	0	1 (2.6%)	0	0
肝胆道系障害					
Total number of patients with at least one AE	2 (3.0%)	0	0	0	0
Total number of events	2	0	0	0	0
胆石症	2 (3.0%)	0	0	0	0

Percentages are based on N.
Multiple occurences of the same AE in one individual counted only once except for "total number of events" where all events are being counted.
Investigator text for Adverse Events encoded using MedDRA Version 20.1.

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[5.3.5.1-nAMD-1 t_ae_SAF を改変]

表 2.7.6.2-4 試験眼の有害事象の集計（BP29647試験）

Summary of Ocular Adverse Events (Study Eye) by System Organ Class, Preferred Term and Highest Intensity by Study Arm, Safety-Evaluable Patients
Protocol: BP29647

MedDRA System Organ Class MedDRA Preferred Term	Intensity	0.5 mg ranibizumab Monthly (N=67)	1.5 mg RO6867461 Monthly (N=46)	6 mg RO6867461 Monthly (N=39)	6 mg RO6867461 Monthly(Wk12), Bi-Monthly (Wk28) (N=46)	0.5 mg ranibizumab Monthly(Wk8), 6 mg RO6867461 Monthly (Wk32) (N=64)
- Any adverse events -	-Any Grade-	28	21	21	27	28
眼障害						
- Overall -	-Any Grade-	27	21	19	26	25
結膜出血	-Any Grade-	13	4	6	6	6
眼痛	-Any Grade-	2	4	2	5	3
硝子体剥離	-Any Grade-	2	5	3	3	3
硝子体浮遊物	-Any Grade-	2	3	4	2	0
眼刺激	-Any Grade-	0	1	4	4	1
霧視	-Any Grade-	2	1	3	2	2
白内障	-Any Grade-	2	2	2	2	1
網膜色素上皮裂孔	-Any Grade-	3	0	2	2	0
眼瞼炎	-Any Grade-	0	1	2	1	2
後嚢部混濁	-Any Grade-	2	0	3	0	1
前房のフレア	-Any Grade-	3	1	0	0	1
流涙増加	-Any Grade-	1	0	1	3	0
視力低下	-Any Grade-	1	2	0	2	0
前房内細胞	-Any Grade-	2	0	2	0	0
眼そう痒症	-Any Grade-	2	1	0	1	0
硝子体出血	-Any Grade-	2	1	0	1	0
乾性加齢黄斑変性	-Any Grade-	2	0	1	0	0
眼乾燥	-Any Grade-	0	0	0	2	1
点状角膜炎	-Any Grade-	0	0	0	0	3
網膜出血	-Any Grade-	2	1	0	0	0
視力障害	-Any Grade-	0	1	0	1	1
眼部不快感	-Any Grade-	0	0	1	0	1
光視症	-Any Grade-	1	0	1	0	0
網膜滲出物	-Any Grade-	0	1	0	0	1
加齢黄斑変性	-Any Grade-	1	0	0	0	0

Only the most severe intensity is counted for multiple occurences of the same AE within a Subject at the Preferred Term Level.
The total number of patients with at least one Event is counted in the "- Any Intensity -" and/or "- Overall -" and/or "- Any Adverse Events -" categories.
Investigator text for Adverse Events encoded using MedDRA Version 20.1.

表 2.7.6.2-4 試験眼の有害事象の集計（BP29647試験）（続）

Summary of Ocular Adverse Events (Study Eye) by System Organ Class, Preferred Term and Highest Intensity by Study Arm, Safety-Evaluable Patients
Protocol: BP29647

MedDRA System Organ Class MedDRA Preferred Term	Intensity	0.5 mg ranibizumab Monthly (N=67)	1.5 mg RO6867461 Monthly (N=46)	6 mg RO6867461 Monthly (N=39)	6 mg RO6867461 Monthly(Wk12), Bi-Monthly (Wk28) (N=46)	0.5 mg ranibizumab Monthly(Wk8), 6 mg RO6867461 Monthly (Wk32) (N=64)
閉塞隅角緑内障	-Any Grade-	0	1	0	0	0
核性白内障	-Any Grade-	0	0	0	0	1
嚢下白内障	-Any Grade-	0	0	1	0	0
霰粒腫	-Any Grade-	0	0	0	0	1
結膜充血	-Any Grade-	0	0	0	1	0
結膜浮腫	-Any Grade-	0	1	0	0	0
角膜障害	-Any Grade-	0	1	0	0	0
角膜混濁	-Any Grade-	1	0	0	0	0
角膜瘢痕	-Any Grade-	0	0	0	1	0
網膜色素上皮剥離	-Any Grade-	0	0	1	0	0
複視	-Any Grade-	1	0	0	0	0
異常３色覚	-Any Grade-	0	0	0	1	0
眼脂	-Any Grade-	0	0	0	0	1
眼の炎症	-Any Grade-	0	1	0	0	0
眼瞼刺激	-Any Grade-	0	0	0	0	1
眼瞼浮腫	-Any Grade-	0	0	0	1	0
眼の異物感	-Any Grade-	0	0	0	0	1
緑内障	-Any Grade-	0	0	0	0	1
虹彩炎	-Any Grade-	0	0	0	0	1
角膜後面沈着物	-Any Grade-	0	1	0	0	0
黄斑線維症	-Any Grade-	0	0	0	1	0
黄斑円孔	-Any Grade-	0	0	0	0	1
マイボーム腺機能不全	-Any Grade-	0	0	0	1	0
変視症	-Any Grade-	0	0	0	1	0
開放隅角緑内障	-Any Grade-	1	0	0	0	0
羞明	-Any Grade-	0	0	0	1	0
網膜血管瘤	-Any Grade-	1	0	0	0	0
網膜動脈塞栓症	-Any Grade-	0	0	1	0	0

Only the most severe intensity is counted for multiple occurences of the same AE within a Subject at the Preferred Term Level.
The total number of patients with at least one Event is counted in the "- Any Intensity -" and/or "- Overall -" and/or "- Any Adverse Events -" categories.
Investigator text for Adverse Events encoded using MedDRA Version 20.1.

表 2.7.6.2-4 試験眼の有害事象の集計（BP29647試験）（続）

Summary of Ocular Adverse Events (Study Eye) by System Organ Class, Preferred Term and Highest Intensity by Study Arm, Safety-Evaluable Patients
Protocol: BP29647

MedDRA System Organ Class MedDRA Preferred Term	Intensity	0.5 mg ranibizumab Monthly (N=67)	1.5 mg RO6867461 Monthly (N=46)	6 mg RO6867461 Monthly (N=39)	6 mg RO6867461 Monthly(Wk12), Bi-Monthly (Wk28) (N=46)	0.5 mg ranibizumab Monthly(Wk8), 6 mg RO6867461 Monthly (Wk32) (N=64)
網膜変性	-Any Grade-	0	0	0	1	0
網膜色素脱失	-Any Grade-	0	0	0	0	1
網膜ドルーゼン	-Any Grade-	0	1	0	0	0
網膜梗塞	-Any Grade-	0	0	1	0	0
網膜瘢痕	-Any Grade-	0	0	0	0	1
網膜分離症	-Any Grade-	0	0	0	1	0
網膜下線維症	-Any Grade-	0	1	0	0	0
網膜下液	-Any Grade-	1	0	0	0	0
硝子体混濁	-Any Grade-	0	1	0	0	0
一般・全身障害および投与部位の状態						
- Overall -	-Any Grade-	0	1	0	2	1
異物感	-Any Grade-	0	1	0	2	0
線維症	-Any Grade-	0	0	0	0	1
傷害、中毒および処置合併症						
- Overall -	-Any Grade-	0	0	2	0	2
角膜擦過傷	-Any Grade-	0	0	1	0	2
前房出血	-Any Grade-	0	0	1	0	0
臨床検査						
- Overall -	-Any Grade-	0	3	0	0	1
眼圧上昇	-Any Grade-	0	3	0	0	1
感染症および寄生虫症						
- Overall -	-Any Grade-	0	1	0	0	2
眼内炎	-Any Grade-	0	1	0	0	1

Only the most severe intensity is counted for multiple occurences of the same AE within a Subject at the Preferred Term Level.
The total number of patients with at least one Event is counted in the "- Any Intensity -" and/or "- Overall -" and/or "- Any Adverse Events -" categories.
Investigator text for Adverse Events encoded using MedDRA Version 20.1.

表 2.7.6.2-4 試験眼の有害事象の集計（BP29647試験）（続）

Summary of Ocular Adverse Events (Study Eye) by System Organ Class, Preferred Term and Highest Intensity by Study Arm, Safety-Evaluable Patients
Protocol: BP29647

MedDRA System Organ Class MedDRA Preferred Term	Intensity	0.5 mg ranibizumab Monthly (N=67)	1.5 mg RO6867461 Monthly (N=46)	6 mg RO6867461 Monthly (N=39)	6 mg RO6867461 Monthly(Wk12), Bi-Monthly (Wk28) (N=46)	0.5 mg ranibizumab Monthly(Wk8), 6 mg RO6867461 Monthly (Wk32) (N=64)
角膜感染	-Any Grade-	0	0	0	0	1
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）						
- Overall -	-Any Grade-	0	0	1	0	1
眼の母斑	-Any Grade-	0	0	1	0	0
メラノサイト性母斑	-Any Grade-	0	0	0	0	1
神経系障害						
- Overall -	-Any Grade-	1	0	0	1	0
視野欠損	-Any Grade-	1	0	0	1	0
精神障害						
- Overall -	-Any Grade-	0	1	0	0	0
幻視	-Any Grade-	0	1	0	0	0
皮膚および皮下組織障害						
- Overall -	-Any Grade-	1	0	0	0	0
黄色板腫	-Any Grade-	1	0	0	0	0

Only the most severe intensity is counted for multiple occurences of the same AE within a Subject at the Preferred Term Level.
The total number of patients with at least one Event is counted in the "- Any Intensity -" and/or "- Overall -" and/or "- Any Adverse Events -" categories.
Investigator text for Adverse Events encoded using MedDRA Version 20.1.

[5.3.5.1-nAMD-1 t_ae_int_ocular_s_SAF を改変]

表 2.7.6.2-5 非試験眼の有害事象の集計（BP29647試験）

Summary of Ocular Adverse Events (Non Study Eye) by System Organ Class, Preferred Term and Highest Intensity by Study Arm, Safety-Evaluable Patients
Protocol: BP29647

MedDRA System Organ Class MedDRA Preferred Term	Intensity	0.5 mg ranibizumab Monthly (N=67)	1.5 mg RO6867461 Monthly (N=46)	6 mg RO6867461 Monthly (N=39)	6 mg RO6867461 Monthly(Wk12), Bi-Monthly (Wk28) (N=46)	0.5 mg ranibizumab Monthly(Wk8), 6 mg RO6867461 Monthly (Wk32) (N=64)
- Any adverse events -	-Any Grade-	21	16	9	18	20
眼障害						
- Overall -	-Any Grade-	21	16	8	17	19
新生血管加齢黄斑変性	-Any Grade-	7	4	3	3	5
硝子体剥離	-Any Grade-	1	4	2	3	2
網膜出血	-Any Grade-	2	1	1	1	3
眼瞼炎	-Any Grade-	0	1	1	1	1
白内障	-Any Grade-	0	1	1	1	1
核性白内障	-Any Grade-	2	0	0	0	2
点状角膜炎	-Any Grade-	0	0	0	0	4
硝子体浮遊物	-Any Grade-	0	1	0	2	1
乾性加齢黄斑変性	-Any Grade-	2	0	0	0	1
眼乾燥	-Any Grade-	1	0	0	2	0
眼そう痒症	-Any Grade-	1	1	0	1	0
霧視	-Any Grade-	1	0	1	0	1
視力障害	-Any Grade-	1	0	1	1	0
結膜出血	-Any Grade-	2	0	0	0	0
複視	-Any Grade-	2	0	0	0	0
後嚢部混濁	-Any Grade-	0	1	1	0	0
加齢黄斑変性	-Any Grade-	1	0	0	0	0
閉塞隅角緑内障	-Any Grade-	0	1	0	0	0
前房のフレア	-Any Grade-	0	1	0	0	0
皮質白内障	-Any Grade-	0	0	0	0	1
嚢下白内障	-Any Grade-	0	0	0	0	1
結膜浮腫	-Any Grade-	0	1	0	0	0
角膜色素沈着	-Any Grade-	0	0	0	1	0
嚢胞様黄斑浮腫	-Any Grade-	0	0	0	1	0
異常３色覚	-Any Grade-	0	0	0	1	0

Only the most severe intensity is counted for multiple occurences of the same AE within a Subject at the Preferred Term Level.
The total number of patients with at least one Event is counted in the "- Any Intensity -" and/or "- Overall -" and/or "- Any Adverse Events -" categories.
Investigator text for Adverse Events encoded using MedDRA Version 20.1.

表 2.7.6.2-5 非試験眼の有害事象の集計（BP29647試験）（続）

Summary of Ocular Adverse Events (Non Study Eye) by System Organ Class, Preferred Term and Highest Intensity by Study Arm, Safety-Evaluable Patients
Protocol: BP29647

MedDRA System Organ Class MedDRA Preferred Term	Intensity	0.5 mg ranibizumab Monthly (N=67)	1.5 mg RO6867461 Monthly (N=46)	6 mg RO6867461 Monthly (N=39)	6 mg RO6867461 Monthly(Wk12), Bi-Monthly (Wk28) (N=46)	0.5 mg ranibizumab Monthly(Wk8), 6 mg RO6867461 Monthly (Wk32) (N=64)
眼出血	-Any Grade-	0	1	0	0	0
流涙増加	-Any Grade-	1	0	0	0	0
黄斑線維症	-Any Grade-	1	0	0	0	0
黄斑円孔	-Any Grade-	0	1	0	0	0
黄斑症	-Any Grade-	0	0	0	0	1
マイボーム腺機能不全	-Any Grade-	0	0	0	1	0
開放隅角緑内障	-Any Grade-	1	0	0	0	0
羞明	-Any Grade-	1	0	0	0	0
光視症	-Any Grade-	0	0	0	1	0
網膜ドルーゼン	-Any Grade-	0	1	0	0	0
網膜滲出物	-Any Grade-	0	1	0	0	0
網膜静脈閉塞	-Any Grade-	0	0	0	0	1
網膜下液	-Any Grade-	1	0	0	0	0
視力低下	-Any Grade-	0	0	0	1	0
一般・全身障害および投与部位の状態						
- Overall -	-Any Grade-	0	1	0	0	0
線維症	-Any Grade-	0	1	0	0	0
感染症および寄生虫症						
- Overall -	-Any Grade-	0	0	0	1	0
結膜炎	-Any Grade-	0	0	0	1	0
筋骨格系および結合組織障害						
- Overall -	-Any Grade-	0	0	0	0	1
筋攣縮	-Any Grade-	0	0	0	0	1

Only the most severe intensity is counted for multiple occurences of the same AE within a Subject at the Preferred Term Level.
The total number of patients with at least one Event is counted in the "- Any Intensity -" and/or "- Overall -" and/or "- Any Adverse Events -" categories.
Investigator text for Adverse Events encoded using MedDRA Version 20.1.

表 2.7.6.2-5 非試験眼の有害事象の集計（BP29647試験）（続）

Summary of Ocular Adverse Events (Non Study Eye) by System Organ Class, Preferred Term and Highest Intensity by Study Arm, Safety-Evaluable Patients
Protocol: BP29647

MedDRA System Organ Class MedDRA Preferred Term	Intensity	0.5 mg ranibizumab Monthly (N=67)	1.5 mg RO6867461 Monthly (N=46)	6 mg RO6867461 Monthly (N=39)	6 mg RO6867461 Monthly(Wk12), Bi-Monthly (Wk28) (N=46)	0.5 mg ranibizumab Monthly(Wk8), 6 mg RO6867461 Monthly (Wk32) (N=64)
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）						
- Overall -	-Any Grade-	0	0	1	0	0
メラノサイト性母斑	-Any Grade-	0	0	1	0	0
精神障害						
- Overall -	-Any Grade-	0	1	0	0	0
幻視	-Any Grade-	0	1	0	0	0
皮膚および皮下組織障害						
- Overall -	-Any Grade-	1	0	0	0	0
黄色板腫	-Any Grade-	1	0	0	0	0

Only the most severe intensity is counted for multiple occurences of the same AE within a Subject at the Preferred Term Level.
The total number of patients with at least one Event is counted in the "- Any Intensity -" and/or "- Overall -" and/or "- Any Adverse Events -" categories.
Investigator text for Adverse Events encoded using MedDRA Version 20.1.

[5.3.5.1-nAMD-1 t_ae_int_ocular_n_SAF を改変]

表 2.7.6.2-6 眼以外の有害事象の集計（BP29647試験）

Summary of Systemic Adverse Events by System Organ Class, Preferred Term and Highest Intensity, Safety-Evaluable Patients
Protocol: BP29647

MedDRA System Organ Class MedDRA Preferred Term	Intensity	0.5 mg ranibizumab Monthly (N=67)	1.5 mg RO6867461 Monthly (N=46)	6 mg RO6867461 Monthly (N=39)	6 mg RO6867461 Monthly(Wk12), Bi-Monthly (Wk28) (N=46)	0.5 mg ranibizumab Monthly(Wk8), 6 mg RO6867461 Monthly (Wk32) (N=64)
- Any adverse events -	-Any Grade-	37	37	23	30	43
感染症および寄生虫症						
- Overall -	-Any Grade-	21	21	8	14	20
尿路感染	-Any Grade-	6	11	2	0	3
上咽頭炎	-Any Grade-	9	4	1	1	5
インフルエンザ	-Any Grade-	3	3	1	0	1
副鼻腔炎	-Any Grade-	2	1	0	1	2
上気道感染	-Any Grade-	1	1	0	2	2
気管支炎	-Any Grade-	0	2	2	0	1
膀胱炎	-Any Grade-	1	1	0	0	3
肺炎	-Any Grade-	0	1	1	3	0
歯膿瘍	-Any Grade-	1	2	1	0	1
ウイルス性胃腸炎	-Any Grade-	3	0	0	1	0
急性副鼻腔炎	-Any Grade-	0	0	0	1	1
蜂巣炎	-Any Grade-	1	0	0	0	1
帯状疱疹	-Any Grade-	0	0	0	1	1
喉頭炎	-Any Grade-	0	0	0	2	0
歯感染	-Any Grade-	0	0	0	1	1
感染性関節炎	-Any Grade-	0	0	0	1	0
憩室炎	-Any Grade-	0	0	1	0	0
真菌性耳感染	-Any Grade-	0	1	0	0	0
大腸菌性尿路感染	-Any Grade-	0	0	0	0	1
真菌感染	-Any Grade-	0	0	1	0	0
せつ	-Any Grade-	0	0	0	0	1
ガードネレラ感染	-Any Grade-	0	0	0	1	0
胃腸炎	-Any Grade-	0	0	0	0	1
感染性大腸炎	-Any Grade-	0	1	0	0	0
腎感染	-Any Grade-	0	0	0	0	1

Only the most severe intensity is counted for multiple occurences of the same AE within a Subject at the Preferred Term Level.
The total number of patients with at least one Event is counted in the "- Any Intensity -" and/or "- Overall -" and/or "- Any Adverse Events -" categories.
Investigator text for Adverse Events encoded using MedDRA Version 20.1.

表 2.7.6.2-6 眼以外の有害事象の集計（BP29647試験）（続）

Summary of Systemic Adverse Events by System Organ Class, Preferred Term and Highest Intensity, Safety-Evaluable Patients
Protocol: BP29647

MedDRA System Organ Class MedDRA Preferred Term	Intensity	0.5 mg ranibizumab Monthly (N=67)	1.5 mg RO6867461 Monthly (N=46)	6 mg RO6867461 Monthly (N=39)	6 mg RO6867461 Monthly(Wk12), Bi-Monthly (Wk28) (N=46)	0.5 mg ranibizumab Monthly(Wk8), 6 mg RO6867461 Monthly (Wk32) (N=64)
限局性感染	-Any Grade-	1	0	0	0	0
口腔ヘルペス	-Any Grade-	0	0	0	1	0
急性中耳炎	-Any Grade-	0	0	0	1	0
細菌性中耳炎	-Any Grade-	0	0	0	0	1
レンサ球菌性咽頭炎	-Any Grade-	0	1	0	0	0
気道感染	-Any Grade-	0	0	1	0	0
鼻炎	-Any Grade-	1	0	0	0	0
ウイルス感染	-Any Grade-	1	0	0	0	0
筋骨格系および結合組織障害						
- Overall -	-Any Grade-	9	6	3	4	10
背部痛	-Any Grade-	1	2	1	0	3
四肢痛	-Any Grade-	2	0	0	2	1
筋骨格痛	-Any Grade-	0	0	1	1	2
関節炎	-Any Grade-	0	0	1	0	2
変形性関節症	-Any Grade-	1	0	0	1	1
リウマチ性多発筋痛	-Any Grade-	1	1	0	0	1
変形性脊椎症	-Any Grade-	1	0	0	0	2
関節痛	-Any Grade-	0	1	1	0	0
関節腫脹	-Any Grade-	0	2	0	0	0
筋痙縮	-Any Grade-	1	1	0	0	0
筋骨格硬直	-Any Grade-	0	0	0	0	2
頚部痛	-Any Grade-	0	0	1	1	0
脊柱管狭窄症	-Any Grade-	0	0	0	1	1
滑液包炎	-Any Grade-	1	0	0	0	0
鼠径部痛	-Any Grade-	0	0	0	0	1
椎間板突出	-Any Grade-	0	0	1	0	0
筋肉痛	-Any Grade-	0	1	0	0	0
骨壊死	-Any Grade-	0	0	1	0	0

Only the most severe intensity is counted for multiple occurences of the same AE within a Subject at the Preferred Term Level.
The total number of patients with at least one Event is counted in the "- Any Intensity -" and/or "- Overall -" and/or "- Any Adverse Events -" categories.
Investigator text for Adverse Events encoded using MedDRA Version 20.1.

表 2.7.6.2-6 眼以外の有害事象の集計（BP29647試験）（続）

Summary of Systemic Adverse Events by System Organ Class, Preferred Term and Highest Intensity, Safety-Evaluable Patients
Protocol: BP29647

MedDRA System Organ Class MedDRA Preferred Term	Intensity	0.5 mg ranibizumab Monthly (N=67)	1.5 mg RO6867461 Monthly (N=46)	6 mg RO6867461 Monthly (N=39)	6 mg RO6867461 Monthly(Wk12), Bi-Monthly (Wk28) (N=46)	0.5 mg ranibizumab Monthly(Wk8), 6 mg RO6867461 Monthly (Wk32) (N=64)
顎痛	-Any Grade-	1	0	0	0	0
関節リウマチ	-Any Grade-	1	0	0	0	0
脊椎炎	-Any Grade-	0	0	0	0	1
呼吸器、胸郭および縦隔障害						
- Overall -	-Any Grade-	8	8	2	3	7
副鼻腔うっ血	-Any Grade-	2	1	0	2	2
慢性閉塞性肺疾患	-Any Grade-	1	1	1	0	1
咳嗽	-Any Grade-	2	1	0	0	0
呼吸困難	-Any Grade-	1	1	0	0	0
鼻出血	-Any Grade-	0	1	0	0	1
胸水	-Any Grade-	1	1	0	0	0
胸膜炎	-Any Grade-	0	1	0	1	0
肺高血圧症	-Any Grade-	1	1	0	0	0
急性呼吸不全	-Any Grade-	0	1	0	0	0
アレルギー性副鼻腔炎	-Any Grade-	0	1	0	0	0
無気肺	-Any Grade-	1	0	0	0	0
肺気腫	-Any Grade-	1	0	0	0	0
低酸素症	-Any Grade-	0	1	0	0	0
鼻閉	-Any Grade-	1	0	0	0	0
副鼻腔分泌過多	-Any Grade-	0	1	0	0	0
胸膜線維症	-Any Grade-	0	1	0	0	0
誤嚥性肺炎	-Any Grade-	1	0	0	0	0
肺うっ血	-Any Grade-	1	0	0	0	0
肺線維症	-Any Grade-	0	0	0	0	1
肺水腫	-Any Grade-	0	1	0	0	0
気道うっ血	-Any Grade-	0	0	0	0	1
副鼻腔障害	-Any Grade-	0	0	1	0	0
睡眠時無呼吸症候群	-Any Grade-	0	0	1	0	0

Only the most severe intensity is counted for multiple occurences of the same AE within a Subject at the Preferred Term Level.
The total number of patients with at least one Event is counted in the "- Any Intensity -" and/or "- Overall -" and/or "- Any Adverse Events -" categories.
Investigator text for Adverse Events encoded using MedDRA Version 20.1.

表 2.7.6.2-6 眼以外の有害事象の集計（BP29647試験）（続）

Summary of Systemic Adverse Events by System Organ Class, Preferred Term and Highest Intensity, Safety-Evaluable Patients
Protocol: BP29647

MedDRA System Organ Class MedDRA Preferred Term	Intensity	0.5 mg ranibizumab Monthly (N=67)	1.5 mg RO6867461 Monthly (N=46)	6 mg RO6867461 Monthly (N=39)	6 mg RO6867461 Monthly(Wk12), Bi-Monthly (Wk28) (N=46)	0.5 mg ranibizumab Monthly(Wk8), 6 mg RO6867461 Monthly (Wk32) (N=64)
くしゃみ	-Any Grade-	0	1	0	0	0
喘鳴	-Any Grade-	0	0	0	0	1
傷害、中毒および処置合併症						
- Overall -	-Any Grade-	4	8	2	5	6
転倒	-Any Grade-	2	2	1	3	3
挫傷	-Any Grade-	0	1	1	1	1
節足動物咬傷	-Any Grade-	0	1	0	0	1
足骨折	-Any Grade-	0	1	0	0	1
裂傷	-Any Grade-	0	1	0	0	1
処置による疼痛	-Any Grade-	1	1	0	0	0
手首関節骨折	-Any Grade-	0	1	1	0	0
骨挫傷	-Any Grade-	0	0	1	0	0
顔面骨骨折	-Any Grade-	1	0	0	0	0
手骨折	-Any Grade-	0	0	1	0	0
頭部損傷	-Any Grade-	0	0	0	0	1
切開部位痛	-Any Grade-	1	0	0	0	0
下肢骨折	-Any Grade-	0	0	0	1	0
多発骨折	-Any Grade-	0	1	0	0	0
過量投与	-Any Grade-	0	1	0	0	0
交通事故	-Any Grade-	1	0	0	0	0
各種物質毒性	-Any Grade-	0	0	0	1	0
上肢骨折	-Any Grade-	0	1	0	0	0
神経系障害						
- Overall -	-Any Grade-	3	8	3	4	7
浮動性めまい	-Any Grade-	1	1	0	2	2
頭痛	-Any Grade-	0	2	0	2	2
認知症	-Any Grade-	0	0	0	1	1
片頭痛	-Any Grade-	0	2	0	0	0

Only the most severe intensity is counted for multiple occurences of the same AE within a Subject at the Preferred Term Level.
The total number of patients with at least one Event is counted in the "- Any Intensity -" and/or "- Overall -" and/or "- Any Adverse Events -" categories.
Investigator text for Adverse Events encoded using MedDRA Version 20.1.

表 2.7.6.2-6 眼以外の有害事象の集計（BP29647試験）（続）

Summary of Systemic Adverse Events by System Organ Class, Preferred Term and Highest Intensity, Safety-Evaluable Patients
Protocol: BP29647

MedDRA System Organ Class MedDRA Preferred Term	Intensity	0.5 mg ranibizumab Monthly (N=67)	1.5 mg RO6867461 Monthly (N=46)	6 mg RO6867461 Monthly (N=39)	6 mg RO6867461 Monthly(Wk12), Bi-Monthly (Wk28) (N=46)	0.5 mg ranibizumab Monthly(Wk8), 6 mg RO6867461 Monthly (Wk32) (N=64)
パーキンソン病	-Any Grade-	1	1	0	0	0
一過性脳虚血発作	-Any Grade-	1	1	0	0	0
健忘	-Any Grade-	0	1	0	0	0
平衡障害	-Any Grade-	0	0	0	0	1
大脳基底核梗塞	-Any Grade-	0	0	0	1	0
手根管症候群	-Any Grade-	0	0	1	0	0
脳血管発作	-Any Grade-	0	0	0	0	1
糖尿病性ニューロパチー	-Any Grade-	0	0	0	0	1
構語障害	-Any Grade-	0	0	0	1	0
神経圧迫	-Any Grade-	0	0	1	0	0
末梢性ニューロパチー	-Any Grade-	0	0	0	0	1
坐骨神経痛	-Any Grade-	0	1	0	0	0
失神	-Any Grade-	0	0	1	0	0
胃腸障害						
- Overall -	-Any Grade-	4	4	5	6	3
下痢	-Any Grade-	1	2	1	2	1
便秘	-Any Grade-	0	2	2	0	0
悪心	-Any Grade-	1	1	1	0	1
胃食道逆流性疾患	-Any Grade-	1	0	1	0	1
腹痛	-Any Grade-	0	1	0	0	0
上腹部痛	-Any Grade-	1	0	0	0	0
齲歯	-Any Grade-	0	0	0	1	0
歯組織の壊死	-Any Grade-	0	0	0	1	0
食中毒	-Any Grade-	0	0	0	1	0
胃障害	-Any Grade-	1	0	0	0	0
鼠径ヘルニア	-Any Grade-	0	0	0	1	0
膵臓障害	-Any Grade-	1	0	0	0	0

Only the most severe intensity is counted for multiple occurences of the same AE within a Subject at the Preferred Term Level.
The total number of patients with at least one Event is counted in the "- Any Intensity -" and/or "- Overall -" and/or "- Any Adverse Events -" categories.
Investigator text for Adverse Events encoded using MedDRA Version 20.1.

表 2.7.6.2-6 眼以外の有害事象の集計（BP29647試験）（続）

Summary of Systemic Adverse Events by System Organ Class, Preferred Term and Highest Intensity, Safety-Evaluable Patients
Protocol: BP29647

MedDRA System Organ Class MedDRA Preferred Term	Intensity	0.5 mg ranibizumab Monthly (N=67)	1.5 mg RO6867461 Monthly (N=46)	6 mg RO6867461 Monthly (N=39)	6 mg RO6867461 Monthly(Wk12), Bi-Monthly (Wk28) (N=46)	0.5 mg ranibizumab Monthly(Wk8), 6 mg RO6867461 Monthly (Wk32) (N=64)
小腸閉塞	-Any Grade-	1	0	0	0	0
嘔吐	-Any Grade-	0	0	0	0	1
臨床検査						
- Overall -	-Any Grade-	4	2	5	5	5
体重減少	-Any Grade-	0	0	2	2	0
血沈亢進	-Any Grade-	0	0	1	0	2
体重増加	-Any Grade-	0	0	2	0	1
血中リン増加	-Any Grade-	0	1	0	0	1
Ｃ－反応性蛋白増加	-Any Grade-	0	0	1	0	1
肝機能検査値上昇	-Any Grade-	0	0	0	1	1
冠血管造影	-Any Grade-	0	0	1	0	0
血中重炭酸塩増加	-Any Grade-	1	0	0	0	0
血球数異常	-Any Grade-	0	0	0	1	0
血中クレアチニン増加	-Any Grade-	0	0	0	1	0
血中ブドウ糖増加	-Any Grade-	1	0	0	0	0
血中カリウム増加	-Any Grade-	1	0	0	0	0
血圧上昇	-Any Grade-	0	1	0	0	0
血中尿素窒素／クレアチニン比増加	-Any Grade-	0	0	0	0	1
骨密度減少	-Any Grade-	0	0	0	1	0
胸部Ｘ線異常	-Any Grade-	1	0	0	0	0
心電図ＱＴ延長	-Any Grade-	0	0	0	1	0
γ－グルタミルトランスフェラーゼ増加	-Any Grade-	0	0	0	0	1
糸球体濾過率減少	-Any Grade-	0	0	0	1	0
グリコヘモグロビン増加	-Any Grade-	1	0	0	0	0
ヘマトクリット減少	-Any Grade-	0	0	0	1	0
リンパ球数減少	-Any Grade-	0	0	0	0	1
血小板数増加	-Any Grade-	0	0	0	1	0
尿検査異常	-Any Grade-	0	0	0	0	1

Only the most severe intensity is counted for multiple occurences of the same AE within a Subject at the Preferred Term Level.
The total number of patients with at least one Event is counted in the "- Any Intensity -" and/or "- Overall -" and/or "- Any Adverse Events -" categories.
Investigator text for Adverse Events encoded using MedDRA Version 20.1.

表 2.7.6.2-6 眼以外の有害事象の集計（BP29647試験）（続）

Summary of Systemic Adverse Events by System Organ Class, Preferred Term and Highest Intensity, Safety-Evaluable Patients
Protocol: BP29647

MedDRA System Organ Class MedDRA Preferred Term	Intensity	0.5 mg ranibizumab Monthly (N=67)	1.5 mg RO6867461 Monthly (N=46)	6 mg RO6867461 Monthly (N=39)	6 mg RO6867461 Monthly(Wk12), Bi-Monthly (Wk28) (N=46)	0.5 mg ranibizumab Monthly(Wk8), 6 mg RO6867461 Monthly (Wk32) (N=64)
血管障害						
- Overall -	-Any Grade-	4	1	4	4	4
高血圧	-Any Grade-	2	1	2	3	3
大動脈瘤	-Any Grade-	1	0	0	0	0
大動脈硬化症	-Any Grade-	0	0	0	0	1
本態性高血圧症	-Any Grade-	0	1	0	0	0
低血圧	-Any Grade-	0	0	1	0	0
リンパ管障害	-Any Grade-	1	0	0	0	0
リンパ浮腫	-Any Grade-	0	0	0	1	0
ショック	-Any Grade-	0	0	1	0	0
心臓障害						
- Overall -	-Any Grade-	4	1	4	2	3
心房細動	-Any Grade-	0	0	1	1	0
冠動脈疾患	-Any Grade-	0	0	1	0	1
心嚢液貯留	-Any Grade-	1	1	0	0	0
急性心筋梗塞	-Any Grade-	0	0	1	0	0
心房粗動	-Any Grade-	0	0	0	1	0
房室ブロック	-Any Grade-	0	0	1	0	0
完全房室ブロック	-Any Grade-	0	0	1	0	0
第一度房室ブロック	-Any Grade-	0	0	0	1	0
徐脈	-Any Grade-	0	0	1	0	0
心停止	-Any Grade-	1	0	0	0	0
心障害	-Any Grade-	1	0	0	0	0
うっ血性心不全	-Any Grade-	0	0	1	0	0
心肺停止	-Any Grade-	0	0	0	0	1
心拡大	-Any Grade-	1	0	0	0	0
心筋症	-Any Grade-	0	0	0	1	0
伝導障害	-Any Grade-	0	0	1	0	0

Only the most severe intensity is counted for multiple occurences of the same AE within a Subject at the Preferred Term Level.
The total number of patients with at least one Event is counted in the "- Any Intensity -" and/or "- Overall -" and/or "- Any Adverse Events -" categories.
Investigator text for Adverse Events encoded using MedDRA Version 20.1.

表 2.7.6.2-6 眼以外の有害事象の集計（BP29647試験）（続）

Summary of Systemic Adverse Events by System Organ Class, Preferred Term and Highest Intensity, Safety-Evaluable Patients
Protocol: BP29647

MedDRA System Organ Class MedDRA Preferred Term	Intensity	0.5 mg ranibizumab Monthly (N=67)	1.5 mg RO6867461 Monthly (N=46)	6 mg RO6867461 Monthly (N=39)	6 mg RO6867461 Monthly(Wk12), Bi-Monthly (Wk28) (N=46)	0.5 mg ranibizumab Monthly(Wk8), 6 mg RO6867461 Monthly (Wk32) (N=64)
心室内伝導障害	-Any Grade-	0	0	1	0	0
変性僧帽弁疾患	-Any Grade-	0	0	0	0	1
洞結節機能不全	-Any Grade-	0	0	1	0	0
精神障害						
- Overall -	-Any Grade-	3	3	2	2	4
不安	-Any Grade-	2	1	1	1	4
うつ病	-Any Grade-	0	2	0	1	0
不眠症	-Any Grade-	1	0	2	0	0
幻視	-Any Grade-	0	1	0	0	0
代謝および栄養障害						
- Overall -	-Any Grade-	2	4	3	2	2
脱水	-Any Grade-	1	2	0	0	0
痛風	-Any Grade-	0	0	1	0	2
高血糖	-Any Grade-	1	1	0	0	0
高脂血症	-Any Grade-	0	1	0	1	0
低カリウム血症	-Any Grade-	0	0	1	1	0
食欲減退	-Any Grade-	0	1	0	0	0
体液貯留	-Any Grade-	0	0	1	0	0
高カリウム血症	-Any Grade-	0	1	0	0	0
高マグネシウム血症	-Any Grade-	0	1	0	0	0
低ナトリウム血症	-Any Grade-	0	1	0	0	0
栄養障害	-Any Grade-	1	0	0	0	0
ビタミンＤ欠乏	-Any Grade-	1	0	0	0	0
皮膚および皮下組織障害						
- Overall -	-Any Grade-	4	4	0	3	2
発疹	-Any Grade-	1	1	0	1	1
乾癬	-Any Grade-	1	1	0	0	0
光線角化症	-Any Grade-	1	0	0	0	0

Only the most severe intensity is counted for multiple occurences of the same AE within a Subject at the Preferred Term Level.
The total number of patients with at least one Event is counted in the "- Any Intensity -" and/or "- Overall -" and/or "- Any Adverse Events -" categories.
Investigator text for Adverse Events encoded using MedDRA Version 20.1.

表 2.7.6.2-6 眼以外の有害事象の集計（BP29647試験）（続）

Summary of Systemic Adverse Events by System Organ Class, Preferred Term and Highest Intensity, Safety-Evaluable Patients
Protocol: BP29647

MedDRA System Organ Class MedDRA Preferred Term	Intensity	0.5 mg ranibizumab Monthly (N=67)	1.5 mg RO6867461 Monthly (N=46)	6 mg RO6867461 Monthly (N=39)	6 mg RO6867461 Monthly(Wk12), Bi-Monthly (Wk28) (N=46)	0.5 mg ranibizumab Monthly(Wk8), 6 mg RO6867461 Monthly (Wk32) (N=64)
皮膚嚢腫	-Any Grade-	0	1	0	0	0
接触皮膚炎	-Any Grade-	0	0	0	1	0
湿疹	-Any Grade-	1	0	0	0	0
紅斑	-Any Grade-	0	1	0	0	0
点状出血	-Any Grade-	0	0	0	0	1
そう痒症	-Any Grade-	0	0	0	1	0
一般・全身障害および投与部位の状態						
- Overall -	-Any Grade-	2	3	2	2	3
胸痛	-Any Grade-	2	0	1	0	0
発熱	-Any Grade-	0	2	0	0	0
無力症	-Any Grade-	0	1	0	0	0
石灰沈着症	-Any Grade-	0	0	0	0	1
嚢胞	-Any Grade-	0	0	0	0	1
滲出液	-Any Grade-	0	1	0	0	0
顔面痛	-Any Grade-	0	0	0	1	0
炎症	-Any Grade-	0	0	0	0	1
インフルエンザ様疾患	-Any Grade-	0	0	1	0	0
非心臓性胸痛	-Any Grade-	0	0	0	1	0
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）						
- Overall -	-Any Grade-	4	3	0	2	2
基底細胞癌	-Any Grade-	1	1	0	0	0
再発膀胱癌	-Any Grade-	0	0	0	0	1
浸潤性乳管癌	-Any Grade-	0	0	0	1	0
乳腺浸潤性小葉癌	-Any Grade-	0	0	0	0	1
Ｌ鎖病	-Any Grade-	0	1	0	0	0
肺腺癌	-Any Grade-	1	0	0	0	0
皮膚の新生物	-Any Grade-	0	0	0	1	0

Only the most severe intensity is counted for multiple occurences of the same AE within a Subject at the Preferred Term Level.
The total number of patients with at least one Event is counted in the "- Any Intensity -" and/or "- Overall -" and/or "- Any Adverse Events -" categories.
Investigator text for Adverse Events encoded using MedDRA Version 20.1.

表 2.7.6.2-6 眼以外の有害事象の集計（BP29647試験）（続）

Summary of Systemic Adverse Events by System Organ Class, Preferred Term and Highest Intensity, Safety-Evaluable Patients
Protocol: BP29647

MedDRA System Organ Class MedDRA Preferred Term	Intensity	0.5 mg ranibizumab Monthly (N=67)	1.5 mg RO6867461 Monthly (N=46)	6 mg RO6867461 Monthly (N=39)	6 mg RO6867461 Monthly(Wk12), Bi-Monthly (Wk28) (N=46)	0.5 mg ranibizumab Monthly(Wk8), 6 mg RO6867461 Monthly (Wk32) (N=64)
膵癌	-Any Grade-	0	1	0	0	0
形質細胞性骨髄腫	-Any Grade-	0	1	0	0	0
腎癌	-Any Grade-	0	1	0	0	0
脂漏性角化症	-Any Grade-	1	0	0	0	0
紡錘細胞肉腫	-Any Grade-	1	0	0	0	0
扁平上皮癌	-Any Grade-	1	0	0	0	0
腎および尿路障害						
- Overall -	-Any Grade-	1	4	2	3	1
腎結石症	-Any Grade-	0	1	1	1	0
腎嚢胞	-Any Grade-	0	1	0	0	1
急性腎障害	-Any Grade-	0	1	0	0	0
糖尿病性腎症	-Any Grade-	0	1	0	0	0
排尿困難	-Any Grade-	0	1	0	0	0
血尿	-Any Grade-	1	0	0	0	0
水腎症	-Any Grade-	0	1	0	0	0
腎不全	-Any Grade-	0	1	0	0	0
腎性高血圧	-Any Grade-	0	0	0	1	0
腎機能障害	-Any Grade-	0	0	1	0	0
尿失禁	-Any Grade-	0	1	0	0	0
尿閉	-Any Grade-	0	0	0	1	0
外科および内科処置						
- Overall -	-Any Grade-	2	4	0	0	2
副鼻腔手術	-Any Grade-	0	1	0	0	1
抜歯	-Any Grade-	0	1	0	0	1
歯内療法	-Any Grade-	1	0	0	0	0
肺切除	-Any Grade-	1	0	0	0	0
皮膚新生物切除	-Any Grade-	0	1	0	0	0

Only the most severe intensity is counted for multiple occurences of the same AE within a Subject at the Preferred Term Level.
The total number of patients with at least one Event is counted in the "- Any Intensity -" and/or "- Overall -" and/or "- Any Adverse Events -" categories.
Investigator text for Adverse Events encoded using MedDRA Version 20.1.

表 2.7.6.2-6 眼以外の有害事象の集計（BP29647試験）（続）

Summary of Systemic Adverse Events by System Organ Class, Preferred Term and Highest Intensity, Safety-Evaluable Patients
Protocol: BP29647

MedDRA System Organ Class MedDRA Preferred Term	Intensity	0.5 mg ranibizumab Monthly (N=67)	1.5 mg RO6867461 Monthly (N=46)	6 mg RO6867461 Monthly (N=39)	6 mg RO6867461 Monthly(Wk12), Bi-Monthly (Wk28) (N=46)	0.5 mg ranibizumab Monthly(Wk8), 6 mg RO6867461 Monthly (Wk32) (N=64)
甲状腺摘除	-Any Grade-	0	1	0	0	0
血液およびリンパ系障害						
- Overall -	-Any Grade-	2	1	1	0	0
貧血	-Any Grade-	1	1	1	0	0
リンパ節症	-Any Grade-	1	0	0	0	0
免疫系障害						
- Overall -	-Any Grade-	1	0	1	1	1
造影剤アレルギー	-Any Grade-	1	0	0	1	0
ワクチンアレルギー	-Any Grade-	0	0	0	0	1
過敏症	-Any Grade-	0	0	1	0	0
耳および迷路障害						
- Overall -	-Any Grade-	0	0	0	1	2
回転性めまい	-Any Grade-	0	0	0	1	2
耳鳴	-Any Grade-	0	0	0	0	1
内分泌障害						
- Overall -	-Any Grade-	1	1	0	0	1
副腎障害	-Any Grade-	1	0	0	0	0
甲状腺機能低下症	-Any Grade-	0	0	0	0	1
甲状腺腫瘤	-Any Grade-	0	1	0	0	0
生殖系および乳房障害						
- Overall -	-Any Grade-	0	1	2	0	0
良性前立腺肥大症	-Any Grade-	0	0	1	0	0
乳房痛	-Any Grade-	0	1	0	0	0
閉経後出血	-Any Grade-	0	0	1	0	0
肝胆道系障害						
- Overall -	-Any Grade-	2	0	0	0	0
胆石症	-Any Grade-	2	0	0	0	0

Only the most severe intensity is counted for multiple occurences of the same AE within a Subject at the Preferred Term Level.
The total number of patients with at least one Event is counted in the "- Any Intensity -" and/or "- Overall -" and/or "- Any Adverse Events -" categories.
Investigator text for Adverse Events encoded using MedDRA Version 20.1.

[5.3.5.1-nAMD-1 t_ae_int_systemic_SAF を改変]

表 2.7.6.2-7 試験眼の副作用の集計（BP29647試験）

MedDRA Preferred Term	0.5 mg ranibizumab Monthly (N=67)	1.5 mg RO6867461 Monthly (N=46)	6 mg RO6867461 Monthly (N=39)	6 mg RO6867461 Monthly (Wk12), Bi-Monthly (Wk28) (N=46)	0.5 mg ranibizumab Monthly(Wk8), 6 mg RO6867461 Monthly(Wk32) (N=64)
STUDY EYE					
Total number of patients with at least one adverse event	3 (4.5%)	4 (8.7%)	3 (7.7%)	3 (6.5%)	0 (0.0%)
Total number of events	5	4	3	3	0
前房のフレア	3 (4.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
網膜色素上皮裂孔	0 (0.0%)	0 (0.0%)	1 (2.6%)	2 (4.3%)	0 (0.0%)
前房内細胞	2 (3.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
眼痛	0 (0.0%)	1 (2.2%)	0 (0.0%)	1 (2.2%)	0 (0.0%)
硝子体浮遊物	0 (0.0%)	1 (2.2%)	1 (2.6%)	0 (0.0%)	0 (0.0%)
眼刺激	0 (0.0%)	0 (0.0%)	1 (2.6%)	0 (0.0%)	0 (0.0%)
網膜出血	0 (0.0%)	1 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
視力障害	0 (0.0%)	1 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Percentages are based on N.
Multiple occurences of the same AE in one individual counted only once except for "total number of events" where all events are being counted.
Investigator text for Adverse Events encoded using MedDRA Version 20.1.
本帳票は, BP29647試験のCSR内, l_ae_systemic_SAF: Listing of Systemic Adverse Events, Safety-Evaluable Patients (Page 1207-), l_ae_ocular_SAF: Listing of Ocular Adverse Events per eye, Safety-Evaluable Patients (Page 1245-), Table 27 Overview of Adverse Events (Safety Evaluable Patients) (Page 139)を基に作成した。

[5.3.5.1-nAMD-1 l_ae_systemic_SAF, l_ae_ocular_SAF 及び Table 27を改変]

表 2.7.6.2-8 試験眼の有害事象の集計（CR39521試験）

MedDRA System Organ Class MedDRA Preferred Term	RO6867461 Q12W (N=24)	RO6867461 Q16W (N=31)	Ranibizumab Q4W (N=16)	Pooled RO6867461 (N=55)
Total number of patients with at least one adverse event	9 (37.5%)	11 (35.5%)	8 (50.0%)	20 (36.4%)
Overall total number of events	18	19	22	37
眼障害				
Total number of patients with at least one adverse event	9 (37.5%)	11 (35.5%)	6 (37.5%)	20 (36.4%)
Total number of events	18	18	15	36
結膜出血	5 (20.8%)	4 (12.9%)	4 (25.0%)	9 (16.4%)
眼痛	2 (8.3%)	0	2 (12.5%)	2 (3.6%)
白内障	1 (4.2%)	1 (3.2%)	0	2 (3.6%)
眼乾燥	0	1 (3.2%)	1 (6.3%)	1 (1.8%)
眼部不快感	0	1 (3.2%)	1 (6.3%)	1 (1.8%)
網膜出血	2 (8.3%)	0	0	2 (3.6%)
前房のフレア	1 (4.2%)	0	0	1 (1.8%)
霰粒腫	1 (4.2%)	0	0	1 (1.8%)
脈絡膜血管新生	1 (4.2%)	0	0	1 (1.8%)
眼出血	0	0	1 (6.3%)	0
眼刺激	1 (4.2%)	0	0	1 (1.8%)
眼そう痒症	1 (4.2%)	0	0	1 (1.8%)
眼の異物感	0	1 (3.2%)	0	1 (1.8%)
虹彩炎	0	1 (3.2%)	0	1 (1.8%)
黄斑症	0	1 (3.2%)	0	1 (1.8%)
高眼圧症	0	0	1 (6.3%)	0
視神経乳頭出血	0	0	1 (6.3%)	0
点状角膜炎	0	1 (3.2%)	0	1 (1.8%)
網膜下線維症	0	1 (3.2%)	0	1 (1.8%)
霧視	0	0	1 (6.3%)	0
視力低下	1 (4.2%)	0	0	1 (1.8%)
硝子体浮遊物	0	0	1 (6.3%)	0
硝子体出血	0	1 (3.2%)	0	1 (1.8%)
臨床検査				
Total number of patients with at least one adverse event	0	0	2 (12.5%)	0
Total number of events	0	0	6	0
眼圧上昇	0	0	1 (6.3%)	0
眼科検査異常	0	0	1 (6.3%)	0
傷害、中毒および処置合併症				
Total number of patients with at least one adverse event	0	0	1 (6.3%)	0
Total number of events	0	0	1	0
結膜擦過傷	0	0	1 (6.3%)	0
血管障害				
Total number of patients with at least one adverse event	0	1 (3.2%)	0	1 (1.8%)
Total number of events	0	1	0	1
動脈瘤	0	1 (3.2%)	0	1 (1.8%)

Investigator text for AEs encoded using MedDRA version 20.1.
Ocular / Non-Ocular AEs defined by location of event specified in eCRF. Events marked as 'Left' or 'Right' are considered as Ocular AEs. 'Not applicable' or unmarked events are considered as Non-Ocular AEs. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of 'Total number of events' rows, multiple occurrences of the same AE in an individual are counted separately.

[5.3.5.1-nAMD-2 Table 26を改変]

表 2.7.6.2-9 非試験眼の有害事象の集計（CR39521試験）

Ocular Adverse Events in the Fellow Eye by System Organ Class and Preferred Term, Safety-Evaluable Patients
Protocol: CR39521

MedDRA System Organ Class MedDRA Preferred Term	RO6867461 Q12W (N=24)	RO6867461 Q16W (N=31)	Ranibizumab Q4W (N=16)	Pooled RO6867461 (N=55)
Total number of patients with at least one adverse event	6 (25.0%)	5 (16.1%)	6 (37.5%)	11 (20.0%)
Overall total number of events	8	8	16	16
眼障害				
Total number of patients with at least one adverse event	5 (20.8%)	5 (16.1%)	6 (37.5%)	10 (18.2%)
Total number of events	7	7	15	14
新生血管加齢黄斑変性	3 (12.5%)	0	2 (12.5%)	3 (5.5%)
白内障	1 (4.2%)	1 (3.2%)	0	2 (3.6%)
網膜出血	0	0	2 (12.5%)	0
硝子体剥離	1 (4.2%)	0	1 (6.3%)	1 (1.8%)
硝子体浮遊物	1 (4.2%)	0	1 (6.3%)	1 (1.8%)
網脈絡膜萎縮	1 (4.2%)	0	0	1 (1.8%)
脈絡膜血管新生	0	0	1 (6.3%)	0
結膜出血	0	0	1 (6.3%)	0
眼の異物感	0	1 (3.2%)	0	1 (1.8%)
黄斑線維症	0	1 (3.2%)	0	1 (1.8%)
黄斑浮腫	0	0	1 (6.3%)	0
黄斑症	0	1 (3.2%)	0	1 (1.8%)
眼部不快感	0	0	1 (6.3%)	0
点状角膜炎	0	1 (3.2%)	0	1 (1.8%)
網膜ドルーゼン	0	1 (3.2%)	0	1 (1.8%)
硝子体障害	0	1 (3.2%)	0	1 (1.8%)
一般・全身障害および投与部位の状態				
Total number of patients with at least one adverse event	0	0	1 (6.3%)	0
Total number of events	0	0	1	0
疼痛	0	0	1 (6.3%)	0
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）				
Total number of patients with at least one adverse event	1 (4.2%)	0	0	1 (1.8%)
Total number of events	1	0	0	1
眼の母斑	1 (4.2%)	0	0	1 (1.8%)
血管障害				
Total number of patients with at least one adverse event	0	1 (3.2%)	0	1 (1.8%)
Total number of events	0	1	0	1
動脈瘤	0	1 (3.2%)	0	1 (1.8%)

Investigator text for AEs encoded using MedDRA version 20.1.
Ocular / Non-Ocular AEs defined by location of event specified in eCRF. Events marked as 'Left' or 'Right' are considered as Ocular AEs. 'Not applicable' or unmarked events are considered as Non-Ocular AEs.
Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.
For frequency counts of 'Total number of events' rows, multiple occurrences of the same AE in an individual are counted separately.

[5.3.5.1-nAMD-2 t_ae_soc_pt_SE_FOCUL を改変]

表 2.7.6.2-10 眼以外の有害事象の集計（CR39521試験）

Non-Ocular Adverse Events by System Organ Class and Preferred Term, Safety-Evaluable Patients
Protocol: CR39521

MedDRA System Organ Class MedDRA Preferred Term	RO6867461 Q12W (N=24)	RO6867461 Q16W (N=31)	Ranibizumab Q4W (N=16)	Pooled RO6867461 (N=55)
Total number of patients with at least one adverse event	14 (58.3%)	20 (64.5%)	9 (56.3%)	34 (61.8%)
Overall total number of events	34	55	19	89
感染症および寄生虫症				
Total number of patients with at least one adverse event	9 (37.5%)	12 (38.7%)	5 (31.3%)	21 (38.2%)
Total number of events	11	18	6	29
上咽頭炎	4 (16.7%)	2 (6.5%)	1 (6.3%)	6 (10.9%)
尿路感染	1 (4.2%)	2 (6.5%)	1 (6.3%)	3 (5.5%)
インフルエンザ	1 (4.2%)	2 (6.5%)	0	3 (5.5%)
副鼻腔炎	1 (4.2%)	1 (3.2%)	0	2 (3.6%)
上気道感染	1 (4.2%)	0	1 (6.3%)	1 (1.8%)
四肢膿瘍	0	1 (3.2%)	0	1 (1.8%)
カテーテル留置部位感染	1 (4.2%)	0	0	1 (1.8%)
蜂巣炎	0	1 (3.2%)	0	1 (1.8%)
耳感染	0	1 (3.2%)	0	1 (1.8%)
皮膚真菌感染	0	0	1 (6.3%)	0
胃腸炎	0	1 (3.2%)	0	1 (1.8%)
ウイルス性胃腸炎	0	1 (3.2%)	0	1 (1.8%)
関節膿瘍	0	1 (3.2%)	0	1 (1.8%)
マイコバクテリウム・アビウムコンプレックス感染	1 (4.2%)	0	0	1 (1.8%)
鼻炎	1 (4.2%)	0	0	1 (1.8%)
敗血症	0	1 (3.2%)	0	1 (1.8%)
皮下組織膿瘍	0	1 (3.2%)	0	1 (1.8%)
歯感染	0	0	1 (6.3%)	0
尿道炎	0	1 (3.2%)	0	1 (1.8%)
膣感染	0	0	1 (6.3%)	0
傷害、中毒および処置合併症				
Total number of patients with at least one adverse event	1 (4.2%)	6 (19.4%)	2 (12.5%)	7 (12.7%)
Total number of events	1	9	2	10
転倒	1 (4.2%)	5 (16.1%)	1 (6.3%)	6 (10.9%)
肉離れ	0	2 (6.5%)	0	2 (3.6%)
肋骨骨折	0	2 (6.5%)	0	2 (3.6%)
眼挫傷	0	0	1 (6.3%)	0

Investigator text for AEs encoded using MedDRA version 20.1.
Ocular / Non-Ocular AEs defined by location of event specified in eCRF. Events marked as 'Left' or 'Right' are considered as Ocular AEs. 'Not applicable' or unmarked events are considered as Non-Ocular AEs.
Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.
For frequency counts of 'Total number of events' rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.6.2-10 眼以外の有害事象の集計（CR39521試験）（続）

Non-Ocular Adverse Events by System Organ Class and Preferred Term, Safety-Evaluable Patients
Protocol: CR39521

MedDRA System Organ Class MedDRA Preferred Term	RO6867461 Q12W (N=24)	RO6867461 Q16W (N=31)	Ranibizumab Q4W (N=16)	Pooled RO6867461 (N=55)
呼吸器、胸郭および縦隔障害				
Total number of patients with at least one adverse event	3 (12.5%)	2 (6.5%)	1 (6.3%)	5 (9.1%)
Total number of events	4	2	1	6
喘息	1 (4.2%)	0	0	1 (1.8%)
慢性閉塞性肺疾患	0	0	1 (6.3%)	0
肺気腫	0	1 (3.2%)	0	1 (1.8%)
低酸素症	1 (4.2%)	0	0	1 (1.8%)
肺水腫	1 (4.2%)	0	0	1 (1.8%)
アレルギー性鼻炎	0	1 (3.2%)	0	1 (1.8%)
鼻漏	1 (4.2%)	0	0	1 (1.8%)
胃腸障害				
Total number of patients with at least one adverse event	1 (4.2%)	2 (6.5%)	2 (12.5%)	3 (5.5%)
Total number of events	1	3	2	4
便秘	0	1 (3.2%)	1 (6.3%)	1 (1.8%)
腹痛	0	0	1 (6.3%)	0
胃食道逆流性疾患	0	1 (3.2%)	0	1 (1.8%)
裂孔ヘルニア	1 (4.2%)	0	0	1 (1.8%)
鼠径ヘルニア	0	1 (3.2%)	0	1 (1.8%)
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）				
Total number of patients with at least one adverse event	2 (8.3%)	2 (6.5%)	1 (6.3%)	4 (7.3%)
Total number of events	2	2	2	4
基底細胞癌	2 (8.3%)	0	0	2 (3.6%)
遠隔転移を伴う新生物	0	1 (3.2%)	0	1 (1.8%)
扁平上皮癌	0	1 (3.2%)	0	1 (1.8%)
皮膚有棘細胞癌	0	0	1 (6.3%)	0
血管障害				
Total number of patients with at least one adverse event	1 (4.2%)	3 (9.7%)	1 (6.3%)	4 (7.3%)
Total number of events	1	3	1	4
高血圧	0	1 (3.2%)	1 (6.3%)	1 (1.8%)
低血圧	1 (4.2%)	1 (3.2%)	0	2 (3.6%)
大動脈狭窄	0	1 (3.2%)	0	1 (1.8%)

Investigator text for AEs encoded using MedDRA version 20.1.
Ocular / Non-Ocular AEs defined by location of event specified in eCRF. Events marked as 'Left' or 'Right' are considered as Ocular AEs. 'Not applicable' or unmarked events are considered as Non-Ocular AEs.
Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.
For frequency counts of 'Total number of events' rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.6.2-10 眼以外の有害事象の集計（CR39521試験）（続）

Non-Ocular Adverse Events by System Organ Class and Preferred Term, Safety-Evaluable Patients
Protocol: CR39521

MedDRA System Organ Class MedDRA Preferred Term	RO6867461 Q12W (N=24)	RO6867461 Q16W (N=31)	Ranibizumab Q4W (N=16)	Pooled RO6867461 (N=55)
心臓障害				
Total number of patients with at least one adverse event	3 (12.5%)	1 (3.2%)	0	4 (7.3%)
Total number of events	4	1	0	5
急性左室不全	1 (4.2%)	0	0	1 (1.8%)
不整脈	1 (4.2%)	0	0	1 (1.8%)
心房細動	0	1 (3.2%)	0	1 (1.8%)
うっ血性心不全	1 (4.2%)	0	0	1 (1.8%)
冠動脈疾患	1 (4.2%)	0	0	1 (1.8%)
筋骨格系および結合組織障害				
Total number of patients with at least one adverse event	0	3 (9.7%)	1 (6.3%)	3 (5.5%)
Total number of events	0	5	1	5
関節痛	0	1 (3.2%)	0	1 (1.8%)
背部痛	0	1 (3.2%)	0	1 (1.8%)
頚部脊柱管狭窄症	0	0	1 (6.3%)	0
変形性関節症	0	1 (3.2%)	0	1 (1.8%)
骨減少症	0	1 (3.2%)	0	1 (1.8%)
神経系障害				
Total number of patients with at least one adverse event	2 (8.3%)	1 (3.2%)	1 (6.3%)	3 (5.5%)
Total number of events	4	1	1	5
頭痛	1 (4.2%)	0	1 (6.3%)	1 (1.8%)
脳梗塞	1 (4.2%)	0	0	1 (1.8%)
虚血性脳小血管疾患	1 (4.2%)	0	0	1 (1.8%)
虚血性脳卒中	1 (4.2%)	0	0	1 (1.8%)
末梢性ニューロパチー	0	1 (3.2%)	0	1 (1.8%)
一般・全身障害および投与部位の状態				
Total number of patients with at least one adverse event	0	2 (6.5%)	1 (6.3%)	2 (3.6%)
Total number of events	0	3	1	3
嚢胞	0	0	1 (6.3%)	0
疲労	0	1 (3.2%)	0	1 (1.8%)
炎症性疼痛	0	1 (3.2%)	0	1 (1.8%)
疼痛	0	1 (3.2%)	0	1 (1.8%)
臨床検査				
Total number of patients with at least one adverse event	1 (4.2%)	1 (3.2%)	1 (6.3%)	2 (3.6%)
Total number of events	1	1	1	2
口蓋生検	0	0	1 (6.3%)	0
血中ナトリウム減少	0	1 (3.2%)	0	1 (1.8%)
心カテーテル検査	1 (4.2%)	0	0	1 (1.8%)

Investigator text for AEs encoded using MedDRA version 20.1.
Ocular / Non-Ocular AEs defined by location of event specified in eCRF. Events marked as 'Left' or 'Right' are considered as Ocular AEs. 'Not applicable' or unmarked events are considered as Non-Ocular AEs.
Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.
For frequency counts of 'Total number of events' rows, multiple occurrences of the same AE in an individual are counted separately.

表 2.7.6.2-10 眼以外の有害事象の集計（CR39521試験）（続）

Non-Ocular Adverse Events by System Organ Class and Preferred Term, Safety-Evaluable Patients
Protocol: CR39521

MedDRA System Organ Class MedDRA Preferred Term	RO6867461 Q12W (N=24)	RO6867461 Q16W (N=31)	Ranibizumab Q4W (N=16)	Pooled RO6867461 (N=55)
精神障害				
Total number of patients with at least one adverse event	1 (4.2%)	2 (6.5%)	0	3 (5.5%)
Total number of events	2	2	0	4
不安	1 (4.2%)	2 (6.5%)	0	3 (5.5%)
精神状態変化	1 (4.2%)	0	0	1 (1.8%)
内分泌障害				
Total number of patients with at least one adverse event	0	2 (6.5%)	0	2 (3.6%)
Total number of events	0	2	0	2
甲状腺機能低下症	0	2 (6.5%)	0	2 (3.6%)
代謝および栄養障害				
Total number of patients with at least one adverse event	0	2 (6.5%)	0	2 (3.6%)
Total number of events	0	2	0	2
糖尿病	0	1 (3.2%)	0	1 (1.8%)
鉄欠乏	0	1 (3.2%)	0	1 (1.8%)
腎および尿路障害				
Total number of patients with at least one adverse event	0	1 (3.2%)	1 (6.3%)	1 (1.8%)
Total number of events	0	1	1	1
膀胱痛	0	1 (3.2%)	0	1 (1.8%)
腎結石症	0	0	1 (6.3%)	0
耳および迷路障害				
Total number of patients with at least one adverse event	1 (4.2%)	0	0	1 (1.8%)
Total number of events	1	0	0	1
回転性めまい	1 (4.2%)	0	0	1 (1.8%)
肝胆道系障害				
Total number of patients with at least one adverse event	1 (4.2%)	0	0	1 (1.8%)
Total number of events	1	0	0	1
胆嚢炎	1 (4.2%)	0	0	1 (1.8%)
免疫系障害				
Total number of patients with at least one adverse event	1 (4.2%)	0	0	1 (1.8%)
Total number of events	1	0	0	1
過敏症	1 (4.2%)	0	0	1 (1.8%)

Investigator text for AEs encoded using MedDRA version 20.1.
Ocular / Non-Ocular AEs defined by location of event specified in eCRF. Events marked as 'Left' or 'Right' are considered as Ocular AEs. 'Not applicable' or unmarked events are considered as Non-Ocular AEs.
Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.
For frequency counts of 'Total number of events' rows, multiple occurrences of the same AE in an individual are counted separately.

[5.3.5.1-nAMD-2 t_ae_soc_pt_SE_NOCUL を改変]

表 2.7.6.2-11 副作用の集計（CR39521試験）

Related AE: Safety Evaluable Patients
Protocol: CR39521

MedDRA Preferred Term	RO6867461 Q12W (N=24)	RO6867461 Q16W (N=31)	Ranibizumab Q4W (N=16)
STUDY EYE			
Total number of patients with at least one adverse event	0 (0.0%)	1 (3.2%)	0 (0.0%)
Total number of events	0	1	0
虹彩炎	0 (0.0%)	1 (3.2%)	0 (0.0%)

Investigator text for AEs encoded using MedDRA version 20.1.
Ocular / Non-Ocular AEs defined by location of event specified in eCRF. Events marked as 'Left' or 'Right' are considered as Ocular AEs. 'Not applicable' or unmarked events are considered as Non-Ocular AEs. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of 'Total number of events' rows, multiple occurrences of the same AE in an individual are counted separately.
本帳票は, CR39521試験のCSR内, l_ae_all_SE3: Listing of Adverse Events, Safety-Evaluable Patients (Page 299-)を基に作成した。

[5.3.5.1-nAMD-2 l_ae_all_SE3を改変]

表 2.7.6.2-12 試験眼の有害事象の集計（GR40306試験）

Ocular Adverse Events in the Study Eye through Week 48, Safety-Evaluable Population
Protocol: GR40306
Clinical Cutoff Date: 26OCT2020

MedDRA Preferred Term	Faricimab 6 mg (N=333)	Aflibercept 2 mg (N=336)
Total number of patients with at least one adverse event	121 (36.3%)	128 (38.1%)
Total number of events	291	254
結膜出血	19 (5.7%)	22 (6.5%)
新生血管加齢黄斑変性	14 (4.2%)	18 (5.4%)
ドライアイ	7 (2.1%)	14 (4.2%)
硝子体剥離	11 (3.3%)	10 (3.0%)
硝子体浮遊物	13 (3.9%)	7 (2.1%)
眼痛	7 (2.1%)	11 (3.3%)
白内障	10 (3.0%)	7 (2.1%)
眼圧上昇	8 (2.4%)	8 (2.4%)
網膜色素上皮裂孔	9 (2.7%)	6 (1.8%)
乾性加齢黄斑変性	5 (1.5%)	7 (2.1%)
眼の異物感	5 (1.5%)	6 (1.8%)
角膜擦過傷	4 (1.2%)	6 (1.8%)
点状角膜炎	5 (1.5%)	5 (1.5%)
眼瞼炎	4 (1.2%)	4 (1.2%)
流涙増加	2 (0.6%)	6 (1.8%)
眼刺激	5 (1.5%)	2 (0.6%)
眼部不快感	4 (1.2%)	3 (0.9%)
光視症	3 (0.9%)	4 (1.2%)
後嚢部混濁	4 (1.2%)	2 (0.6%)
核性白内障	2 (0.6%)	3 (0.9%)
眼そう痒症	2 (0.6%)	3 (0.9%)
眼充血	3 (0.9%)	2 (0.6%)
視神経乳頭出血	2 (0.6%)	3 (0.9%)
霧視	3 (0.9%)	2 (0.6%)

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).
AE reported as neovascular age-related macular degeneration in the study eye indicates an accelerated worsening of the condition, as judged by the investigator.

表 2.7.6.2-12 試験眼の有害事象の集計（GR40306試験）（続）

Ocular Adverse Events in the Study Eye through Week 48, Safety-Evaluable Population
Protocol: GR40306
Clinical Cutoff Date: 26OCT2020

MedDRA Preferred Term	Faricimab 6 mg (N=333)	Aflibercept 2 mg (N=336)
結膜炎	1 (0.3%)	3 (0.9%)
不快感	1 (0.3%)	3 (0.9%)
麦粒腫	2 (0.6%)	2 (0.6%)
投薬過誤	2 (0.6%)	2 (0.6%)
高眼圧症	2 (0.6%)	2 (0.6%)
網膜下線維症	3 (0.9%)	1 (0.3%)
視力低下	1 (0.3%)	3 (0.9%)
アレルギー性結膜炎	1 (0.3%)	2 (0.6%)
角膜びらん	2 (0.6%)	1 (0.3%)
黄斑網膜色素上皮剥離	2 (0.6%)	1 (0.3%)
複視	1 (0.3%)	2 (0.6%)
虹彩炎	2 (0.6%)	1 (0.3%)
変視症	2 (0.6%)	1 (0.3%)
そう痒症	3 (0.9%)	0
加齢黄斑変性	0	2 (0.6%)
境界域緑内障	2 (0.6%)	0
皮質白内障	1 (0.3%)	1 (0.3%)
顔面痛	0	2 (0.6%)
回避された投薬過誤	2 (0.6%)	0
黄斑円孔	2 (0.6%)	0
黄斑部瘢痕	0	2 (0.6%)
疼痛	1 (0.3%)	1 (0.3%)
処置による疼痛	2 (0.6%)	0
ぶどう膜炎	1 (0.3%)	1 (0.3%)
視力障害	1 (0.3%)	1 (0.3%)
硝子体網膜牽引症候群	0	2 (0.6%)
硝子体出血	1 (0.3%)	1 (0.3%)

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).
AE reported as neovascular age-related macular degeneration in the study eye indicates an accelerated worsening of the condition, as judged by the investigator.

表 2.7.6.2-12 試験眼の有害事象の集計（GR40306試験）（続）

Ocular Adverse Events in the Study Eye through Week 48, Safety-Evaluable Population
Protocol: GR40306
Clinical Cutoff Date: 26OCT2020

MedDRA Preferred Term	Faricimab 6 mg (N=333)	Aflibercept 2 mg (N=336)
角膜リポイド環	1 (0.3%)	0
眼精疲労	0	1 (0.3%)
両眼球運動障害	0	1 (0.3%)
眼瞼乳頭腫	0	1 (0.3%)
霰粒腫	0	1 (0.3%)
結膜沈着物	0	1 (0.3%)
結膜浮腫	0	1 (0.3%)
ウイルス性結膜炎	1 (0.3%)	0
角膜浸潤	0	1 (0.3%)
角膜瘢痕	1 (0.3%)	0
網膜色素上皮剥離	1 (0.3%)	0
眼瞼紅斑	1 (0.3%)	0
落屑症候群	0	1 (0.3%)
眼脂	1 (0.3%)	0
眼瞼痛	0	1 (0.3%)
眼瞼腫瘍	1 (0.3%)	0
眼内異物	1 (0.3%)	0
緑内障	0	1 (0.3%)
頭痛	1 (0.3%)	0
星状硝子体症	1 (0.3%)	0
遠視	1 (0.3%)	0
低眼圧	0	1 (0.3%)
涙道の炎症	1 (0.3%)	0
角膜後面沈着物	1 (0.3%)	0
涙液分泌低下	1 (0.3%)	0
黄斑変性	1 (0.3%)	0
黄斑線維症	1 (0.3%)	0

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).
AE reported as neovascular age-related macular degeneration in the study eye indicates an accelerated worsening of the condition, as judged by the investigator.

表 2.7.6.2-12 試験眼の有害事象の集計（GR40306試験）（続）

Ocular Adverse Events in the Study Eye through Week 48, Safety-Evaluable Population
Protocol: GR40306
Clinical Cutoff Date: 26OCT2020

MedDRA Preferred Term	Faricimab 6 mg (N=333)	Aflibercept 2 mg (N=336)
メラノサイト性母斑	0	1 (0.3%)
前房狭隅角	1 (0.3%)	0
視神経乳頭陥凹	0	1 (0.3%)
末梢血管障害	0	1 (0.3%)
瞼裂斑	1 (0.3%)	0
そう痒性皮疹	1 (0.3%)	0
網膜ドルーゼン	0	1 (0.3%)
網膜滲出物	0	1 (0.3%)
網膜出血	1 (0.3%)	0
皮膚病変	0	1 (0.3%)
皮膚乳頭腫	1 (0.3%)	0
眼瞼腫脹	1 (0.3%)	0
ウイルス性ぶどう膜炎	1 (0.3%)	0
硝子体炎	1 (0.3%)	0

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).
AE reported as neovascular age-related macular degeneration in the study eye indicates an accelerated worsening of the condition, as judged by the investigator.

[5.3.5.1-nAMD-3 t_ae_pt_SOCUL_W48_SE_26OCT2020_40306を改変]

表 2.7.6.2-13 非試験眼の有害事象の集計（GR40306試験）

Ocular Adverse Events in the Fellow Eye through Week 48, Safety-Evaluable Population
Protocol: GR40306
Clinical Cutoff Date: 26OCT2020

MedDRA Preferred Term	Faricimab 6 mg (N=333)	Aflibercept 2 mg (N=336)
Total number of patients with at least one adverse event	76 (22.8%)	81 (24.1%)
Total number of events	105	113
新生血管加齢黄斑変性	25 (7.5%)	29 (8.6%)
白内障	9 (2.7%)	5 (1.5%)
硝子体剥離	5 (1.5%)	9 (2.7%)
ドライアイ	4 (1.2%)	9 (2.7%)
結膜出血	6 (1.8%)	6 (1.8%)
眼瞼炎	3 (0.9%)	3 (0.9%)
乾性加齢黄斑変性	2 (0.6%)	4 (1.2%)
点状角膜炎	2 (0.6%)	4 (1.2%)
硝子体浮遊物	3 (0.9%)	3 (0.9%)
アレルギー性結膜炎	2 (0.6%)	2 (0.6%)
後嚢部混濁	2 (0.6%)	2 (0.6%)
結膜炎	1 (0.3%)	2 (0.6%)
黄斑網膜色素上皮剥離	1 (0.3%)	2 (0.6%)
眼そう痒症	0	3 (0.9%)
霧視	1 (0.3%)	2 (0.6%)
視力障害	1 (0.3%)	2 (0.6%)

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).
AE reported as neovascular age-related macular degeneration in the study eye indicates an accelerated worsening of the condition, as judged by the investigator.

表 2.7.6.2-13 非試験眼の有害事象の集計（GR40306試験）（続）

Ocular Adverse Events in the Fellow Eye through Week 48, Safety-Evaluable Population
Protocol: GR40306
Clinical Cutoff Date: 26OCT2020

MedDRA Preferred Term	Faricimab 6 mg (N=333)	Aflibercept 2 mg (N=336)
ウイルス性結膜炎	2 (0.6%)	0
角膜擦過傷	1 (0.3%)	1 (0.3%)
糖尿病網膜症	2 (0.6%)	0
眼の異物感	2 (0.6%)	0
眼圧上昇	1 (0.3%)	1 (0.3%)
黄斑線維症	0	2 (0.6%)
メラノサイト性母斑	1 (0.3%)	1 (0.3%)
疼痛	1 (0.3%)	1 (0.3%)
光視症	1 (0.3%)	1 (0.3%)
処置後炎症	1 (0.3%)	1 (0.3%)
裂孔原性網膜剥離	0	2 (0.6%)
硝子体網膜牽引症候群	0	2 (0.6%)
眼精疲労	0	1 (0.3%)
境界域緑内障	1 (0.3%)	0
皮質白内障	0	1 (0.3%)
核性白内障	0	1 (0.3%)
嚢下白内障	1 (0.3%)	0
霰粒腫	1 (0.3%)	0
細菌性結膜炎	1 (0.3%)	0
角膜内皮炎	1 (0.3%)	0
角膜浮腫	1 (0.3%)	0
角膜瘢痕	1 (0.3%)	0
嚢胞様黄斑浮腫	0	1 (0.3%)
眼瞼皮膚弛緩症	1 (0.3%)	0
複視	1 (0.3%)	0
眼の母斑	1 (0.3%)	0
眼痛	1 (0.3%)	0

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).
AE reported as neovascular age-related macular degeneration in the study eye indicates an accelerated worsening of the condition, as judged by the investigator.

表 2.7.6.2-13 非試験眼の有害事象の集計（GR40306試験）（続）

Ocular Adverse Events in the Fellow Eye through Week 48, Safety-Evaluable Population
Protocol: GR40306
Clinical Cutoff Date: 26OCT2020

MedDRA Preferred Term	Faricimab 6 mg (N=333)	Aflibercept 2 mg (N=336)
眼瞼血腫	1 (0.3%)	0
麦粒腫	0	1 (0.3%)
星状硝子体症	1 (0.3%)	0
虹彩障害	0	1 (0.3%)
角膜炎	1 (0.3%)	0
涙液分泌低下	1 (0.3%)	0
流涙増加	1 (0.3%)	0
黄斑変性	0	1 (0.3%)
黄斑偽円孔	0	1 (0.3%)
筋攣縮	0	1 (0.3%)
前房狭隅角	1 (0.3%)	0
高眼圧症	1 (0.3%)	0
乳頭腫	0	1 (0.3%)
瞼裂斑	1 (0.3%)	0
網膜嚢胞	1 (0.3%)	0
網膜変性	0	1 (0.3%)
網膜出血	1 (0.3%)	0
網膜色素上皮裂孔	1 (0.3%)	0
ぶどう膜炎	0	1 (0.3%)
硝子体変性	1 (0.3%)	0

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).
AE reported as neovascular age-related macular degeneration in the study eye indicates an accelerated worsening of the condition, as judged by the investigator.

[5.3.5.1-nAMD-3 t_ae_pt_FOCUL_W48_SE_26OCT2020_40306を改変]

表 2.7.6.2-14 眼以外の有害事象の集計（GR40306試験）

Non-Ocular Adverse Events through Week 48, Safety-Evaluable Population
Protocol: GR40306
Clinical Cutoff Date: 26OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg (N=333)	Aflibercept 2 mg (N=336)
Total number of patients with at least one adverse event	174 (52.3%)	174 (51.8%)
Overall total number of events	462	445
感染症および寄生虫症		
Total number of patients with at least one adverse event	80 (24.0%)	82 (24.4%)
Total number of events	113	112
上咽頭炎	18 (5.4%)	28 (8.3%)
尿路感染	17 (5.1%)	10 (3.0%)
気管支炎	9 (2.7%)	4 (1.2%)
上気道感染	6 (1.8%)	6 (1.8%)
副鼻腔炎	6 (1.8%)	5 (1.5%)
肺炎	4 (1.2%)	5 (1.5%)
インフルエンザ	3 (0.9%)	5 (1.5%)
膀胱炎	2 (0.6%)	3 (0.9%)
下気道感染	1 (0.3%)	4 (1.2%)
口腔ヘルペス	2 (0.6%)	3 (0.9%)
歯膿瘍	1 (0.3%)	4 (1.2%)
ＣＯＶＩＤ－１９	2 (0.6%)	2 (0.6%)
胃腸炎	3 (0.9%)	1 (0.3%)
蜂巣炎	2 (0.6%)	0
耳感染	2 (0.6%)	0
ウイルス性胃腸炎	0	2 (0.6%)
帯状疱疹	1 (0.3%)	1 (0.3%)
中耳炎	2 (0.6%)	0
咽頭炎	2 (0.6%)	0
ウイルス性気道感染	0	2 (0.6%)
ライノウイルス感染	2 (0.6%)	0
敗血症	0	2 (0.6%)
敗血症性ショック	2 (0.6%)	0
扁桃炎	1 (0.3%)	1 (0.3%)
創傷感染	2 (0.6%)	0
腹部膿瘍	0	1 (0.3%)
腹部感染	1 (0.3%)	0
急性副鼻腔炎	0	1 (0.3%)
細菌性関節炎	1 (0.3%)	0
無症候性ＣＯＶＩＤ－１９	1 (0.3%)	0
胆道性敗血症	1 (0.3%)	0
クロストリジウム・ディフィシレ感染	0	1 (0.3%)
医療機器関連感染	1 (0.3%)	0
憩室炎	0	1 (0.3%)
真菌感染	1 (0.3%)	0
せつ	0	1 (0.3%)
感染性皮膚嚢腫	1 (0.3%)	0
椎間板炎	1 (0.3%)	0
限局性感染	0	1 (0.3%)
肺膿瘍	1 (0.3%)	0
敗血症性心筋炎	1 (0.3%)	0

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Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).

表 2.7.6.2-14 眼以外の有害事象の集計（GR40306試験）（続）

Non-Ocular Adverse Events through Week 48, Safety-Evaluable Population
Protocol: GR40306
Clinical Cutoff Date: 26OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg (N=333)	Aflibercept 2 mg (N=336)
食道カンジダ症	1 (0.3%)	0
口腔カンジダ症	0	1 (0.3%)
急性中耳炎	1 (0.3%)	0
骨盤内炎症性疾患	0	1 (0.3%)
歯周炎	1 (0.3%)	0
眼窩周囲蜂巣炎	0	1 (0.3%)
細菌性肺炎	1 (0.3%)	0
処置後感染	0	1 (0.3%)
歯髄炎	1 (0.3%)	0
鼻炎	1 (0.3%)	0
皮膚感染	0	1 (0.3%)
全身性細菌感染	0	1 (0.3%)
歯感染	0	1 (0.3%)
ウイルス性上気道感染	0	1 (0.3%)
筋骨格系および結合組織障害		
Total number of patients with at least one adverse event	41 (12.3%)	38 (11.3%)
Total number of events	47	47
関節痛	11 (3.3%)	6 (1.8%)
背部痛	7 (2.1%)	10 (3.0%)
関節炎	5 (1.5%)	4 (1.2%)
変形性関節症	4 (1.2%)	3 (0.9%)
骨粗鬆症	2 (0.6%)	2 (0.6%)
腱炎	0	4 (1.2%)
筋痙縮	1 (0.3%)	2 (0.6%)
頚部痛	2 (0.6%)	1 (0.3%)
四肢痛	2 (0.6%)	1 (0.3%)
関節周囲炎	3 (0.9%)	0
肩回旋筋腱板症候群	1 (0.3%)	2 (0.6%)
関節腫脹	1 (0.3%)	1 (0.3%)
筋骨格痛	1 (0.3%)	1 (0.3%)
筋肉痛	1 (0.3%)	1 (0.3%)
骨減少症	0	2 (0.6%)
変形性脊椎症	2 (0.6%)	0
滑液包炎	1 (0.3%)	0
側腹部痛	1 (0.3%)	0
椎間板突出	0	1 (0.3%)
四肢腫瘤	1 (0.3%)	0
筋拘縮	0	1 (0.3%)
筋骨格硬直	0	1 (0.3%)
閉経後骨粗鬆症	0	1 (0.3%)
脊椎すべり症	0	1 (0.3%)
椎間孔狭窄	0	1 (0.3%)

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).

表 2.7.6.2-14 眼以外の有害事象の集計（GR40306試験）（続）

Non-Ocular Adverse Events through Week 48, Safety-Evaluable Population
Protocol: GR40306
Clinical Cutoff Date: 26OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg (N=333)	Aflibercept 2 mg (N=336)
傷害、中毒および処置合併症		
Total number of patients with at least one adverse event	24 (7.2%)	31 (9.2%)
Total number of events	34	44
転倒	4 (1.2%)	10 (3.0%)
挫傷	2 (0.6%)	3 (0.9%)
脊椎圧迫骨折	2 (0.6%)	2 (0.6%)
靱帯捻挫	1 (0.3%)	2 (0.6%)
肉離れ	2 (0.6%)	1 (0.3%)
処置による疼痛	0	3 (0.9%)
肋骨骨折	1 (0.3%)	2 (0.6%)
皮膚裂傷	1 (0.3%)	2 (0.6%)
動物咬傷	2 (0.6%)	0
大腿骨骨折	0	2 (0.6%)
足骨折	2 (0.6%)	0
漿液腫	1 (0.3%)	1 (0.3%)
歯牙破折	1 (0.3%)	1 (0.3%)
術後貧血	0	1 (0.3%)
節足動物咬傷	1 (0.3%)	0
胸部損傷	0	1 (0.3%)
圧迫骨折	0	1 (0.3%)
歯科修復不成功	1 (0.3%)	0
眼挫傷	1 (0.3%)	0
顔面損傷	1 (0.3%)	0
顔面骨骨折	0	1 (0.3%)
手骨折	1 (0.3%)	0
股関節部骨折	0	1 (0.3%)
上腕骨骨折	0	1 (0.3%)
関節脱臼	0	1 (0.3%)
四肢損傷	0	1 (0.3%)
半月板損傷	1 (0.3%)	0
粘膜擦過傷	1 (0.3%)	0
神経損傷	1 (0.3%)	0
骨盤骨折	0	1 (0.3%)
外傷後頚部症候群	1 (0.3%)	0
放射線肺臓炎	1 (0.3%)	0
交通事故	1 (0.3%)	0
皮膚擦過傷	0	1 (0.3%)
ストレス骨折	0	1 (0.3%)
各種物質毒性	0	1 (0.3%)
外傷性血腫	0	1 (0.3%)

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).

表 2.7.6.2-14 眼以外の有害事象の集計（GR40306試験）（続）

Non-Ocular Adverse Events through Week 48, Safety-Evaluable Population
Protocol: GR40306
Clinical Cutoff Date: 26OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg (N=333)	Aflibercept 2 mg (N=336)
神経系障害		
Total number of patients with at least one adverse event	28 (8.4%)	26 (7.7%)
Total number of events	36	34
浮動性めまい	8 (2.4%)	4 (1.2%)
頭痛	7 (2.1%)	5 (1.5%)
坐骨神経痛	3 (0.9%)	5 (1.5%)
脳血管発作	3 (0.9%)	1 (0.3%)
失神	1 (0.3%)	2 (0.6%)
手根管症候群	1 (0.3%)	1 (0.3%)
腰髄神経根障害	1 (0.3%)	1 (0.3%)
片頭痛	0	2 (0.6%)
パーキンソン病	1 (0.3%)	1 (0.3%)
一過性脳虚血発作	2 (0.6%)	0
健忘	1 (0.3%)	0
平衡障害	0	1 (0.3%)
大脳萎縮	0	1 (0.3%)
脳梗塞	0	1 (0.3%)
頚髄神経根障害	1 (0.3%)	0
認知障害	1 (0.3%)	0
脳症	1 (0.3%)	0
頭蓋内出血	1 (0.3%)	0
嗅覚減退	0	1 (0.3%)
ＩＣＵ関連筋力低下	1 (0.3%)	0
末梢性ニューロパチー	0	1 (0.3%)
周期性四肢運動障害	0	1 (0.3%)
外傷後頭痛	1 (0.3%)	0
傾眠	0	1 (0.3%)
三叉神経痛	1 (0.3%)	0

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Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).

表 2.7.6.2-14 眼以外の有害事象の集計（GR40306試験）（続）

Non-Ocular Adverse Events through Week 48, Safety-Evaluable Population
Protocol: GR40306
Clinical Cutoff Date: 26OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg (N=333)	Aflibercept 2 mg (N=336)
胃腸障害		
Total number of patients with at least one adverse event	22 (6.6%)	26 (7.7%)
Total number of events	29	41
下痢	2 (0.6%)	9 (2.7%)
便秘	5 (1.5%)	2 (0.6%)
上腹部痛	2 (0.6%)	2 (0.6%)
悪心	1 (0.3%)	3 (0.9%)
腹痛	3 (0.9%)	0
齲歯	1 (0.3%)	2 (0.6%)
鼠径ヘルニア	1 (0.3%)	2 (0.6%)
腹部不快感	1 (0.3%)	1 (0.3%)
憩室	1 (0.3%)	1 (0.3%)
胃腸出血	0	2 (0.6%)
胃食道逆流性疾患	1 (0.3%)	1 (0.3%)
痔核	0	2 (0.6%)
上部消化管出血	1 (0.3%)	1 (0.3%)
腹部ヘルニア	1 (0.3%)	0
腸憩室	0	1 (0.3%)
消化不良	1 (0.3%)	0
糞塊	0	1 (0.3%)
鼓腸	0	1 (0.3%)
胃腸潰瘍	1 (0.3%)	0
裂孔ヘルニア	1 (0.3%)	0
イレウス	0	1 (0.3%)
嵌頓鼠径ヘルニア	0	1 (0.3%)
腸管虚血	1 (0.3%)	0
腸閉塞	0	1 (0.3%)
大腸閉塞	0	1 (0.3%)
大腸ポリープ	0	1 (0.3%)
下部消化管出血	1 (0.3%)	0
口腔内潰瘍形成	0	1 (0.3%)
非感染性歯肉炎	0	1 (0.3%)
口腔粘膜血腫	1 (0.3%)	0
口腔内痛	0	1 (0.3%)
口内炎	1 (0.3%)	0
歯痛	0	1 (0.3%)
嘔吐	0	1 (0.3%)

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Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).

表 2.7.6.2-14 眼以外の有害事象の集計（GR40306試験）（続）

Non-Ocular Adverse Events through Week 48, Safety-Evaluable Population
Protocol: GR40306
Clinical Cutoff Date: 26OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg (N=333)	Aflibercept 2 mg (N=336)
呼吸器、胸郭および縦隔障害		
Total number of patients with at least one adverse event	20 (6.0%)	26 (7.7%)
Total number of events	20	33
咳嗽	6 (1.8%)	6 (1.8%)
喘息	3 (0.9%)	2 (0.6%)
口腔咽頭痛	1 (0.3%)	3 (0.9%)
鼻漏	1 (0.3%)	3 (0.9%)
慢性閉塞性肺疾患	2 (0.6%)	0
下気道うっ血	1 (0.3%)	1 (0.3%)
鼻閉	1 (0.3%)	1 (0.3%)
誤嚥性肺炎	1 (0.3%)	1 (0.3%)
肺塞栓症	0	2 (0.6%)
無気肺	0	1 (0.3%)
慢性気管支炎	0	1 (0.3%)
咳喘息	0	1 (0.3%)
呼吸困難	0	1 (0.3%)
労作性呼吸困難	1 (0.3%)	0
鼻出血	1 (0.3%)	0
副鼻腔分泌過多	0	1 (0.3%)
胸水	1 (0.3%)	0
肺肉芽腫	1 (0.3%)	0
呼吸不全	0	1 (0.3%)
アレルギー性鼻炎	0	1 (0.3%)
副鼻腔ポリープ	0	1 (0.3%)
上気道の炎症	0	1 (0.3%)

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Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).

表 2.7.6.2-14 眼以外の有害事象の集計（GR40306試験）（続）

Non-Ocular Adverse Events through Week 48, Safety-Evaluable Population
Protocol: GR40306
Clinical Cutoff Date: 26OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg (N=333)	Aflibercept 2 mg (N=336)
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）		
Total number of patients with at least one adverse event	19 (5.7%)	20 (6.0%)
Total number of events	28	20
基底細胞癌	5 (1.5%)	2 (0.6%)
扁平上皮癌	3 (0.9%)	3 (0.9%)
肺の悪性新生物	2 (0.6%)	1 (0.3%)
良性新生物	2 (0.6%)	0
新生物	1 (0.3%)	1 (0.3%)
皮膚癌	2 (0.6%)	0
皮膚乳頭腫	0	2 (0.6%)
皮膚有棘細胞癌	1 (0.3%)	1 (0.3%)
アクロコルドン	0	1 (0.3%)
肛門癌	0	1 (0.3%)
胆道新生物	0	1 (0.3%)
乳癌	0	1 (0.3%)
真珠腫	0	1 (0.3%)
皮膚Ｔ細胞性リンパ腫	1 (0.3%)	0
胃癌	1 (0.3%)	0
良性毛包腫瘍	0	1 (0.3%)
浸潤性乳管癌	0	1 (0.3%)
遠隔転移を伴う肺癌	1 (0.3%)	0
悪性黒色腫	1 (0.3%)	0
髄膜腫	0	1 (0.3%)
遠隔転移を伴う神経内分泌癌	0	1 (0.3%)
前立腺癌	1 (0.3%)	0
直腸癌	1 (0.3%)	0
脂漏性角化症	1 (0.3%)	0
舌の悪性新生物、病期不明	0	1 (0.3%)
血管障害		
Total number of patients with at least one adverse event	19 (5.7%)	13 (3.9%)
Total number of events	20	16
高血圧	16 (4.8%)	7 (2.1%)
深部静脈血栓症	0	2 (0.6%)
低血圧	1 (0.3%)	1 (0.3%)
コントロール不良の血圧	0	1 (0.3%)
本態性高血圧症	1 (0.3%)	0
血腫	0	1 (0.3%)
起立性高血圧	0	1 (0.3%)
起立性低血圧	0	1 (0.3%)
末梢動脈閉塞性疾患	0	1 (0.3%)
表在性血栓性静脈炎	1 (0.3%)	0
四肢静脈血栓症	1 (0.3%)	0

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).

表 2.7.6.2-14 眼以外の有害事象の集計（GR40306試験）（続）

Non-Ocular Adverse Events through Week 48, Safety-Evaluable Population
Protocol: GR40306
Clinical Cutoff Date: 26OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg (N=333)	Aflibercept 2 mg (N=336)
一般・全身障害および投与部位の状態		
Total number of patients with at least one adverse event	16 (4.8%)	13 (3.9%)
Total number of events	17	14
無力症	4 (1.2%)	3 (0.9%)
胸痛	1 (0.3%)	2 (0.6%)
疲労	3 (0.9%)	0
歩行障害	0	2 (0.6%)
インフルエンザ様疾患	2 (0.6%)	0
末梢性浮腫	1 (0.3%)	1 (0.3%)
疼痛	0	2 (0.6%)
発熱	1 (0.3%)	1 (0.3%)
医薬品副作用	0	1 (0.3%)
悪寒	1 (0.3%)	0
嚢胞	1 (0.3%)	0
薬物不耐性	1 (0.3%)	0
倦怠感	0	1 (0.3%)
多臓器機能不全症候群	1 (0.3%)	0
心臓障害		
Total number of patients with at least one adverse event	12 (3.6%)	11 (3.3%)
Total number of events	18	13
心房細動	5 (1.5%)	4 (1.2%)
急性心筋梗塞	1 (0.3%)	1 (0.3%)
うっ血性心不全	1 (0.3%)	1 (0.3%)
頻脈	1 (0.3%)	1 (0.3%)
急性左室不全	1 (0.3%)	0
狭心症	1 (0.3%)	0
不安定狭心症	0	1 (0.3%)
心不全	1 (0.3%)	0
慢性心不全	1 (0.3%)	0
心タンポナーデ	1 (0.3%)	0
慢性左室不全	0	1 (0.3%)
肺性心	1 (0.3%)	0
冠動脈疾患	1 (0.3%)	0
左室拡大	0	1 (0.3%)
僧帽弁閉鎖不全症	0	1 (0.3%)
僧帽弁逸脱	0	1 (0.3%)
動悸	1 (0.3%)	0
収縮性心膜炎	1 (0.3%)	0
心室性期外収縮	0	1 (0.3%)

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).

表 2.7.6.2-14 眼以外の有害事象の集計（GR40306試験）（続）

Non-Ocular Adverse Events through Week 48, Safety-Evaluable Population
Protocol: GR40306
Clinical Cutoff Date: 26OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg (N=333)	Aflibercept 2 mg (N=336)
臨床検査		
Total number of patients with at least one adverse event	12 (3.6%)	10 (3.0%)
Total number of events	22	11
血圧上昇	0	3 (0.9%)
好中球数増加	2 (0.6%)	1 (0.3%)
白血球数増加	2 (0.6%)	1 (0.3%)
血中カリウム増加	2 (0.6%)	0
尿中蛋白陽性	2 (0.6%)	0
アラニンアミノトランスフェラーゼ増加	0	1 (0.3%)
アスパラギン酸アミノトランスフェラーゼ増加	0	1 (0.3%)
胸腔吸引	1 (0.3%)	0
前立腺生検	1 (0.3%)	0
血中コレステロール増加	1 (0.3%)	0
血中ブドウ糖増加	1 (0.3%)	0
血中トリグリセリド増加	1 (0.3%)	0
血中尿酸増加	1 (0.3%)	0
尿中血	0	1 (0.3%)
グリコヘモグロビン増加	0	1 (0.3%)
肝機能検査値上昇	1 (0.3%)	0
リンパ球数増加	1 (0.3%)	0
単球数増加	1 (0.3%)	0
前立腺特異性抗原増加	1 (0.3%)	0
血沈亢進	0	1 (0.3%)
尿潜血陽性	1 (0.3%)	0
ビタミンＢ１２減少	0	1 (0.3%)
ビタミンＤ減少	1 (0.3%)	0
尿中白血球陽性	1 (0.3%)	0
代謝および栄養障害		
Total number of patients with at least one adverse event	9 (2.7%)	12 (3.6%)
Total number of events	10	12
２型糖尿病	2 (0.6%)	2 (0.6%)
高脂血症	1 (0.3%)	2 (0.6%)
低カリウム血症	1 (0.3%)	2 (0.6%)
高コレステロール血症	2 (0.6%)	0
ビタミンＢ群欠乏	1 (0.3%)	1 (0.3%)
ビタミンＢ１２欠乏	0	2 (0.6%)
食欲減退	0	1 (0.3%)
脱水	0	1 (0.3%)
糖尿病	0	1 (0.3%)
脂質異常症	1 (0.3%)	0
ビタミン欠乏症	1 (0.3%)	0
鉄欠乏	1 (0.3%)	0

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).

表 2.7.6.2-14 眼以外の有害事象の集計（GR40306試験）（続）

Non-Ocular Adverse Events through Week 48, Safety-Evaluable Population
Protocol: GR40306
Clinical Cutoff Date: 26OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg (N=333)	Aflibercept 2 mg (N=336)
腎および尿路障害		
Total number of patients with at least one adverse event	11 (3.3%)	10 (3.0%)
Total number of events	13	12
急性腎障害	2 (0.6%)	2 (0.6%)
血尿	2 (0.6%)	2 (0.6%)
腎結石症	0	3 (0.9%)
尿閉	1 (0.3%)	2 (0.6%)
慢性腎臓病	2 (0.6%)	0
膀胱嚢胞	1 (0.3%)	0
排尿困難	1 (0.3%)	0
多尿	1 (0.3%)	0
腎嚢胞	1 (0.3%)	0
腎不全	0	1 (0.3%)
腎損傷	1 (0.3%)	0
腹圧性尿失禁	1 (0.3%)	0
尿失禁	0	1 (0.3%)
尿路閉塞	0	1 (0.3%)
皮膚および皮下組織障害		
Total number of patients with at least one adverse event	13 (3.9%)	8 (2.4%)
Total number of events	18	9
光線角化症	3 (0.9%)	2 (0.6%)
発疹	3 (0.9%)	1 (0.3%)
アレルギー性皮膚炎	1 (0.3%)	1 (0.3%)
蕁麻疹	1 (0.3%)	1 (0.3%)
ざ瘡様皮膚炎	1 (0.3%)	0
乾癬様皮膚炎	0	1 (0.3%)
湿疹	1 (0.3%)	0
手皮膚炎	1 (0.3%)	0
そう痒症	1 (0.3%)	0
紅斑性皮疹	0	1 (0.3%)
脂漏性皮膚炎	1 (0.3%)	0
皮膚潰瘍	0	1 (0.3%)
中毒性皮疹	1 (0.3%)	0
精神障害		
Total number of patients with at least one adverse event	7 (2.1%)	9 (2.7%)
Total number of events	7	9
うつ病	3 (0.9%)	1 (0.3%)
不眠症	2 (0.6%)	2 (0.6%)
不安	0	1 (0.3%)
錯乱状態	0	1 (0.3%)
抑うつ気分	0	1 (0.3%)
遺糞	1 (0.3%)	0
大うつ病	0	1 (0.3%)
混合性不安抑うつ障害	0	1 (0.3%)
ストレス	0	1 (0.3%)
物質誘発性精神病性障害	1 (0.3%)	0

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).

表 2.7.6.2-14 眼以外の有害事象の集計（GR40306試験）（続）

Non-Ocular Adverse Events through Week 48, Safety-Evaluable Population
Protocol: GR40306
Clinical Cutoff Date: 26OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg (N=333)	Aflibercept 2 mg (N=336)
耳および迷路障害		
Total number of patients with at least one adverse event	8 (2.4%)	4 (1.2%)
Total number of events	8	4
回転性めまい	3 (0.9%)	4 (1.2%)
耳垢栓塞	1 (0.3%)	0
両耳難聴	1 (0.3%)	0
耳痛	1 (0.3%)	0
耳鳴	1 (0.3%)	0
頭位性回転性めまい	1 (0.3%)	0
免疫系障害		
Total number of patients with at least one adverse event	7 (2.1%)	2 (0.6%)
Total number of events	7	2
季節性アレルギー	5 (1.5%)	1 (0.3%)
造影剤アレルギー	0	1 (0.3%)
薬物過敏症	1 (0.3%)	0
過敏症	1 (0.3%)	0
生殖系および乳房障害		
Total number of patients with at least one adverse event	5 (1.5%)	3 (0.9%)
Total number of events	6	4
勃起不全	2 (0.6%)	0
萎縮性外陰膣炎	1 (0.3%)	0
膀胱瘤	0	1 (0.3%)
不正子宮出血	1 (0.3%)	0
乳頭痛	1 (0.3%)	0
骨盤痛	0	1 (0.3%)
子宮脱	0	1 (0.3%)
膣出血	1 (0.3%)	0
膣脱	0	1 (0.3%)
血液およびリンパ系障害		
Total number of patients with at least one adverse event	3 (0.9%)	4 (1.2%)
Total number of events	3	4
貧血	1 (0.3%)	3 (0.9%)
鉄欠乏性貧血	1 (0.3%)	1 (0.3%)
ビタミンＢ１２欠乏性貧血	1 (0.3%)	0
眼障害		
Total number of patients with at least one adverse event	2 (0.6%)	2 (0.6%)
Total number of events	2	2
糖尿病網膜症	0	1 (0.3%)
新生血管加齢黄斑変性	0	1 (0.3%)
眼窩周囲痛	1 (0.3%)	0
光視症	1 (0.3%)	0

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).

表 2.7.6.2-14 眼以外の有害事象の集計（GR40306試験）（続）

Non-Ocular Adverse Events through Week 48, Safety-Evaluable Population
Protocol: GR40306
Clinical Cutoff Date: 26OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg (N=333)	Aflibercept 2 mg (N=336)
肝胆道系障害		
Total number of patients with at least one adverse event	3 (0.9%)	1 (0.3%)
Total number of events	4	1
胆石症	1 (0.3%)	1 (0.3%)
胆嚢炎	1 (0.3%)	0
肝嚢胞	1 (0.3%)	0
水腫性胆嚢炎	1 (0.3%)	0
外科および内科処置		
Total number of patients with at least one adverse event	0	1 (0.3%)
Total number of events	0	1
智歯抜歯	0	1 (0.3%)

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).
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[5.3.5.3-nAMD-1 t_ae_NOCUL_W48_SE_26OCT2020_40306を改変]

表 2.7.6.2-15 試験眼の副作用の集計（GR40306試験）

Ocular Adverse Events Related to Study Treatment in the Study Eye through Week 48, Safety-Evaluable Population
Protocol: GR40306
Clinical Cutoff Date: 26OCT2020

MedDRA Preferred Term	Faricimab 6 mg (N=333)	Aflibercept 2 mg (N=336)
Total number of patients with at least one adverse event	9 (2.7%)	9 (2.7%)
Total number of events	11	9
網膜色素上皮裂孔	5 (1.5%)	1 (0.3%)
眼圧上昇	0	2 (0.6%)
高眼圧症	0	2 (0.6%)
ぶどう膜炎	1 (0.3%)	1 (0.3%)
角膜びらん	0	1 (0.3%)
乾性加齢黄斑変性	0	1 (0.3%)
星状硝子体症	1 (0.3%)	0
虹彩炎	1 (0.3%)	0
点状角膜炎	1 (0.3%)	0
視力低下	0	1 (0.3%)
硝子体炎	1 (0.3%)	0

MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1.
Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).

[5.3.5.1-nAMD-3 t_ae_pt_SOCUL_SREL_W48_SE_26OCT2020_40306を改変]

表 2.7.6.2-16 非試験眼の副作用の集計（GR40306試験）

Ocular Adverse Events Related to Study Treatment in the Fellow Eye through Week 48, Safety-Evaluable Population
Protocol: GR40306
Clinical Cutoff Date: 26OCT2020

Null Report: No observations met the reporting criteria for inclusion in this output.

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).

Program: root/clinical_studies/RO6867461/CDPT7716/GR40306/data_analysis/CTD_Tenaya/qa/program/t_ae.sas
Output: root/clinical_studies/RO6867461/CDPT7716/GR40306/data_analysis/CTD_Tenaya/qa/output/t_ae_FOCUL_SREL_W48_SE_amd.out
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[5.3.5.3-nAMD-1 t_ae_FOCUL_SREL_W48_SE_amd を再掲]

表 2.7.6.2-17 眼以外の副作用の集計（GR40306試験）

Non-Ocular Adverse Events Related to Study Treatment through Week 48, Safety-Evaluable Population
Protocol: GR40306
Clinical Cutoff Date: 26OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg (N=333)	Aflibercept 2 mg run (N=336)
Total number of patients with at least one adverse event	0	2 (0.6%)
Overall total number of events	0	2
血管障害		
Total number of patients with at least one adverse event	0	1 (0.3%)
Total number of events	0	1
高血圧	0	1 (0.3%)
神経系障害		
Total number of patients with at least one adverse event	0	1 (0.3%)
Total number of events	0	1
脳血管発作	0	1 (0.3%)

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).

Program: root/clinical_studies/RO6867461/CDPT7716/GR40306/data_analysis/CTD_Tenaya/prod/program/t_ae.sas
Output: root/clinical_studies/RO6867461/CDPT7716/GR40306/data_analysis/CTD_Tenaya/prod/output/t_ae_NOCUL_SREL_W48_SE_amd.out
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[5.3.5.3-nAMD-1 t_ae_NOCUL_SREL_W48_SE_amd を再掲]

表 2.7.6.2-18 試験眼の有害事象の集計（GR40844試験）

Ocular Adverse Events in the Study Eye through Week 48, Safety-Evaluable Population
Protocol: GR40844
Clinical Cutoff Date: 05OCT2020

MedDRA Preferred Term	Faricimab 6 mg (N=331)	Aflibercept 2 mg (N=326)
Total number of patients with at least one adverse event	133 (40.2%)	118 (36.2%)
Total number of events	228	235
結膜出血	26 (7.9%)	29 (8.9%)
新生血管加齢黄斑変性	24 (7.3%)	20 (6.1%)
硝子体剥離	11 (3.3%)	10 (3.1%)
眼痛	10 (3.0%)	9 (2.8%)
白内障	10 (3.0%)	7 (2.1%)
眼圧上昇	9 (2.7%)	7 (2.1%)
ドライアイ	6 (1.8%)	8 (2.5%)
網膜色素上皮裂孔	10 (3.0%)	3 (0.9%)
眼の異物感	5 (1.5%)	7 (2.1%)
点状角膜炎	4 (1.2%)	8 (2.5%)
後嚢部混濁	6 (1.8%)	5 (1.5%)
硝子体浮遊物	7 (2.1%)	4 (1.2%)
眼瞼炎	5 (1.5%)	4 (1.2%)
流涙増加	4 (1.2%)	3 (0.9%)
光視症	3 (0.9%)	4 (1.2%)
眼刺激	4 (1.2%)	2 (0.6%)
緑内障	2 (0.6%)	3 (0.9%)
麦粒腫	4 (1.2%)	1 (0.3%)
虹彩毛様体炎	3 (0.9%)	2 (0.6%)
黄斑線維症	2 (0.6%)	3 (0.9%)
眼部不快感	4 (1.2%)	1 (0.3%)
乾性加齢黄斑変性	3 (0.9%)	1 (0.3%)
投薬過誤	1 (0.3%)	3 (0.9%)
変視症	2 (0.6%)	2 (0.6%)
高眼圧症	1 (0.3%)	3 (0.9%)

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).
AE reported as neovascular age-related macular degeneration in the study eye indicates an accelerated worsening of the condition, as judged by the investigator.

表 2.7.6.2-18 試験眼の有害事象の集計（GR40844試験）（続）

Ocular Adverse Events in the Study Eye through Week 48, Safety-Evaluable Population
Protocol: GR40844
Clinical Cutoff Date: 05OCT2020

MedDRA Preferred Term	Faricimab 6 mg (N=331)	Aflibercept 2 mg (N=326)
眼そう痒症	3 (0.9%)	0
眼瞼下垂	1 (0.3%)	2 (0.6%)
眼充血	1 (0.3%)	2 (0.6%)
網膜下線維症	2 (0.6%)	1 (0.3%)
硝子体網膜牽引症候群	1 (0.3%)	2 (0.6%)
硝子体炎	2 (0.6%)	1 (0.3%)
境界域緑内障	2 (0.6%)	0
霰粒腫	0	2 (0.6%)
結膜充血	0	2 (0.6%)
結膜炎	1 (0.3%)	1 (0.3%)
アレルギー性結膜炎	0	2 (0.6%)
角膜擦過傷	0	2 (0.6%)
角膜浮腫	0	2 (0.6%)
後天性涙道狭窄	0	2 (0.6%)
黄斑網膜色素上皮剥離	1 (0.3%)	1 (0.3%)
回避された投薬過誤	2 (0.6%)	0
虹彩炎	1 (0.3%)	1 (0.3%)
黄斑円孔	0	2 (0.6%)
マイボーム腺機能不全	1 (0.3%)	1 (0.3%)
網膜滲出物	0	2 (0.6%)
ぶどう膜炎	1 (0.3%)	1 (0.3%)
ウイルス性ぶどう膜炎	2 (0.6%)	0
視力障害	1 (0.3%)	1 (0.3%)
硝子体変性	1 (0.3%)	1 (0.3%)
硝子体出血	0	2 (0.6%)
アレルギー性角膜炎	0	1 (0.3%)
閉塞隅角緑内障	1 (0.3%)	0

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).
AE reported as neovascular age-related macular degeneration in the study eye indicates an accelerated worsening of the condition, as judged by the investigator.

表 2.7.6.2-18 試験眼の有害事象の集計（GR40844試験）（続）

Ocular Adverse Events in the Study Eye through Week 48, Safety-Evaluable Population
Protocol: GR40844
Clinical Cutoff Date: 05OCT2020

MedDRA Preferred Term	Faricimab 6 mg (N=331)	Aflibercept 2 mg (N=326)
角膜リポイド環	1 (0.3%)	0
基底細胞癌	0	1 (0.3%)
一過性失明	0	1 (0.3%)
灼熱感	1 (0.3%)	0
皮質白内障	0	1 (0.3%)
嚢下白内障	0	1 (0.3%)
脈絡網膜炎	1 (0.3%)	0
結膜びらん	1 (0.3%)	0
角膜ジストロフィー	0	1 (0.3%)
角膜びらん	1 (0.3%)	0
眼瞼皮膚弛緩症	1 (0.3%)	0
薬物不耐性	0	1 (0.3%)
眼内炎	0	1 (0.3%)
落屑緑内障	1 (0.3%)	0
眼球突出症	0	1 (0.3%)
眼のアレルギー	0	1 (0.3%)
眼脂	1 (0.3%)	0
眼の母斑	0	1 (0.3%)
眼部腫脹	0	1 (0.3%)
眼瞼挫傷	0	1 (0.3%)
眼瞼浮腫	0	1 (0.3%)
顔面骨骨折	0	1 (0.3%)
転倒	0	1 (0.3%)
眼内異物	1 (0.3%)	0
頭部損傷	0	1 (0.3%)
眼の知覚低下	0	1 (0.3%)
注射部位疼痛	0	1 (0.3%)

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).
AE reported as neovascular age-related macular degeneration in the study eye indicates an accelerated worsening of the condition, as judged by the investigator.

表 2.7.6.2-18 試験眼の有害事象の集計（GR40844試験）（続）

Ocular Adverse Events in the Study Eye through Week 48, Safety-Evaluable Population
Protocol: GR40844
Clinical Cutoff Date: 05OCT2020

MedDRA Preferred Term	Faricimab 6 mg (N=331)	Aflibercept 2 mg (N=326)
虹彩徹照異常	1 (0.3%)	0
角膜炎	1 (0.3%)	0
水晶体混濁	1 (0.3%)	0
正常眼圧緑内障	1 (0.3%)	0
黄疸眼	0	1 (0.3%)
開放隅角緑内障	0	1 (0.3%)
眼部単純ヘルペス	1 (0.3%)	0
視神経乳頭出血	0	1 (0.3%)
眼窩周囲痛	1 (0.3%)	0
処置後炎症	0	1 (0.3%)
そう痒症	0	1 (0.3%)
読字障害	1 (0.3%)	0
先天性網膜異常	1 (0.3%)	0
網膜動脈塞栓症	1 (0.3%)	0
網膜障害	0	1 (0.3%)
網膜出血	0	1 (0.3%)
高血圧性網膜症	1 (0.3%)	0
斜視	1 (0.3%)	0
外傷性出血	0	1 (0.3%)
潰瘍性角膜炎	1 (0.3%)	0
霧視	0	1 (0.3%)
視力低下	0	1 (0.3%)

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).
AE reported as neovascular age-related macular degeneration in the study eye indicates an accelerated worsening of the condition, as judged by the investigator.

[5.3.5.1-nAMD-4 t_ae_pt_SOCUL_W48_SE_05OCT2020_40844を改変]

表 2.7.6.2-19 非試験眼の有害事象の集計（GR40844試験）

Ocular Adverse Events in the Fellow Eye through Week 48, Safety-Evaluable Population
Protocol: GR40844
Clinical Cutoff Date: 05OCT2020

MedDRA Preferred Term	Faricimab 6 mg (N=331)	Aflibercept 2 mg (N=326)
Total number of patients with at least one adverse event	93 (28.1%)	81 (24.8%)
Total number of events	132	132
新生血管加齢黄斑変性	29 (8.8%)	22 (6.7%)
硝子体剥離	4 (1.2%)	11 (3.4%)
眼瞼炎	8 (2.4%)	6 (1.8%)
白内障	6 (1.8%)	6 (1.8%)
結膜出血	6 (1.8%)	6 (1.8%)
ドライアイ	7 (2.1%)	5 (1.5%)
後嚢部混濁	5 (1.5%)	4 (1.2%)
緑内障	1 (0.3%)	7 (2.1%)
眼圧上昇	2 (0.6%)	3 (0.9%)
流涙増加	3 (0.9%)	2 (0.6%)
点状角膜炎	2 (0.6%)	3 (0.9%)
麦粒腫	3 (0.9%)	1 (0.3%)
硝子体浮遊物	4 (1.2%)	0
結膜炎	1 (0.3%)	2 (0.6%)
眼そう痒症	3 (0.9%)	0
眼の異物感	2 (0.6%)	1 (0.3%)
高眼圧症	1 (0.3%)	2 (0.6%)
視神経乳頭出血	3 (0.9%)	0
網膜出血	0	3 (0.9%)
硝子体出血	2 (0.6%)	1 (0.3%)

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).
AE reported as neovascular age-related macular degeneration in the study eye indicates an accelerated worsening of the condition, as judged by the investigator.

表 2.7.6.2-19 非試験眼の有害事象の集計（GR40844試験）（続）

Ocular Adverse Events in the Fellow Eye through Week 48, Safety-Evaluable Population
Protocol: GR40844
Clinical Cutoff Date: 05OCT2020

MedDRA Preferred Term	Faricimab 6 mg (N=331)	Aflibercept 2 mg (N=326)
境界域緑内障	2 (0.6%)	0
霰粒腫	1 (0.3%)	1 (0.3%)
結膜充血	0	2 (0.6%)
嚢胞様黄斑浮腫	0	2 (0.6%)
後天性涙道狭窄	0	2 (0.6%)
眼痛	1 (0.3%)	1 (0.3%)
眼瞼下垂	0	2 (0.6%)
虹彩炎	1 (0.3%)	1 (0.3%)
マイボーム腺機能不全	1 (0.3%)	1 (0.3%)
網膜ドルーゼン	0	2 (0.6%)
網膜分離症	2 (0.6%)	0
霧視	1 (0.3%)	1 (0.3%)
光線角化症	1 (0.3%)	0
加齢黄斑変性	1 (0.3%)	0
閉塞隅角緑内障	1 (0.3%)	0
角膜リポイド環	1 (0.3%)	0
眼精疲労	0	1 (0.3%)
皮質白内障	0	1 (0.3%)
嚢下白内障	1 (0.3%)	0
アレルギー性結膜炎	0	1 (0.3%)
細菌性結膜炎	1 (0.3%)	0
角膜ジストロフィー	0	1 (0.3%)
眼瞼皮膚弛緩症	1 (0.3%)	0
薬物不耐性	0	1 (0.3%)
乾性加齢黄斑変性	1 (0.3%)	0
眼内炎	0	1 (0.3%)
眼球陥入	0	1 (0.3%)

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).
AE reported as neovascular age-related macular degeneration in the study eye indicates an accelerated worsening of the condition, as judged by the investigator.

表 2.7.6.2-19 非試験眼の有害事象の集計（GR40844試験）（続）

Ocular Adverse Events in the Fellow Eye through Week 48, Safety-Evaluable Population
Protocol: GR40844
Clinical Cutoff Date: 05OCT2020

MedDRA Preferred Term	Faricimab 6 mg (N=331)	Aflibercept 2 mg (N=326)
落屑緑内障	1 (0.3%)	0
眼脂	1 (0.3%)	0
眼感染	0	1 (0.3%)
眼刺激	1 (0.3%)	0
出血	0	1 (0.3%)
ヘルペス眼感染	0	1 (0.3%)
虹彩毛様体炎	0	1 (0.3%)
虹彩徹照異常	1 (0.3%)	0
角膜炎	0	1 (0.3%)
黄斑変性	1 (0.3%)	0
黄斑線維症	0	1 (0.3%)
黄斑円孔	0	1 (0.3%)
黄斑浮腫	0	1 (0.3%)
非感染性結膜炎	0	1 (0.3%)
正常眼圧緑内障	1 (0.3%)	0
眼部不快感	0	1 (0.3%)
眼充血	1 (0.3%)	0
黄疸眼	0	1 (0.3%)
開放隅角緑内障	0	1 (0.3%)
眼窩周囲出血	0	1 (0.3%)
光視症	0	1 (0.3%)
処置後炎症	1 (0.3%)	0
そう痒症	0	1 (0.3%)
読字障害	1 (0.3%)	0
先天性網膜異常	1 (0.3%)	0
網膜嚢胞	0	1 (0.3%)
網膜変性	1 (0.3%)	0

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).
AE reported as neovascular age-related macular degeneration in the study eye indicates an accelerated worsening of the condition, as judged by the investigator.

表 2.7.6.2-19 非試験眼の有害事象の集計（GR40844試験）（続）

Ocular Adverse Events in the Fellow Eye through Week 48, Safety-Evaluable Population
Protocol: GR40844
Clinical Cutoff Date: 05OCT2020

MedDRA Preferred Term	Faricimab 6 mg (N=331)	Aflibercept 2 mg (N=326)
網膜滲出物	0	1 (0.3%)
網膜裂孔	1 (0.3%)	0
網膜静脈閉塞	1 (0.3%)	0
高血圧性網膜症	1 (0.3%)	0
斜視	1 (0.3%)	0
網膜下線維症	1 (0.3%)	0
縫合関連合併症	1 (0.3%)	0
ウイルス性ぶどう膜炎	0	1 (0.3%)
硝子体混濁	1 (0.3%)	0
硝子体脱出	0	1 (0.3%)

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).
AE reported as neovascular age-related macular degeneration in the study eye indicates an accelerated worsening of the condition, as judged by the investigator.

[5.3.5.1-nAMD-4 t_ae_pt_FOCUL_W48_SE_05OCT2020_40844を改変]

表 2.7.6.2-20 眼以外の有害事象の集計（GR40844試験）

Non-Ocular Adverse Events through Week 48, Safety-Evaluable Population
Protocol: GR40844
Clinical Cutoff Date: 05OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg (N=331)	Aflibercept 2 mg (N=326)
Total number of patients with at least one adverse event	172 (52.0%)	189 (58.0%)
Overall total number of events	452	479
感染症および寄生虫症		
Total number of patients with at least one adverse event	88 (26.6%)	80 (24.5%)
Total number of events	131	110
上咽頭炎	24 (7.3%)	16 (4.9%)
尿路感染	10 (3.0%)	11 (3.4%)
上気道感染	9 (2.7%)	11 (3.4%)
気管支炎	8 (2.4%)	5 (1.5%)
副鼻腔炎	7 (2.1%)	6 (1.8%)
インフルエンザ	8 (2.4%)	4 (1.2%)
帯状疱疹	5 (1.5%)	2 (0.6%)
ウイルス性胃腸炎	4 (1.2%)	2 (0.6%)
ＣＯＶＩＤ－１９	3 (0.9%)	2 (0.6%)
膀胱炎	3 (0.9%)	2 (0.6%)
肺炎	2 (0.6%)	3 (0.9%)
下気道感染	3 (0.9%)	1 (0.3%)
爪真菌症	3 (0.9%)	1 (0.3%)
鼻炎	0	4 (1.2%)
歯膿瘍	2 (0.6%)	2 (0.6%)
創傷感染	0	4 (1.2%)
蜂巣炎	1 (0.3%)	2 (0.6%)
歯肉炎	2 (0.6%)	1 (0.3%)
限局性感染	3 (0.9%)	0
外耳炎	0	3 (0.9%)
気道感染	2 (0.6%)	1 (0.3%)
憩室炎	0	2 (0.6%)
耳感染	1 (0.3%)	1 (0.3%)
皮膚真菌感染	1 (0.3%)	1 (0.3%)
口腔ヘルペス	2 (0.6%)	0
骨髄炎	1 (0.3%)	1 (0.3%)
咽頭炎	2 (0.6%)	0
敗血症	0	2 (0.6%)
歯感染	1 (0.3%)	1 (0.3%)
四肢膿瘍	0	1 (0.3%)
急性副鼻腔炎	1 (0.3%)	0
感染性水疱	1 (0.3%)	0
体部白癬	1 (0.3%)	0
慢性副鼻腔炎	0	1 (0.3%)
丹毒	1 (0.3%)	0
胃腸炎	1 (0.3%)	0
消化管感染	1 (0.3%)	0
ヘルペスウイルス感染	1 (0.3%)	0
感染性胸水	0	1 (0.3%)
感染による慢性閉塞性気道疾患の増悪	0	1 (0.3%)
腎感染	1 (0.3%)	0

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).

表 2.7.6.2-20 眼以外の有害事象の集計（GR40844試験）（続）

Non-Ocular Adverse Events through Week 48, Safety-Evaluable Population
Protocol: GR40844
Clinical Cutoff Date: 05OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg (N=331)	Aflibercept 2 mg (N=326)
迷路炎	1 (0.3%)	0
壊死性筋膜炎	0	1 (0.3%)
口腔カンジダ症	0	1 (0.3%)
耳下腺炎	0	1 (0.3%)
歯周炎	1 (0.3%)	0
細菌性肺炎	0	1 (0.3%)
歯髄炎	0	1 (0.3%)
急性腎盂腎炎	0	1 (0.3%)
ウイルス性気道感染	1 (0.3%)	0
膣感染	1 (0.3%)	0
ウイルス性上気道感染	0	1 (0.3%)
筋骨格系および結合組織障害		
Total number of patients with at least one adverse event	34 (10.3%)	30 (9.2%)
Total number of events	42	35
関節痛	9 (2.7%)	5 (1.5%)
変形性関節症	3 (0.9%)	4 (1.2%)
背部痛	5 (1.5%)	1 (0.3%)
頚部痛	5 (1.5%)	0
四肢痛	0	5 (1.5%)
筋痙縮	2 (0.6%)	2 (0.6%)
脊柱管狭窄症	1 (0.3%)	3 (0.9%)
関節炎	2 (0.6%)	1 (0.3%)
肩回旋筋腱板症候群	2 (0.6%)	1 (0.3%)
椎間板突出	1 (0.3%)	1 (0.3%)
関節滲出液	2 (0.6%)	0
関節腫脹	1 (0.3%)	1 (0.3%)
筋骨格系胸痛	1 (0.3%)	1 (0.3%)
関節リウマチ	1 (0.3%)	1 (0.3%)
骨折による偽関節	1 (0.3%)	0
椎間板変性症	0	1 (0.3%)
脊柱後弯症	0	1 (0.3%)
腰部脊柱管狭窄症	1 (0.3%)	0
筋緊張	1 (0.3%)	0
筋力低下	0	1 (0.3%)
筋骨格障害	0	1 (0.3%)
筋骨格硬直	0	1 (0.3%)
骨壊死	1 (0.3%)	0
横紋筋融解症	0	1 (0.3%)
リウマチ性障害	0	1 (0.3%)
脊椎痛	1 (0.3%)	0

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).

表 2.7.6.2-20 眼以外の有害事象の集計（GR40844試験）（続）

Non-Ocular Adverse Events through Week 48, Safety-Evaluable Population
Protocol: GR40844
Clinical Cutoff Date: 05OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg (N=331)	Aflibercept 2 mg (N=326)
胃腸障害		
Total number of patients with at least one adverse event	25 (7.6%)	33 (10.1%)
Total number of events	28	48
便秘	2 (0.6%)	5 (1.5%)
齲歯	3 (0.9%)	3 (0.9%)
下痢	4 (1.2%)	2 (0.6%)
歯痛	3 (0.9%)	3 (0.9%)
悪心	1 (0.3%)	4 (1.2%)
上腹部痛	1 (0.3%)	3 (0.9%)
胃炎	1 (0.3%)	3 (0.9%)
腹部不快感	1 (0.3%)	1 (0.3%)
食中毒	2 (0.6%)	0
裂孔ヘルニア	2 (0.6%)	0
鼠径ヘルニア	0	2 (0.6%)
大腸ポリープ	1 (0.3%)	1 (0.3%)
腹部膨満	1 (0.3%)	0
腹部ヘルニア	1 (0.3%)	0
腹痛	0	1 (0.3%)
下腹部痛	0	1 (0.3%)
肛門湿疹	0	1 (0.3%)
腹水	0	1 (0.3%)
慢性胃炎	0	1 (0.3%)
腹腔動脈圧迫症候群	1 (0.3%)	0
憩室	0	1 (0.3%)
腸憩室	0	1 (0.3%)
胃粘膜病変	0	1 (0.3%)
胃腸管血管異形成	0	1 (0.3%)
胃腸出血	0	1 (0.3%)
胃腸の炎症	1 (0.3%)	0
消化器痛	0	1 (0.3%)
痔出血	0	1 (0.3%)
痔核	1 (0.3%)	0
機械的イレウス	1 (0.3%)	0
上部消化管出血	0	1 (0.3%)
食道静脈瘤	0	1 (0.3%)
嘔吐	0	1 (0.3%)

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).

表 2.7.6.2-20 眼以外の有害事象の集計（GR40844試験）（続）

Non-Ocular Adverse Events through Week 48, Safety-Evaluable Population
Protocol: GR40844
Clinical Cutoff Date: 05OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg (N=331)	Aflibercept 2 mg (N=326)
傷害、中毒および処置合併症		
Total number of patients with at least one adverse event	24 (7.3%)	26 (8.0%)
Total number of events	38	35
転倒	8 (2.4%)	9 (2.8%)
挫傷	4 (1.2%)	4 (1.2%)
靱帯捻挫	1 (0.3%)	2 (0.6%)
四肢損傷	2 (0.6%)	1 (0.3%)
肋骨骨折	1 (0.3%)	2 (0.6%)
皮膚裂傷	1 (0.3%)	2 (0.6%)
上肢骨折	2 (0.6%)	1 (0.3%)
足骨折	1 (0.3%)	1 (0.3%)
股関節部骨折	2 (0.6%)	0
腰椎骨折	0	2 (0.6%)
交通事故	0	2 (0.6%)
手首関節骨折	0	2 (0.6%)
寛骨臼骨折	1 (0.3%)	0
節足動物咬傷	1 (0.3%)	0
節足動物刺傷	1 (0.3%)	0
石綿肺症	0	1 (0.3%)
脳振盪	1 (0.3%)	0
顔面骨骨折	1 (0.3%)	0
大腿骨頚部骨折	0	1 (0.3%)
手骨折	0	1 (0.3%)
頭部損傷	1 (0.3%)	0
上腕骨骨折	0	1 (0.3%)
損傷	1 (0.3%)	0
関節脱臼	0	1 (0.3%)
人工関節周囲骨折	1 (0.3%)	0
処置による疼痛	1 (0.3%)	0
漿液腫	1 (0.3%)	0
皮膚擦過傷	0	1 (0.3%)
皮膚損傷	1 (0.3%)	0
歯牙破折	0	1 (0.3%)

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).

表 2.7.6.2-20 眼以外の有害事象の集計（GR40844試験）（続）

Non-Ocular Adverse Events through Week 48, Safety-Evaluable Population
Protocol: GR40844
Clinical Cutoff Date: 05OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg (N=331)	Aflibercept 2 mg (N=326)
神経系障害		
Total number of patients with at least one adverse event	24 (7.3%)	25 (7.7%)
Total number of events	29	33
頭痛	8 (2.4%)	6 (1.8%)
浮動性めまい	3 (0.9%)	4 (1.2%)
脳血管発作	1 (0.3%)	3 (0.9%)
失神	1 (0.3%)	3 (0.9%)
虚血性脳卒中	0	2 (0.6%)
末梢性ニューロパチー	2 (0.6%)	0
失神寸前の状態	2 (0.6%)	0
坐骨神経痛	0	2 (0.6%)
一過性脳虚血発作	1 (0.3%)	1 (0.3%)
失語症	1 (0.3%)	0
脳浮腫	1 (0.3%)	0
頚動脈狭窄	0	1 (0.3%)
大脳萎縮	1 (0.3%)	0
脳出血	0	1 (0.3%)
頚髄神経根障害	0	1 (0.3%)
認知障害	1 (0.3%)	0
脳症	0	1 (0.3%)
感覚鈍麻	1 (0.3%)	0
ラクナ脳卒中	0	1 (0.3%)
片頭痛	0	1 (0.3%)
発作後麻痺	1 (0.3%)	0
痙攣発作	0	1 (0.3%)
副鼻腔炎に伴う頭痛	0	1 (0.3%)
くも膜下出血	1 (0.3%)	0
血栓性脳梗塞	1 (0.3%)	0
三叉神経痛	1 (0.3%)	0

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Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).

表 2.7.6.2-20 眼以外の有害事象の集計（GR40844試験）（続）

Non-Ocular Adverse Events through Week 48, Safety-Evaluable Population
Protocol: GR40844
Clinical Cutoff Date: 05OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg (N=331)	Aflibercept 2 mg (N=326)
呼吸器、胸郭および縦隔障害		
Total number of patients with at least one adverse event	21 (6.3%)	19 (5.8%)
Total number of events	27	22
呼吸困難	1 (0.3%)	7 (2.1%)
慢性閉塞性肺疾患	4 (1.2%)	3 (0.9%)
咳嗽	6 (1.8%)	1 (0.3%)
喘息	2 (0.6%)	2 (0.6%)
口腔咽頭痛	2 (0.6%)	1 (0.3%)
鼻漏	3 (0.9%)	0
肺塞栓症	1 (0.3%)	1 (0.3%)
無気肺	0	1 (0.3%)
気管支拡張症	0	1 (0.3%)
低酸素症	0	1 (0.3%)
間質性肺疾患	0	1 (0.3%)
アレルギー性喉頭炎	1 (0.3%)	0
肺穿孔	0	1 (0.3%)
閉塞性気道障害	1 (0.3%)	0
肺臓炎	0	1 (0.3%)
肺腫瘤	1 (0.3%)	0
アレルギー性鼻炎	1 (0.3%)	0
副鼻腔障害	1 (0.3%)	0
代謝および栄養障害		
Total number of patients with at least one adverse event	19 (5.7%)	19 (5.8%)
Total number of events	22	27
高コレステロール血症	4 (1.2%)	3 (0.9%)
痛風	2 (0.6%)	2 (0.6%)
ビタミンＢ１２欠乏	2 (0.6%)	2 (0.6%)
脱水	1 (0.3%)	2 (0.6%)
糖尿病	2 (0.6%)	1 (0.3%)
高血糖	2 (0.6%)	1 (0.3%)
高脂血症	1 (0.3%)	2 (0.6%)
低カリウム血症	0	3 (0.9%)
低マグネシウム血症	1 (0.3%)	2 (0.6%)
ビタミンＤ欠乏	1 (0.3%)	2 (0.6%)
水分過負荷	1 (0.3%)	1 (0.3%)
高カリウム血症	1 (0.3%)	1 (0.3%)
低ナトリウム血症	1 (0.3%)	1 (0.3%)
異常体重減少	1 (0.3%)	0
脂質異常症	0	1 (0.3%)
体液貯留	1 (0.3%)	0
耐糖能障害	1 (0.3%)	0
高トリグリセリド血症	0	1 (0.3%)
鉄欠乏	0	1 (0.3%)
乳酸アシドーシス	0	1 (0.3%)

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).

表 2.7.6.2-20 眼以外の有害事象の集計（GR40844試験）（続）

Non-Ocular Adverse Events through Week 48, Safety-Evaluable Population
Protocol: GR40844
Clinical Cutoff Date: 05OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg (N=331)	Aflibercept 2 mg (N=326)
心臓障害		
Total number of patients with at least one adverse event	16 (4.8%)	20 (6.1%)
Total number of events	23	34
うっ血性心不全	4 (1.2%)	4 (1.2%)
心房細動	2 (0.6%)	4 (1.2%)
心不全	1 (0.3%)	3 (0.9%)
冠動脈疾患	2 (0.6%)	2 (0.6%)
狭心症	1 (0.3%)	1 (0.3%)
急性心筋梗塞	1 (0.3%)	0
大動脈弁閉鎖不全症	0	1 (0.3%)
不整脈	1 (0.3%)	0
冠動脈硬化症	0	1 (0.3%)
徐脈	1 (0.3%)	0
心機能障害	0	1 (0.3%)
心拡大	0	1 (0.3%)
心肺不全	0	1 (0.3%)
慢性左室不全	0	1 (0.3%)
うっ血性心筋症	0	1 (0.3%)
ドレスラー症候群	1 (0.3%)	0
左室機能不全	0	1 (0.3%)
心筋梗塞	0	1 (0.3%)
心筋虚血	1 (0.3%)	0
動悸	1 (0.3%)	0
発作性房室ブロック	0	1 (0.3%)
心嚢液貯留	1 (0.3%)	0
心膜炎	1 (0.3%)	0
洞性頻脈	0	1 (0.3%)
上室性期外収縮	0	1 (0.3%)
心室性期外収縮	1 (0.3%)	0
心室細動	1 (0.3%)	0

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Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).

表 2.7.6.2-20 眼以外の有害事象の集計（GR40844試験）（続）

Non-Ocular Adverse Events through Week 48, Safety-Evaluable Population
Protocol: GR40844
Clinical Cutoff Date: 05OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg (N=331)	Aflibercept 2 mg (N=326)
血管障害		
Total number of patients with at least one adverse event	14 (4.2%)	20 (6.1%)
Total number of events	17	21
高血圧	8 (2.4%)	9 (2.8%)
静脈瘤	2 (0.6%)	1 (0.3%)
大動脈拡張	0	2 (0.6%)
血腫	1 (0.3%)	1 (0.3%)
起立性低血圧	1 (0.3%)	1 (0.3%)
末梢静脈疾患	0	2 (0.6%)
血栓性静脈炎	2 (0.6%)	0
大動脈硬化症	0	1 (0.3%)
大動脈狭窄	1 (0.3%)	0
高血圧クリーゼ	1 (0.3%)	0
低血圧	0	1 (0.3%)
リンパ浮腫	0	1 (0.3%)
末梢冷感	0	1 (0.3%)
血栓症	1 (0.3%)	0
静脈虚脱	0	1 (0.3%)

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Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).

表 2.7.6.2-20 眼以外の有害事象の集計（GR40844試験）（続）

Non-Ocular Adverse Events through Week 48, Safety-Evaluable Population
Protocol: GR40844
Clinical Cutoff Date: 05OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg (N=331)	Aflibercept 2 mg (N=326)
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）		
Total number of patients with at least one adverse event	16 (4.8%)	16 (4.9%)
Total number of events	18	20
基底細胞癌	5 (1.5%)	3 (0.9%)
メラノサイト性母斑	1 (0.3%)	1 (0.3%)
膵癌	1 (0.3%)	1 (0.3%)
扁平上皮癌	2 (0.6%)	0
腺癌	1 (0.3%)	0
食道の良性新生物	1 (0.3%)	0
胆管癌	0	1 (0.3%)
膀胱新生物	0	1 (0.3%)
乳癌第４期	1 (0.3%)	0
大腸腺腫	0	1 (0.3%)
本態性血小板血症	1 (0.3%)	0
節外性辺縁帯Ｂ細胞リンパ腫（ＭＡＬＴ型）	0	1 (0.3%)
消化器癌	0	1 (0.3%)
多形性神経膠芽細胞腫	0	1 (0.3%)
皮膚血管腫	0	1 (0.3%)
良性若年性黒色腫	1 (0.3%)	0
遠隔転移を伴う肺癌	0	1 (0.3%)
肺の悪性新生物	1 (0.3%)	0
リンパ管腫	1 (0.3%)	0
髄膜腫	0	1 (0.3%)
肝転移	0	1 (0.3%)
骨髄異形成症候群	0	1 (0.3%)
遠隔転移を伴う卵巣癌	1 (0.3%)	0
前立腺癌	0	1 (0.3%)
肉腫様癌	0	1 (0.3%)
肺肉腫様癌	0	1 (0.3%)
肺扁平上皮癌	1 (0.3%)	0

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).

表 2.7.6.2-20 眼以外の有害事象の集計（GR40844試験）（続）

Non-Ocular Adverse Events through Week 48, Safety-Evaluable Population
Protocol: GR40844
Clinical Cutoff Date: 05OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg (N=331)	Aflibercept 2 mg (N=326)
一般・全身障害および投与部位の状態		
Total number of patients with at least one adverse event	17 (5.1%)	10 (3.1%)
Total number of events	18	11
末梢腫脹	4 (1.2%)	1 (0.3%)
末梢性浮腫	1 (0.3%)	3 (0.9%)
疲労	2 (0.6%)	1 (0.3%)
無力症	2 (0.6%)	0
疼痛	0	2 (0.6%)
発熱	2 (0.6%)	0
医薬品副作用	1 (0.3%)	0
乳房インプラント関連被膜拘縮	1 (0.3%)	0
カテーテル留置部位血腫	0	1 (0.3%)
胸部不快感	1 (0.3%)	0
胸痛	0	1 (0.3%)
嚢胞	1 (0.3%)	0
死亡	0	1 (0.3%)
不明確な障害	1 (0.3%)	0
インフルエンザ様疾患	1 (0.3%)	0
倦怠感	1 (0.3%)	0
非心臓性胸痛	0	1 (0.3%)
皮膚および皮下組織障害		
Total number of patients with at least one adverse event	12 (3.6%)	12 (3.7%)
Total number of events	15	13
発疹	3 (0.9%)	2 (0.6%)
蕁麻疹	3 (0.9%)	0
光線角化症	1 (0.3%)	1 (0.3%)
皮膚嚢腫	1 (0.3%)	1 (0.3%)
接触皮膚炎	1 (0.3%)	1 (0.3%)
皮膚乾燥	1 (0.3%)	1 (0.3%)
褥瘡性潰瘍	0	1 (0.3%)
皮膚炎	0	1 (0.3%)
湿疹	0	1 (0.3%)
貨幣状湿疹	0	1 (0.3%)
過角化	1 (0.3%)	0
硬化性苔癬	0	1 (0.3%)
神経皮膚炎	0	1 (0.3%)
そう痒症	1 (0.3%)	0
紅斑性皮疹	0	1 (0.3%)
皮膚病変	1 (0.3%)	0

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).

表 2.7.6.2-20 眼以外の有害事象の集計（GR40844試験）（続）

Non-Ocular Adverse Events through Week 48, Safety-Evaluable Population
Protocol: GR40844
Clinical Cutoff Date: 05OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg (N=331)	Aflibercept 2 mg (N=326)
臨床検査		
Total number of patients with at least one adverse event	10 (3.0%)	11 (3.4%)
Total number of events	11	15
血圧上昇	1 (0.3%)	5 (1.5%)
体重減少	1 (0.3%)	2 (0.6%)
アラニンアミノトランスフェラーゼ増加	1 (0.3%)	0
細菌検査陽性	0	1 (0.3%)
血中クレアチニン増加	1 (0.3%)	0
血圧低下	1 (0.3%)	0
心カテーテル検査	1 (0.3%)	0
凝固因子増加	0	1 (0.3%)
尿中結晶陽性	0	1 (0.3%)
心電図異常	1 (0.3%)	0
グリコヘモグロビン増加	1 (0.3%)	0
心拍数不整	1 (0.3%)	0
酸素飽和度低下	1 (0.3%)	0
前立腺特異性抗原増加	1 (0.3%)	0
尿中蛋白陽性	0	1 (0.3%)
血沈亢進	0	1 (0.3%)
尿円柱陽性	0	1 (0.3%)
白血球数増加	0	1 (0.3%)
精神障害		
Total number of patients with at least one adverse event	10 (3.0%)	7 (2.1%)
Total number of events	10	7
不安	2 (0.6%)	3 (0.9%)
うつ病	4 (1.2%)	1 (0.3%)
不眠症	1 (0.3%)	1 (0.3%)
不安障害	1 (0.3%)	0
コミュニケーション障害	0	1 (0.3%)
恐怖	1 (0.3%)	0
混合性不安抑うつ障害	1 (0.3%)	0
処置に対する不安	0	1 (0.3%)
耳および迷路障害		
Total number of patients with at least one adverse event	6 (1.8%)	10 (3.1%)
Total number of events	6	11
回転性めまい	3 (0.9%)	5 (1.5%)
耳痛	2 (0.6%)	0
耳鳴	1 (0.3%)	1 (0.3%)
難聴	0	1 (0.3%)
耳管閉塞	0	1 (0.3%)
外耳の炎症	0	1 (0.3%)
頭位性回転性めまい	0	1 (0.3%)

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).

表 2.7.6.2-20 眼以外の有害事象の集計（GR40844試験）（続）

Non-Ocular Adverse Events through Week 48, Safety-Evaluable Population
Protocol: GR40844
Clinical Cutoff Date: 05OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg (N=331)	Aflibercept 2 mg (N=326)
血液およびリンパ系障害		
Total number of patients with at least one adverse event	5 (1.5%)	9 (2.8%)
Total number of events	5	11
貧血	3 (0.9%)	1 (0.3%)
鉄欠乏性貧血	1 (0.3%)	2 (0.6%)
汎血球減少症	0	3 (0.9%)
血小板減少症	1 (0.3%)	1 (0.3%)
溶血性貧血	0	1 (0.3%)
肺門リンパ節腫脹	0	1 (0.3%)
白血球減少症	0	1 (0.3%)
血小板増加症	0	1 (0.3%)
肝胆道系障害		
Total number of patients with at least one adverse event	2 (0.6%)	6 (1.8%)
Total number of events	2	6
胆石症	2 (0.6%)	0
胆道閉塞	0	1 (0.3%)
胆嚢炎	0	1 (0.3%)
急性胆嚢炎	0	1 (0.3%)
肝線維症	0	1 (0.3%)
脂肪肝	0	1 (0.3%)
肝静脈血栓症	0	1 (0.3%)
免疫系障害		
Total number of patients with at least one adverse event	4 (1.2%)	4 (1.2%)
Total number of events	5	4
季節性アレルギー	4 (1.2%)	2 (0.6%)
節足動物咬傷アレルギー	0	1 (0.3%)
ダニアレルギー	1 (0.3%)	0
ゴム過敏症	0	1 (0.3%)
腎および尿路障害		
Total number of patients with at least one adverse event	2 (0.6%)	6 (1.8%)
Total number of events	2	7
腎結石症	0	2 (0.6%)
急性腎障害	0	1 (0.3%)
慢性腎臓病	0	1 (0.3%)
出血性膀胱炎	0	1 (0.3%)
緊張性膀胱	1 (0.3%)	0
夜間頻尿	1 (0.3%)	0
尿失禁	0	1 (0.3%)
尿閉	0	1 (0.3%)

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).

表 2.7.6.2-20 眼以外の有害事象の集計（GR40844試験）（続）

Non-Ocular Adverse Events through Week 48, Safety-Evaluable Population
Protocol: GR40844
Clinical Cutoff Date: 05OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg (N=331)	Aflibercept 2 mg (N=326)
生殖系および乳房障害		
Total number of patients with at least one adverse event	3 (0.9%)	4 (1.2%)
Total number of events	3	4
前立腺腫大	0	3 (0.9%)
良性前立腺肥大症	1 (0.3%)	1 (0.3%)
骨盤痛	1 (0.3%)	0
外陰腟そう痒症	1 (0.3%)	0
眼障害		
Total number of patients with at least one adverse event	0	3 (0.9%)
Total number of events	0	3
ドライアイ	0	1 (0.3%)
流涙増加	0	1 (0.3%)
新生血管加齢黄斑変性	0	1 (0.3%)
内分泌障害		
Total number of patients with at least one adverse event	0	1 (0.3%)
Total number of events	0	1
甲状腺機能低下症	0	1 (0.3%)
製品の問題		
Total number of patients with at least one adverse event	0	1 (0.3%)
Total number of events	0	1
医療機器機能不良	0	1 (0.3%)

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).

[5.3.5.3-nAMD-1 t_ae_NOCUL_W48_SE_05OCT2020_40844を改変]

表 2.7.6.2-21 試験眼の副作用の集計（GR40844試験）

Ocular Adverse Events Related to Study Treatment in the Study Eye through Week 48, Safety-Evaluable Population
Protocol: GR40844
Clinical Cutoff Date: 05OCT2020

MedDRA Preferred Term	Faricimab 6 mg (N=331)	Aflibercept 2 mg (N=326)
Total number of patients with at least one adverse event	10 (3.0%)	8 (2.5%)
Total number of events	11	9
網膜色素上皮裂孔	3 (0.9%)	1 (0.3%)
眼圧上昇	2 (0.6%)	1 (0.3%)
虹彩毛様体炎	2 (0.6%)	1 (0.3%)
硝子体炎	2 (0.6%)	1 (0.3%)
ぶどう膜炎	1 (0.3%)	1 (0.3%)
硝子体浮遊物	1 (0.3%)	1 (0.3%)
虹彩炎	0	1 (0.3%)
処置後炎症	0	1 (0.3%)

MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1.
Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 349 (last day of Week 48 analysis visit window).

[5.3.5.1-nAMD-4 t_ae_pt_SOCUL_SREL_W48_SE_05OCT2020_40844を改変]

表 2.7.6.2-22 試験眼の有害事象の集計（BP30099試験）

Summary of Ocular Adverse Events (Study Eye) by System Organ Class, Preferred Term and Highest Intensity up to Week 24, Safety-Evaluable Patients
Protocol: BP30099

MedDRA System Organ Class MedDRA Preferred Term	Intensity	0.3 mg Ranibizumab (N=89)	1.5 mg RO6867461 (N=55)	6 mg RO6867461 (N=80)
- Any adverse events -	-Any Grade-	22	16	22
眼障害				
- Overall -	-Any Grade-	22	16	22
結膜出血	-Any Grade-	4	2	8
眼痛	-Any Grade-	2	3	2
硝子体浮遊物	-Any Grade-	1	2	2
白内障	-Any Grade-	2	0	2
眼乾燥	-Any Grade-	1	0	3
網膜滲出物	-Any Grade-	1	1	2
霧視	-Any Grade-	1	2	1
硝子体剥離	-Any Grade-	1	2	1
硝子体出血	-Any Grade-	3	0	1
眼そう痒症	-Any Grade-	1	1	1
核性白内障	-Any Grade-	0	1	1
嚢下白内障	-Any Grade-	1	1	0
糖尿病性網膜浮腫	-Any Grade-	1	1	0
眼瞼浮腫	-Any Grade-	0	2	0
流涙増加	-Any Grade-	1	0	1
高眼圧症	-Any Grade-	0	1	1
羞明	-Any Grade-	1	0	1
点状角膜炎	-Any Grade-	1	0	1
視力障害	-Any Grade-	0	1	1
眼瞼炎	-Any Grade-	1	0	0
境界域緑内障	-Any Grade-	0	0	1
網脈絡膜萎縮	-Any Grade-	0	1	0
糖尿病網膜症	-Any Grade-	1	0	0
複視	-Any Grade-	0	1	0
眼部腫脹	-Any Grade-	1	0	0
緑内障	-Any Grade-	0	0	1
角膜症	-Any Grade-	1	0	0
水晶体障害	-Any Grade-	0	0	1
黄斑嚢胞	-Any Grade-	1	0	0
色素散乱症候群	-Any Grade-	1	0	0
後嚢部混濁	-Any Grade-	0	1	0
一般・全身障害および投与部位の状態				
- Overall -	-Any Grade-	0	1	1
医薬品副作用	-Any Grade-	0	1	0
異物感	-Any Grade-	0	0	1
免疫系障害				
- Overall -	-Any Grade-	0	0	1
季節性アレルギー	-Any Grade-	0	0	1
傷害、中毒および処置合併症				
- Overall -	-Any Grade-	0	1	0
角膜擦過傷	-Any Grade-	0	1	0
臨床検査				
- Overall -	-Any Grade-	0	1	0
眼圧上昇	-Any Grade-	0	1	0

Only the most severe intensity is counted for multiple occurences of the same AE within a Subject at the Preferred Term Level.
The total number of patients with at least one Event is counted in the "- Any Intensity -" and/or "- Overall -" and/or "- Any Adverse Events -" categories.
Investigator text for Adverse Events encoded using MedDRA Version 20.1.
Includes only events within 28 days of the Week 20 visit

[5.3.5.1-DME-1 t_ae_int_ocular_s_SAF を改変]

表 2.7.6.2-23 非試験眼の有害事象の集計（BP30099試験）

Summary of Ocular Adverse Events (Fellow Eye) by System Organ Class, Preferred Term and Highest Intensity up to Week 24, Safety-Evaluable Patients
Protocol: BP30099

MedDRA System Organ Class MedDRA Preferred Term	Intensity	0.3 mg Ranibizumab (N=89)	1.5 mg RO6867461 (N=55)	6 mg RO6867461 (N=80)
- Any adverse events -	-Any Grade-	19	14	18
眼障害				
- Overall -	-Any Grade-	18	14	17
糖尿病性網膜浮腫	-Any Grade-	2	2	4
霧視	-Any Grade-	1	2	2
眼乾燥	-Any Grade-	2	0	2
白内障	-Any Grade-	2	0	1
後嚢部混濁	-Any Grade-	2	1	0
網膜滲出物	-Any Grade-	1	1	1
網膜出血	-Any Grade-	2	1	0
硝子体浮遊物	-Any Grade-	1	1	1
核性白内障	-Any Grade-	0	1	1
嚢下白内障	-Any Grade-	0	2	0
結膜出血	-Any Grade-	2	0	0
黄斑浮腫	-Any Grade-	2	0	0
点状角膜炎	-Any Grade-	1	0	1
視力低下	-Any Grade-	0	1	1
深径覚の変化	-Any Grade-	1	0	0
境界域緑内障	-Any Grade-	0	0	1
網脈絡膜萎縮	-Any Grade-	0	1	0
複視	-Any Grade-	0	1	0
眼痛	-Any Grade-	1	0	0
緑内障	-Any Grade-	0	0	1
流涙増加	-Any Grade-	1	0	0
黄斑円孔	-Any Grade-	0	0	1
高眼圧症	-Any Grade-	0	1	0
色素散乱症候群	-Any Grade-	1	0	0
網膜血管新生	-Any Grade-	0	0	1
網膜静脈閉塞	-Any Grade-	0	0	1
視力障害	-Any Grade-	0	1	0
硝子体剥離	-Any Grade-	1	0	0
一般・全身障害および投与部位の状態				
- Overall -	-Any Grade-	0	0	1
異物感	-Any Grade-	0	0	1
感染症および寄生虫症				
- Overall -	-Any Grade-	0	0	1
麦粒腫	-Any Grade-	0	0	1
傷害、中毒および処置合併症				
- Overall -	-Any Grade-	1	0	0
角膜擦過傷	-Any Grade-	1	0	0
臨床検査				
- Overall -	-Any Grade-	0	1	0
眼圧上昇	-Any Grade-	0	1	0
血管障害				
- Overall -	-Any Grade-	1	0	0
血管新生	-Any Grade-	1	0	0

Only the most severe intensity is counted for multiple occurences of the same AE within a Subject at the Preferred Term Level.
The total number of patients with at least one Event is counted in the "- Any Intensity -" and/or "- Overall -" and/or "- Any Adverse Events -" categories.
Investigator text for Adverse Events encoded using MedDRA Version 20.1.
Includes only events within 28 days of the Week 20 visit

[5.3.5.1-DME-1 t_ae_int_ocular_n_SAF を改変]

表 2.7.6.2-24 眼以外の有害事象の集計（BP30099試験）

Summary of Systemic Adverse Events by System Organ Class, Preferred Term and Highest Intensity up to Week 24, Safety-Evaluable Patients
Protocol: BP30099

MedDRA System Organ Class MedDRA Preferred Term	Intensity	0.3 mg Ranibizumab (N=89)	1.5 mg RO6867461 (N=55)	6 mg RO6867461 (N=80)
- Any adverse events -	-Any Grade-	51	30	46
感染症および寄生虫症				
- Overall -	-Any Grade-	18	14	15
上咽頭炎	-Any Grade-	3	3	4
尿路感染	-Any Grade-	4	3	1
気管支炎	-Any Grade-	3	4	0
上気道感染	-Any Grade-	0	0	4
蜂巣炎	-Any Grade-	2	0	1
ウイルス性胃腸炎	-Any Grade-	0	2	1
インフルエンザ	-Any Grade-	2	0	1
限局性感染	-Any Grade-	0	1	2
壊疽	-Any Grade-	1	1	0
腎感染	-Any Grade-	2	0	0
骨髄炎	-Any Grade-	0	1	1
肺炎	-Any Grade-	0	1	1
歯膿瘍	-Any Grade-	1	1	0
クロストリジウム・ディフィシレ大腸炎	-Any Grade-	1	0	0
クロストリジウム・ディフィシレ感染	-Any Grade-	0	0	1
膀胱炎	-Any Grade-	1	0	0
糖尿病性足感染	-Any Grade-	1	0	0
耳感染	-Any Grade-	1	0	0
せつ	-Any Grade-	0	0	1
ヘリコバクター性胃炎	-Any Grade-	0	0	1
迷路炎	-Any Grade-	0	0	1
下気道感染	-Any Grade-	1	0	0
軟骨膜炎	-Any Grade-	1	0	0
敗血症	-Any Grade-	0	0	1
副鼻腔炎	-Any Grade-	0	1	0
創部膿瘍	-Any Grade-	0	0	1
創傷感染	-Any Grade-	1	0	0
臨床検査				
- Overall -	-Any Grade-	15	4	13
血沈亢進	-Any Grade-	2	0	3
血中トリグリセリド増加	-Any Grade-	1	0	3
血圧上昇	-Any Grade-	3	0	0
血中尿素増加	-Any Grade-	1	0	2
血中クレアチンホスホキナーゼ異常	-Any Grade-	1	0	1

Only the most severe intensity is counted for multiple occurences of the same AE within a Subject at the Preferred Term Level.
The total number of patients with at least one Event is counted in the "- Any Intensity -" and/or "- Overall -" and/or "- Any Adverse Events -" categories.
Investigator text for Adverse Events encoded using MedDRA Version 20.1.
Includes only events within 28 days of the Week 20 visit

表 2.7.6.2-24 眼以外の有害事象の集計（BP30099試験）（続）

Summary of Systemic Adverse Events by System Organ Class, Preferred Term and Highest Intensity up to Week 24, Safety-Evaluable Patients
Protocol: BP30099

MedDRA System Organ Class MedDRA Preferred Term	Intensity	0.3 mg Ranibizumab (N=89)	1.5 mg RO6867461 (N=55)	6 mg RO6867461 (N=80)
血中クレアチニン増加	-Any Grade-	0	0	2
血中ブドウ糖減少	-Any Grade-	1	1	0
血中ブドウ糖増加	-Any Grade-	0	0	2
血中カリウム増加	-Any Grade-	1	0	1
活性化部分トロンボプラスチン時間延長	-Any Grade-	0	0	1
血中コレステロール増加	-Any Grade-	0	0	1
血中クレアチンホスホキナーゼ増加	-Any Grade-	1	0	0
血中鉄減少	-Any Grade-	1	0	0
血中リン減少	-Any Grade-	0	1	0
骨密度減少	-Any Grade-	1	0	0
脳性ナトリウム利尿ペプチド増加	-Any Grade-	0	0	1
Ｃ－反応性蛋白増加	-Any Grade-	0	0	1
心雑音	-Any Grade-	1	0	0
グリコヘモグロビン増加	-Any Grade-	0	1	0
ヘマトクリット減少	-Any Grade-	1	0	0
ヘモグロビン減少	-Any Grade-	1	0	0
リパーゼ増加	-Any Grade-	0	1	0
赤血球数減少	-Any Grade-	1	0	0
筋骨格系および結合組織障害				
- Overall -	-Any Grade-	8	8	12
関節痛	-Any Grade-	3	2	2
背部痛	-Any Grade-	0	2	2
頚部痛	-Any Grade-	1	0	2
四肢痛	-Any Grade-	0	0	3
筋骨格痛	-Any Grade-	1	0	1
変形性関節症	-Any Grade-	0	0	2
足底筋膜炎	-Any Grade-	0	0	2
関節炎	-Any Grade-	0	1	0
線維筋痛	-Any Grade-	0	1	0
足変形	-Any Grade-	1	0	0
四肢不快感	-Any Grade-	0	0	1
筋痙縮	-Any Grade-	0	1	0
筋骨格系胸痛	-Any Grade-	1	0	0
筋肉痛	-Any Grade-	1	0	0
神経障害性関節症	-Any Grade-	0	1	0
肩回旋筋腱板症候群	-Any Grade-	0	0	1
腱炎	-Any Grade-	0	1	0

Only the most severe intensity is counted for multiple occurences of the same AE within a Subject at the Preferred Term Level.
The total number of patients with at least one Event is counted in the "- Any Intensity -" and/or "- Overall -" and/or "- Any Adverse Events -" categories.
Investigator text for Adverse Events encoded using MedDRA Version 20.1.
Includes only events within 28 days of the Week 20 visit

表 2.7.6.2-24 眼以外の有害事象の集計（BP30099試験）（続）

Summary of Systemic Adverse Events by System Organ Class, Preferred Term and Highest Intensity up to Week 24, Safety-Evaluable Patients
Protocol: BP30099

MedDRA System Organ Class MedDRA Preferred Term	Intensity	0.3 mg Ranibizumab (N=89)	1.5 mg RO6867461 (N=55)	6 mg RO6867461 (N=80)
代謝および栄養障害				
- Overall -	-Any Grade-	9	4	10
高コレステロール血症	-Any Grade-	2	2	0
糖尿病	-Any Grade-	0	1	2
高血糖	-Any Grade-	0	1	2
高脂血症	-Any Grade-	3	0	0
低血糖	-Any Grade-	2	0	1
高カリウム血症	-Any Grade-	1	1	0
高トリグリセリド血症	-Any Grade-	1	0	1
低ナトリウム血症	-Any Grade-	1	0	1
異常体重減少	-Any Grade-	0	0	1
コントロール不良の糖尿病	-Any Grade-	1	0	0
体液貯留	-Any Grade-	1	0	0
痛風	-Any Grade-	0	0	1
低アルブミン血症	-Any Grade-	0	0	1
低カリウム血症	-Any Grade-	1	0	0
ビタミンＢ１２欠乏	-Any Grade-	1	0	0
ビタミンＤ欠乏	-Any Grade-	1	0	0
胃腸障害				
- Overall -	-Any Grade-	6	6	10
下痢	-Any Grade-	1	2	4
悪心	-Any Grade-	1	2	2
嘔吐	-Any Grade-	3	0	2
腹部膨満	-Any Grade-	0	1	1
上腹部痛	-Any Grade-	0	0	2
腹水	-Any Grade-	0	1	1
消化不良	-Any Grade-	1	1	0
胃腸出血	-Any Grade-	0	0	2
腹痛	-Any Grade-	0	0	1
便秘	-Any Grade-	1	0	0
憩室	-Any Grade-	1	0	0
食中毒	-Any Grade-	0	0	1
胃炎	-Any Grade-	1	0	0
胃食道逆流性疾患	-Any Grade-	1	0	0
裂孔ヘルニア	-Any Grade-	1	0	0
胃排出不全	-Any Grade-	0	0	1

Only the most severe intensity is counted for multiple occurences of the same AE within a Subject at the Preferred Term Level.
The total number of patients with at least one Event is counted in the "- Any Intensity -" and/or "- Overall -" and/or "- Any Adverse Events -" categories.
Investigator text for Adverse Events encoded using MedDRA Version 20.1.
Includes only events within 28 days of the Week 20 visit

表 2.7.6.2-24 眼以外の有害事象の集計（BP30099試験）（続）

Summary of Systemic Adverse Events by System Organ Class, Preferred Term and Highest Intensity up to Week 24, Safety-Evaluable Patients
Protocol: BP30099

MedDRA System Organ Class MedDRA Preferred Term	Intensity	0.3 mg Ranibizumab (N=89)	1.5 mg RO6867461 (N=55)	6 mg RO6867461 (N=80)
転位歯	-Any Grade-	0	1	0
急性膵炎	-Any Grade-	0	1	0
直腸脱	-Any Grade-	1	0	0
歯痛	-Any Grade-	0	0	1
傷害、中毒および処置合併症				
- Overall -	-Any Grade-	7	5	5
転倒	-Any Grade-	2	3	1
四肢損傷	-Any Grade-	2	0	0
アルコール中毒	-Any Grade-	0	1	0
足関節部骨折	-Any Grade-	1	0	0
骨挫傷	-Any Grade-	1	0	0
第２度熱傷	-Any Grade-	0	1	0
脳振盪	-Any Grade-	1	0	0
挫傷	-Any Grade-	1	0	0
体内異物	-Any Grade-	0	0	1
転位骨折	-Any Grade-	0	1	0
上腕骨骨折	-Any Grade-	0	1	0
関節損傷	-Any Grade-	0	0	1
裂傷	-Any Grade-	0	0	1
筋断裂	-Any Grade-	0	0	1
肉離れ	-Any Grade-	1	0	0
爪損傷	-Any Grade-	0	0	1
処置合併症	-Any Grade-	0	0	1
血液およびリンパ系障害				
- Overall -	-Any Grade-	9	1	6
貧血	-Any Grade-	8	0	5
鉄欠乏性貧血	-Any Grade-	1	0	0
類白血病反応	-Any Grade-	0	1	0
小球性貧血	-Any Grade-	0	0	1
呼吸器、胸郭および縦隔障害				
- Overall -	-Any Grade-	4	3	8
咳嗽	-Any Grade-	0	2	1
呼吸困難	-Any Grade-	1	0	2
鼻閉	-Any Grade-	1	0	1
急性呼吸不全	-Any Grade-	1	0	0
気管支痙攣	-Any Grade-	0	1	0
慢性閉塞性肺疾患	-Any Grade-	1	0	0
労作性呼吸困難	-Any Grade-	0	0	1
鼻出血	-Any Grade-	0	0	1

Only the most severe intensity is counted for multiple occurences of the same AE within a Subject at the Preferred Term Level.
The total number of patients with at least one Event is counted in the "- Any Intensity -" and/or "- Overall -" and/or "- Any Adverse Events -" categories.
Investigator text for Adverse Events encoded using MedDRA Version 20.1.
Includes only events within 28 days of the Week 20 visit

表 2.7.6.2-24 眼以外の有害事象の集計（BP30099試験）（続）

Summary of Systemic Adverse Events by System Organ Class, Preferred Term and Highest Intensity up to Week 24, Safety-Evaluable Patients
Protocol: BP30099

MedDRA System Organ Class MedDRA Preferred Term	Intensity	0.3 mg Ranibizumab (N=89)	1.5 mg RO6867461 (N=55)	6 mg RO6867461 (N=80)
口腔咽頭痛	-Any Grade-	1	0	0
胸水	-Any Grade-	0	0	1
アレルギー性鼻炎	-Any Grade-	0	0	1
副鼻腔うっ血	-Any Grade-	0	0	1
一般・全身障害および投与部位の状態				
- Overall -	-Any Grade-	6	3	5
末梢性浮腫	-Any Grade-	2	2	3
無力症	-Any Grade-	0	0	1
胸痛	-Any Grade-	1	0	0
死亡	-Any Grade-	0	0	1
疲労	-Any Grade-	1	0	0
不明確な障害	-Any Grade-	1	0	0
疼痛	-Any Grade-	1	0	0
末梢腫脹	-Any Grade-	0	1	0
神経系障害				
- Overall -	-Any Grade-	5	4	5
頭痛	-Any Grade-	1	2	2
代謝性脳症	-Any Grade-	1	0	1
末梢性ニューロパチー	-Any Grade-	0	1	1
失神寸前の状態	-Any Grade-	2	0	0
中枢神経系病変	-Any Grade-	0	1	0
浮動性めまい	-Any Grade-	1	0	0
感覚鈍麻	-Any Grade-	0	0	1
多発ニューロパチー	-Any Grade-	1	0	0
振戦	-Any Grade-	0	1	0
血管障害				
- Overall -	-Any Grade-	6	5	2
高血圧	-Any Grade-	5	5	1
本態性高血圧症	-Any Grade-	1	0	0
高血圧クリーゼ	-Any Grade-	0	0	1
心臓障害				
- Overall -	-Any Grade-	7	2	2
うっ血性心不全	-Any Grade-	2	2	0
急性左室不全	-Any Grade-	1	0	1
大動脈弁狭窄	-Any Grade-	1	0	0

Only the most severe intensity is counted for multiple occurences of the same AE within a Subject at the Preferred Term Level.
The total number of patients with at least one Event is counted in the "- Any Intensity -" and/or "- Overall -" and/or "- Any Adverse Events -" categories.
Investigator text for Adverse Events encoded using MedDRA Version 20.1.
Includes only events within 28 days of the Week 20 visit

表 2.7.6.2-24 眼以外の有害事象の集計（BP30099試験）（続）

Summary of Systemic Adverse Events by System Organ Class, Preferred Term and Highest Intensity up to Week 24, Safety-Evaluable Patients
Protocol: BP30099

MedDRA System Organ Class MedDRA Preferred Term	Intensity	0.3 mg Ranibizumab (N=89)	1.5 mg RO6867461 (N=55)	6 mg RO6867461 (N=80)
心房細動	-Any Grade-	1	0	0
心房粗動	-Any Grade-	1	0	0
心停止	-Any Grade-	1	0	0
うっ血性心筋症	-Any Grade-	1	0	0
冠動脈疾患	-Any Grade-	0	0	1
無症候性心筋梗塞	-Any Grade-	1	0	0
腎および尿路障害				
- Overall -	-Any Grade-	6	2	3
慢性腎臓病	-Any Grade-	2	1	0
蛋白尿	-Any Grade-	0	0	2
急性腎障害	-Any Grade-	1	0	0
血尿	-Any Grade-	0	0	1
腎症	-Any Grade-	1	0	0
ネフローゼ症候群	-Any Grade-	0	0	1
腎嚢胞	-Any Grade-	0	1	0
腎不全	-Any Grade-	1	0	0
腎機能障害	-Any Grade-	1	0	0
尿管結石症	-Any Grade-	1	0	0
尿失禁	-Any Grade-	0	1	0
精神障害				
- Overall -	-Any Grade-	2	1	4
精神状態変化	-Any Grade-	1	1	1
不眠症	-Any Grade-	1	0	1
不安	-Any Grade-	0	0	1
双極性障害	-Any Grade-	0	1	0
幻覚	-Any Grade-	0	0	1
心的外傷後ストレス障害	-Any Grade-	0	0	1
皮膚および皮下組織障害				
- Overall -	-Any Grade-	5	0	1
皮膚潰瘍	-Any Grade-	2	0	1
接触皮膚炎	-Any Grade-	1	0	0
過角化	-Any Grade-	1	0	0
発疹	-Any Grade-	1	0	0
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）				
- Overall -	-Any Grade-	2	1	2
良性新生物	-Any Grade-	0	0	1
肝細胞癌	-Any Grade-	0	1	0

Only the most severe intensity is counted for multiple occurences of the same AE within a Subject at the Preferred Term Level.
The total number of patients with at least one Event is counted in the "- Any Intensity -" and/or "- Overall -" and/or "- Any Adverse Events -" categories.
Investigator text for Adverse Events encoded using MedDRA Version 20.1.
Includes only events within 28 days of the Week 20 visit

表 2.7.6.2-24 眼以外の有害事象の集計（BP30099試験）（続）

Summary of Systemic Adverse Events by System Organ Class, Preferred Term and Highest Intensity up to Week 24, Safety-Evaluable Patients
Protocol: BP30099

MedDRA System Organ Class MedDRA Preferred Term	Intensity	0.3 mg Ranibizumab (N=89)	1.5 mg RO6867461 (N=55)	6 mg RO6867461 (N=80)
メラノサイト性母斑	-Any Grade-	1	0	0
骨転移	-Any Grade-	0	1	0
肺転移	-Any Grade-	0	1	0
脂漏性角化症	-Any Grade-	0	0	1
扁平上皮癌	-Any Grade-	1	0	0
頭頸部扁平上皮癌	-Any Grade-	1	0	0
耳および迷路障害				
- Overall -	-Any Grade-	1	0	2
回転性めまい	-Any Grade-	1	0	2
免疫系障害				
- Overall -	-Any Grade-	3	0	0
ワクチンアレルギー	-Any Grade-	1	0	0
造影剤アレルギー	-Any Grade-	1	0	0
季節性アレルギー	-Any Grade-	1	0	0
内分泌障害				
- Overall -	-Any Grade-	1	0	1
甲状腺機能低下症	-Any Grade-	1	0	1
肝胆道系障害				
- Overall -	-Any Grade-	0	0	1
肝硬変	-Any Grade-	0	0	1

Only the most severe intensity is counted for multiple occurences of the same AE within a Subject at the Preferred Term Level.
The total number of patients with at least one Event is counted in the "- Any Intensity -" and/or "- Overall -" and/or "- Any Adverse Events -" categories.
Investigator text for Adverse Events encoded using MedDRA Version 20.1.
Includes only events within 28 days of the Week 20 visit

[5.3.5.1-DME-1 t_ae_int_systemic_SAF を改変]

表 2.7.6.2-25 副作用の集計（BP30099試験）

Related AE up to Week 24: Safety Evaluable Patients
Protocol: BP30099

MedDRA Preferred Term	0.3 mg Ranibizumab (N=89)	1.5 mg RO6867461 (N=55)	6 mg RO6867461 (N=80)
Total number of patients with at least one adverse event	1 (1.1%)	0 (0.0%)	4 (5.0%)
Overall Total number of events	1	0	5
STUDY EYE			
Total number of patients with at least one adverse event	1 (1.1%)	0 (0.0%)	2 (2.5%)
Total number of events	1	0	3
白内障	0 (0.0%)	0 (0.0%)	1 (1.3%)
水晶体障害	0 (0.0%)	0 (0.0%)	1 (1.3%)
硝子体剥離	1 (1.1%)	0 (0.0%)	0 (0.0%)
硝子体浮遊物	0 (0.0%)	0 (0.0%)	1 (1.3%)
Systemic			
Total number of patients with at least one adverse event	0 (0.0%)	0 (0.0%)	2 (2.5%)
Total number of events	0	0	2
血中クレアチンホスホキナーゼ異常	0 (0.0%)	0 (0.0%)	1 (1.3%)
血沈亢進	0 (0.0%)	0 (0.0%)	1 (1.3%)

Percentages are based on N.
Multiple occurences of the same AE in one individual counted only once.
Includes only events within 28 days of the Week 20 visit.
Investigator text for Adverse Events encoded using MedDRA Version 20.1.
本帳票は，BP30099試験のCSR内，l_ae_ocular_SAF: Listing of Ocular Adverse Events per eye, Safety-Evaluable Patients (Page 1071-)，l_ae_systemic_SAF: Listing of Systemic Adverse Events, Safety-Evaluable Patients (Page 1095-)，Table 26 Safety Summary to Week 24 (Safety Evaluable Patients) (Page 129)を基に作成した。

[5.3.5.1-DME-1 l_ae_ocular_SAF，l_ae_systemic_SAF 及び Table 26を改変]

表 2.7.6.2-26 試験眼の有害事象の集計（GR40349試験）

Ocular Adverse Events in the Study Eye through Week 56, Safety-Evaluable Population
Protocol: GR40349
Clinical Cutoff Date: 20OCT2020

MedDRA Preferred Term	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Faricimab 6 mg All (N=626)	Aflibercept 2 mg Q8W (N=311)
Total number of patients with at least one adverse event	98 (31.3%)	106 (33.9%)	204 (32.6%)	102 (32.8%)
Total number of events	196	208	404	169
結膜出血	20 (6.4%)	22 (7.0%)	42 (6.7%)	19 (6.1%)
白内障	14 (4.5%)	11 (3.5%)	25 (4.0%)	17 (5.5%)
硝子体剥離	10 (3.2%)	11 (3.5%)	21 (3.4%)	9 (2.9%)
眼痛	8 (2.6%)	7 (2.2%)	15 (2.4%)	9 (2.9%)
硝子体浮遊物	15 (4.8%)	6 (1.9%)	21 (3.4%)	2 (0.6%)
眼圧上昇	10 (3.2%)	5 (1.6%)	15 (2.4%)	5 (1.6%)
ドライアイ	8 (2.6%)	3 (1.0%)	11 (1.8%)	4 (1.3%)
後嚢部混濁	2 (0.6%)	4 (1.3%)	6 (1.0%)	6 (1.9%)
皮質白内障	1 (0.3%)	2 (0.6%)	3 (0.5%)	7 (2.3%)
点状角膜炎	3 (1.0%)	3 (1.0%)	6 (1.0%)	4 (1.3%)
霧視	4 (1.3%)	3 (1.0%)	7 (1.1%)	3 (1.0%)
硝子体出血	5 (1.6%)	4 (1.3%)	9 (1.4%)	1 (0.3%)
結膜炎	2 (0.6%)	4 (1.3%)	6 (1.0%)	3 (1.0%)
糖尿病性網膜浮腫	5 (1.6%)	1 (0.3%)	6 (1.0%)	3 (1.0%)
核性白内障	2 (0.6%)	3 (1.0%)	5 (0.8%)	3 (1.0%)
眼部不快感	3 (1.0%)	3 (1.0%)	6 (1.0%)	2 (0.6%)
糖尿病網膜症	2 (0.6%)	4 (1.3%)	6 (1.0%)	1 (0.3%)
流涙増加	1 (0.3%)	3 (1.0%)	4 (0.6%)	3 (1.0%)
嚢下白内障	2 (0.6%)	2 (0.6%)	4 (0.6%)	2 (0.6%)
網膜滲出物	3 (1.0%)	3 (1.0%)	6 (1.0%)	0
視力障害	1 (0.3%)	3 (1.0%)	4 (0.6%)	2 (0.6%)

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.6.2-26 試験眼の有害事象の集計（GR40349試験）（続）

Ocular Adverse Events in the Study Eye through Week 56, Safety-Evaluable Population
Protocol: GR40349
Clinical Cutoff Date: 20OCT2020

MedDRA Preferred Term	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Faricimab 6 mg All (N=626)	Aflibercept 2 mg Q8W (N=311)
霰粒腫	3 (1.0%)	1 (0.3%)	4 (0.6%)	1 (0.3%)
眼刺激	2 (0.6%)	2 (0.6%)	4 (0.6%)	1 (0.3%)
眼そう痒症	0	3 (1.0%)	3 (0.5%)	2 (0.6%)
麦粒腫	1 (0.3%)	1 (0.3%)	2 (0.3%)	3 (1.0%)
黄斑線維症	1 (0.3%)	1 (0.3%)	2 (0.3%)	3 (1.0%)
ぶどう膜炎	2 (0.6%)	3 (1.0%)	5 (0.8%)	0
硝子体炎	2 (0.6%)	1 (0.3%)	3 (0.5%)	2 (0.6%)
角膜擦過傷	1 (0.3%)	2 (0.6%)	3 (0.5%)	1 (0.3%)
角膜びらん	2 (0.6%)	1 (0.3%)	3 (0.5%)	1 (0.3%)
虹彩炎	0	3 (1.0%)	3 (0.5%)	1 (0.3%)
高眼圧症	1 (0.3%)	3 (1.0%)	4 (0.6%)	0
網膜出血	1 (0.3%)	1 (0.3%)	2 (0.3%)	2 (0.6%)
異物感	2 (0.6%)	1 (0.3%)	3 (0.5%)	1 (0.3%)
硝子体障害	0	3 (1.0%)	3 (0.5%)	1 (0.3%)
動脈瘤	0	1 (0.3%)	1 (0.2%)	2 (0.6%)
眼瞼炎	2 (0.6%)	0	2 (0.3%)	1 (0.3%)
緑内障	1 (0.3%)	0	1 (0.2%)	2 (0.6%)
虹彩毛様体炎	2 (0.6%)	1 (0.3%)	3 (0.5%)	0
黄斑虚血	2 (0.6%)	1 (0.3%)	3 (0.5%)	0
投薬過誤	3 (1.0%)	0	3 (0.5%)	0
眼充血	1 (0.3%)	1 (0.3%)	2 (0.3%)	1 (0.3%)
羞明	1 (0.3%)	1 (0.3%)	2 (0.3%)	1 (0.3%)
光視症	2 (0.6%)	1 (0.3%)	3 (0.5%)	0
そう痒症	1 (0.3%)	2 (0.6%)	3 (0.5%)	0
強膜炎	1 (0.3%)	1 (0.3%)	2 (0.3%)	1 (0.3%)

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.6.2-26 試験眼の有害事象の集計（GR40349試験）（続）

Ocular Adverse Events in the Study Eye through Week 56, Safety-Evaluable Population
Protocol: GR40349
Clinical Cutoff Date: 20OCT2020

MedDRA Preferred Term	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Faricimab 6 mg All (N=626)	Aflibercept 2 mg Q8W (N=311)
結膜充血	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
角膜ジストロフィー	0	2 (0.6%)	2 (0.3%)	0
嚢胞様黄斑浮腫	2 (0.6%)	0	2 (0.3%)	0
不快感	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
眼内炎	0	2 (0.6%)	2 (0.3%)	0
眼脂	0	0	0	2 (0.6%)
眼窩周囲痛	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
網膜静脈閉塞	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
腫脹	0	2 (0.6%)	2 (0.3%)	0
視力低下	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
硝子体網膜牽引症候群	0	0	0	2 (0.6%)
眼の異常感	1 (0.3%)	0	1 (0.2%)	0
アデノウイルス結膜炎	0	0	0	1 (0.3%)
化学物質アレルギー	0	1 (0.3%)	1 (0.2%)	0
前房の炎症	0	1 (0.3%)	1 (0.2%)	0
境界域緑内障	0	1 (0.3%)	1 (0.2%)	0
灼熱感	1 (0.3%)	0	1 (0.2%)	0
白内障手術合併症	0	0	0	1 (0.3%)
脈絡網膜炎	0	1 (0.3%)	1 (0.2%)	0
結膜乳頭	1 (0.3%)	0	1 (0.2%)	0
造影剤アレルギー	1 (0.3%)	0	1 (0.2%)	0
角膜障害	1 (0.3%)	0	1 (0.2%)	0
角膜血管新生	0	0	0	1 (0.3%)
角膜浮腫	0	1 (0.3%)	1 (0.2%)	0
後天性涙道狭窄	0	1 (0.3%)	1 (0.2%)	0
網膜色素上皮剥離	1 (0.3%)	0	1 (0.2%)	0
医療機器位置異常	1 (0.3%)	0	1 (0.2%)	0
複視	0	1 (0.3%)	1 (0.2%)	0

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.6.2-26 試験眼の有害事象の集計（GR40349試験）（続）

Ocular Adverse Events in the Study Eye through Week 56, Safety-Evaluable Population
Protocol: GR40349
Clinical Cutoff Date: 20OCT2020

MedDRA Preferred Term	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Faricimab 6 mg All (N=626)	Aflibercept 2 mg Q8W (N=311)
薬物過敏症	0	0	0	1 (0.3%)
視測障害	1 (0.3%)	0	1 (0.2%)	0
上強膜炎	0	1 (0.3%)	1 (0.2%)	0
眼瞼紅斑	0	1 (0.3%)	1 (0.2%)	0
眼のアレルギー	1 (0.3%)	0	1 (0.2%)	0
眼出血	0	0	0	1 (0.3%)
眼運動障害	0	0	0	1 (0.3%)
眼瞼縁痂皮	1 (0.3%)	0	1 (0.2%)	0
眼瞼浮腫	0	0	0	1 (0.3%)
眼瞼下垂	0	0	0	1 (0.3%)
グレア	0	0	0	1 (0.3%)
帯状疱疹	1 (0.3%)	0	1 (0.2%)	0
過敏症	0	1 (0.3%)	1 (0.2%)	0
第３脳神経麻痺	0	0	0	1 (0.3%)
回避された投薬過誤	1 (0.3%)	0	1 (0.2%)	0
眼圧変動	0	1 (0.3%)	1 (0.2%)	0
虹彩癒着	0	0	0	1 (0.3%)
角膜後面沈着物	0	1 (0.3%)	1 (0.2%)	0
ウイルス性角膜炎	0	1 (0.3%)	1 (0.2%)	0
角膜ぶどう膜炎	0	1 (0.3%)	1 (0.2%)	0
水晶体混濁	0	0	0	1 (0.3%)
結石症	0	1 (0.3%)	1 (0.2%)	0
黄斑円孔	0	0	0	1 (0.3%)
黄斑浮腫	1 (0.3%)	0	1 (0.2%)	0
黄斑色素沈着	0	1 (0.3%)	1 (0.2%)	0
黄斑肥厚	0	0	0	1 (0.3%)
マイボーム腺機能不全	1 (0.3%)	0	1 (0.2%)	0
前房狭隅角	1 (0.3%)	0	1 (0.2%)	0

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.6.2-26 試験眼の有害事象の集計（GR40349試験）（続）

Ocular Adverse Events in the Study Eye through Week 56, Safety-Evaluable Population
Protocol: GR40349
Clinical Cutoff Date: 20OCT2020

MedDRA Preferred Term	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Faricimab 6 mg All (N=626)	Aflibercept 2 mg Q8W (N=311)
開放隅角緑内障	0	1 (0.3%)	1 (0.2%)	0
視神経乳頭出血	0	1 (0.3%)	1 (0.2%)	0
視神経乳頭陥凹／乳頭比増加	0	0	0	1 (0.3%)
錯感覚	1 (0.3%)	0	1 (0.2%)	0
色素散乱症候群	0	1 (0.3%)	1 (0.2%)	0
瞼裂斑	1 (0.3%)	0	1 (0.2%)	0
処置による疼痛	0	1 (0.3%)	1 (0.2%)	0
網膜血管瘤	1 (0.3%)	0	1 (0.2%)	0
網膜動脈閉塞	0	0	0	1 (0.3%)
網膜嚢胞	0	1 (0.3%)	1 (0.2%)	0
網膜障害	0	1 (0.3%)	1 (0.2%)	0
網膜色素沈着	0	1 (0.3%)	1 (0.2%)	0
網膜裂孔	0	1 (0.3%)	1 (0.2%)	0
高血圧性網膜症	0	0	0	1 (0.3%)
網膜分離症	1 (0.3%)	0	1 (0.2%)	0
裂孔原性網膜剥離	1 (0.3%)	0	1 (0.2%)	0
瘢痕	0	1 (0.3%)	1 (0.2%)	0
眼瞼腫脹	0	1 (0.3%)	1 (0.2%)	0
ぶどう膜炎性緑内障	0	1 (0.3%)	1 (0.2%)	0
ウイルス性角膜ぶどう膜炎	1 (0.3%)	0	1 (0.2%)	0
視野欠損	0	0	0	1 (0.3%)
角膜生体染色陽性	0	0	0	1 (0.3%)
硝子体変性	0	1 (0.3%)	1 (0.2%)	0
硝子体混濁	0	1 (0.3%)	1 (0.2%)	0

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

[5.3.5.1-DME-2 t_ae_pt_SOCUL_W56_SE_20OCT2020_40349を改変]

表 2.7.6.2-27 非試験眼の有害事象の集計（GR40349試験）

Ocular Adverse Events in the Fellow Eye through Week 56, Safety-Evaluable Population
Protocol: GR40349
Clinical Cutoff Date: 20OCT2020

MedDRA Preferred Term	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Faricimab 6 mg All (N=626)	Aflibercept 2 mg Q8W (N=311)
Total number of patients with at least one adverse event	89 (28.4%)	104 (33.2%)	193 (30.8%)	106 (34.1%)
Total number of events	155	172	327	164
糖尿病性網膜浮腫	9 (2.9%)	18 (5.8%)	27 (4.3%)	18 (5.8%)
白内障	13 (4.2%)	12 (3.8%)	25 (4.0%)	17 (5.5%)
結膜出血	8 (2.6%)	10 (3.2%)	18 (2.9%)	6 (1.9%)
糖尿病網膜症	6 (1.9%)	9 (2.9%)	15 (2.4%)	8 (2.6%)
硝子体剥離	8 (2.6%)	8 (2.6%)	16 (2.6%)	6 (1.9%)
ドライアイ	5 (1.6%)	5 (1.6%)	10 (1.6%)	5 (1.6%)
網膜滲出物	5 (1.6%)	7 (2.2%)	12 (1.9%)	3 (1.0%)
硝子体出血	8 (2.6%)	4 (1.3%)	12 (1.9%)	3 (1.0%)
眼痛	4 (1.3%)	3 (1.0%)	7 (1.1%)	5 (1.6%)
黄斑浮腫	3 (1.0%)	4 (1.3%)	7 (1.1%)	4 (1.3%)
後嚢部混濁	3 (1.0%)	6 (1.9%)	9 (1.4%)	2 (0.6%)
眼圧上昇	4 (1.3%)	2 (0.6%)	6 (1.0%)	4 (1.3%)
皮質白内障	2 (0.6%)	3 (1.0%)	5 (0.8%)	4 (1.3%)
網膜出血	2 (0.6%)	4 (1.3%)	6 (1.0%)	3 (1.0%)
核性白内障	1 (0.3%)	5 (1.6%)	6 (1.0%)	2 (0.6%)
硝子体浮遊物	3 (1.0%)	2 (0.6%)	5 (0.8%)	3 (1.0%)
結膜炎	3 (1.0%)	1 (0.3%)	4 (0.6%)	3 (1.0%)
嚢下白内障	2 (0.6%)	2 (0.6%)	4 (0.6%)	2 (0.6%)
黄斑線維症	0	3 (1.0%)	3 (0.5%)	3 (1.0%)
点状角膜炎	2 (0.6%)	1 (0.3%)	3 (0.5%)	3 (1.0%)
霧視	2 (0.6%)	2 (0.6%)	4 (0.6%)	1 (0.3%)
視力低下	3 (1.0%)	1 (0.3%)	4 (0.6%)	1 (0.3%)

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.6.2-27 非試験眼の有害事象の集計（GR40349試験）（続）

Ocular Adverse Events in the Fellow Eye through Week 56, Safety-Evaluable Population
Protocol: GR40349
Clinical Cutoff Date: 20OCT2020

MedDRA Preferred Term	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Faricimab 6 mg All (N=626)	Aflibercept 2 mg Q8W (N=311)
眼瞼炎	1 (0.3%)	1 (0.3%)	2 (0.3%)	2 (0.6%)
眼そう痒症	1 (0.3%)	2 (0.6%)	3 (0.5%)	1 (0.3%)
眼部不快感	4 (1.3%)	0	4 (0.6%)	0
眼充血	1 (0.3%)	2 (0.6%)	3 (0.5%)	1 (0.3%)
光視症	2 (0.6%)	1 (0.3%)	3 (0.5%)	1 (0.3%)
視力障害	2 (0.6%)	0	2 (0.3%)	2 (0.6%)
動脈瘤	0	1 (0.3%)	1 (0.2%)	2 (0.6%)
境界域緑内障	0	3 (1.0%)	3 (0.5%)	0
角膜擦過傷	1 (0.3%)	0	1 (0.2%)	2 (0.6%)
緑内障	1 (0.3%)	0	1 (0.2%)	2 (0.6%)
黄斑虚血	2 (0.6%)	1 (0.3%)	3 (0.5%)	0
黄斑肥厚	0	1 (0.3%)	1 (0.2%)	2 (0.6%)
網膜血管新生	0	1 (0.3%)	1 (0.2%)	2 (0.6%)
網膜肥厚	2 (0.6%)	0	2 (0.3%)	1 (0.3%)
ぶどう膜炎	0	1 (0.3%)	1 (0.2%)	2 (0.6%)
角膜生体染色陽性	0	1 (0.3%)	1 (0.2%)	2 (0.6%)
硝子体炎	0	0	0	3 (1.0%)

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.6.2-27 非試験眼の有害事象の集計（GR40349試験）（続）

Ocular Adverse Events in the Fellow Eye through Week 56, Safety-Evaluable Population
Protocol: GR40349
Clinical Cutoff Date: 20OCT2020

MedDRA Preferred Term	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Faricimab 6 mg All (N=626)	Aflibercept 2 mg Q8W (N=311)
外傷性白内障	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
霰粒腫	1 (0.3%)	0	1 (0.2%)	1 (0.3%)
角膜ジストロフィー	0	2 (0.6%)	2 (0.3%)	0
角膜びらん	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
嚢胞様黄斑浮腫	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
眼脂	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
眼刺激	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
流涙増加	1 (0.3%)	0	1 (0.2%)	1 (0.3%)
投薬過誤	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
開放隅角緑内障	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
眼窩周囲蜂巣炎	0	0	0	2 (0.6%)
羞明	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
そう痒症	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
網膜障害	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
網膜分離症	2 (0.6%)	0	2 (0.3%)	0
閉塞隅角緑内障	0	0	0	1 (0.3%)
前眼房混濁	0	0	0	1 (0.3%)
アレルギー性眼瞼炎	0	1 (0.3%)	1 (0.2%)	0
灼熱感	1 (0.3%)	0	1 (0.2%)	0
脈絡膜血管新生	1 (0.3%)	0	1 (0.2%)	0
結膜充血	0	1 (0.3%)	1 (0.2%)	0
結膜刺激	0	0	0	1 (0.3%)
アレルギー性結膜炎	0	1 (0.3%)	1 (0.2%)	0
ウイルス性結膜炎	0	1 (0.3%)	1 (0.2%)	0
造影剤アレルギー	1 (0.3%)	0	1 (0.2%)	0
後天性涙道狭窄	0	1 (0.3%)	1 (0.2%)	0
皮膚嚢腫	0	0	0	1 (0.3%)
不快感	1 (0.3%)	0	1 (0.2%)	0

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.6.2-27 非試験眼の有害事象の集計（GR40349試験）（続）

Ocular Adverse Events in the Fellow Eye through Week 56, Safety-Evaluable Population
Protocol: GR40349
Clinical Cutoff Date: 20OCT2020

MedDRA Preferred Term	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Faricimab 6 mg All (N=626)	Aflibercept 2 mg Q8W (N=311)
眼内炎	0	1 (0.3%)	1 (0.2%)	0
眼瞼紅斑	0	1 (0.3%)	1 (0.2%)	0
眼挫傷	0	1 (0.3%)	1 (0.2%)	0
眼出血	1 (0.3%)	0	1 (0.2%)	0
眼外傷	1 (0.3%)	0	1 (0.2%)	0
眼運動障害	0	0	0	1 (0.3%)
眼瞼刺激	0	0	0	1 (0.3%)
眼瞼縁痂皮	1 (0.3%)	0	1 (0.2%)	0
眼瞼痛	1 (0.3%)	0	1 (0.2%)	0
出血	0	1 (0.3%)	1 (0.2%)	0
麦粒腫	0	0	0	1 (0.3%)
眼圧変動	0	1 (0.3%)	1 (0.2%)	0
虹彩毛様体炎	1 (0.3%)	0	1 (0.2%)	0
ウイルス性角膜炎	0	1 (0.3%)	1 (0.2%)	0
黄斑剥離	0	1 (0.3%)	1 (0.2%)	0
黄斑円孔	0	0	0	1 (0.3%)
前兆を伴う片頭痛	1 (0.3%)	0	1 (0.2%)	0
前房狭隅角	1 (0.3%)	0	1 (0.2%)	0
血管新生	1 (0.3%)	0	1 (0.2%)	0
視神経乳頭陥凹／乳頭比増加	0	0	0	1 (0.3%)
乳頭腫	0	0	0	1 (0.3%)
錯感覚	1 (0.3%)	0	1 (0.2%)	0
瞼裂斑	1 (0.3%)	0	1 (0.2%)	0
網膜動脈塞栓症	0	1 (0.3%)	1 (0.2%)	0
網膜嚢胞	1 (0.3%)	0	1 (0.2%)	0
網膜変性	1 (0.3%)	0	1 (0.2%)	0
網膜色素脱失	0	0	0	1 (0.3%)
網膜色素沈着	1 (0.3%)	0	1 (0.2%)	0

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.6.2-27 非試験眼の有害事象の集計（GR40349試験）（続）

Ocular Adverse Events in the Fellow Eye through Week 56, Safety-Evaluable Population
Protocol: GR40349
Clinical Cutoff Date: 20OCT2020

MedDRA Preferred Term	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Faricimab 6 mg All (N=626)	Aflibercept 2 mg Q8W (N=311)
網膜裂孔	1 (0.3%)	0	1 (0.2%)	0
網膜症	1 (0.3%)	0	1 (0.2%)	0
高血圧性網膜症	0	0	0	1 (0.3%)
強膜色素沈着	0	1 (0.3%)	1 (0.2%)	0
強膜炎	1 (0.3%)	0	1 (0.2%)	0
異物感	0	0	0	1 (0.3%)
腫脹	0	1 (0.3%)	1 (0.2%)	0
硝子体変性	1 (0.3%)	0	1 (0.2%)	0
硝子体障害	0	1 (0.3%)	1 (0.2%)	0

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

[5.3.5.1-DME-2 t_ae_pt_FOCUL_W56_SE_20OCT2020_40349を改変]

表 2.7.6.2-28 眼以外の有害事象の集計（GR40349試験）

Non-Ocular Adverse Events through Week 56, Safety-Evaluable Population
Protocol: GR40349
Clinical Cutoff Date: 20OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Faricimab 6 mg All (N=626)	Aflibercept 2 mg Q8W (N=311)
Total number of patients with at least one adverse event	204 (65.2%)	210 (67.1%)	414 (66.1%)	203 (65.3%)
Overall total number of events	711	636	1347	605
感染症および寄生虫症				
Total number of patients with at least one adverse event	97 (31.0%)	84 (26.8%)	181 (28.9%)	102 (32.8%)
Total number of events	150	122	272	155
上咽頭炎	21 (6.7%)	15 (4.8%)	36 (5.8%)	22 (7.1%)
尿路感染	13 (4.2%)	8 (2.6%)	21 (3.4%)	13 (4.2%)
気管支炎	14 (4.5%)	8 (2.6%)	22 (3.5%)	11 (3.5%)
副鼻腔炎	8 (2.6%)	7 (2.2%)	15 (2.4%)	9 (2.9%)
上気道感染	7 (2.2%)	10 (3.2%)	17 (2.7%)	6 (1.9%)
肺炎	6 (1.9%)	6 (1.9%)	12 (1.9%)	8 (2.6%)
蜂巣炎	9 (2.9%)	5 (1.6%)	14 (2.2%)	5 (1.6%)
インフルエンザ	4 (1.3%)	7 (2.2%)	11 (1.8%)	6 (1.9%)
ＣＯＶＩＤ－１９	2 (0.6%)	6 (1.9%)	8 (1.3%)	4 (1.3%)
敗血症	4 (1.3%)	2 (0.6%)	6 (1.0%)	6 (1.9%)
帯状疱疹	5 (1.6%)	3 (1.0%)	8 (1.3%)	2 (0.6%)
限局性感染	2 (0.6%)	3 (1.0%)	5 (0.8%)	3 (1.0%)
骨髄炎	3 (1.0%)	1 (0.3%)	4 (0.6%)	4 (1.3%)
胃腸炎	2 (0.6%)	3 (1.0%)	5 (0.8%)	1 (0.3%)
咽頭炎	2 (0.6%)	2 (0.6%)	4 (0.6%)	2 (0.6%)
歯膿瘍	1 (0.3%)	4 (1.3%)	5 (0.8%)	1 (0.3%)
ウイルス性胃腸炎	1 (0.3%)	1 (0.3%)	2 (0.3%)	3 (1.0%)
中耳炎	0	3 (1.0%)	3 (0.5%)	1 (0.3%)
糖尿病性足感染	0	1 (0.3%)	1 (0.2%)	2 (0.6%)
喉頭炎	1 (0.3%)	1 (0.3%)	2 (0.3%)	1 (0.3%)
腎盂腎炎	1 (0.3%)	1 (0.3%)	2 (0.3%)	1 (0.3%)
気道感染	1 (0.3%)	1 (0.3%)	2 (0.3%)	1 (0.3%)
鼻炎	0	1 (0.3%)	1 (0.2%)	2 (0.6%)
歯感染	1 (0.3%)	0	1 (0.2%)	2 (0.6%)
ウイルス性上気道感染	1 (0.3%)	0	1 (0.2%)	2 (0.6%)
外陰腟真菌感染	1 (0.3%)	0	1 (0.2%)	2 (0.6%)
ウイルス性気管支炎	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
クロストリジウム・ディフィシレ大腸炎	1 (0.3%)	0	1 (0.2%)	1 (0.3%)
糖尿病性壊疽	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
耳感染	1 (0.3%)	0	1 (0.2%)	1 (0.3%)
丹毒	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
真菌感染	2 (0.6%)	0	2 (0.3%)	0
歯肉炎	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
腎感染	2 (0.6%)	0	2 (0.3%)	0
下気道感染	1 (0.3%)	0	1 (0.2%)	1 (0.3%)
口腔ヘルペス	0	1 (0.3%)	1 (0.2%)	1 (0.3%)

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Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.6.2-28 眼以外の有害事象の集計（GR40349試験）（続）

Non-Ocular Adverse Events through Week 56, Safety-Evaluable Population
Protocol: GR40349
Clinical Cutoff Date: 20OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Faricimab 6 mg All (N=626)	Aflibercept 2 mg Q8W (N=311)
歯髄炎	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
扁桃炎	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
ウイルス感染	0	2 (0.6%)	2 (0.3%)	0
腹部膿瘍	0	1 (0.3%)	1 (0.2%)	0
四肢膿瘍	0	0	0	1 (0.3%)
急性副鼻腔炎	0	0	0	1 (0.3%)
肛門膿瘍	0	0	0	1 (0.3%)
菌血症	1 (0.3%)	0	1 (0.2%)	0
カンジダ感染	0	0	0	1 (0.3%)
壊疽性蜂巣炎	0	0	0	1 (0.3%)
感染性胆嚢炎	0	1 (0.3%)	1 (0.2%)	0
合併症を伴う虫垂炎	0	0	0	1 (0.3%)
コロナウイルス感染	0	0	0	1 (0.3%)
膀胱炎	1 (0.3%)	0	1 (0.2%)	0
真菌性膀胱炎	1 (0.3%)	0	1 (0.2%)	0
皮膚真菌感染	0	1 (0.3%)	1 (0.2%)	0
胃感染	0	0	0	1 (0.3%)
ノロウイルス性胃腸炎	1 (0.3%)	0	1 (0.2%)	0
消化管内細菌過剰増殖	0	0	0	1 (0.3%)
消化管感染	0	1 (0.3%)	1 (0.2%)	0
ヘリコバクター感染	1 (0.3%)	0	1 (0.2%)	0
耳帯状疱疹	0	0	0	1 (0.3%)
埋込み部位感染	1 (0.3%)	0	1 (0.2%)	0
咬傷感染	1 (0.3%)	0	1 (0.2%)	0
感染性嚢腫	0	1 (0.3%)	1 (0.2%)	0
感染性皮膚嚢腫	0	0	0	1 (0.3%)
感染性皮膚潰瘍	1 (0.3%)	0	1 (0.2%)	0
椎間板炎	0	0	0	1 (0.3%)
迷路炎	1 (0.3%)	0	1 (0.2%)	0
ライム病	0	1 (0.3%)	1 (0.2%)	0
爪真菌症	1 (0.3%)	0	1 (0.2%)	0
急性骨髄炎	0	0	0	1 (0.3%)
細菌性骨髄炎	0	1 (0.3%)	1 (0.2%)	0
爪囲炎	0	1 (0.3%)	1 (0.2%)	0
レンサ球菌性咽頭炎	1 (0.3%)	0	1 (0.2%)	0
細菌性肺炎	0	0	0	1 (0.3%)
大腸菌性肺炎	0	0	0	1 (0.3%)
シュードモナス性敗血症	0	0	0	1 (0.3%)
慢性腎盂腎炎	0	0	0	1 (0.3%)
ウイルス性気道感染	1 (0.3%)	0	1 (0.2%)	0
敗血症症候群	1 (0.3%)	0	1 (0.2%)	0
敗血症性ショック	0	1 (0.3%)	1 (0.2%)	0
皮膚感染	0	0	0	1 (0.3%)
ブドウ球菌感染	1 (0.3%)	0	1 (0.2%)	0
尿道炎	0	0	0	1 (0.3%)
尿路性敗血症	1 (0.3%)	0	1 (0.2%)	0

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.6.2-28 眼以外の有害事象の集計（GR40349試験）（続）

Non-Ocular Adverse Events through Week 56, Safety-Evaluable Population
Protocol: GR40349
Clinical Cutoff Date: 20OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Faricimab 6 mg All (N=626)	Aflibercept 2 mg Q8W (N=311)
代謝および栄養障害				
Total number of patients with at least one adverse event	51 (16.3%)	35 (11.2%)	86 (13.7%)	37 (11.9%)
Total number of events	64	54	118	50
高血糖	10 (3.2%)	6 (1.9%)	16 (2.6%)	5 (1.6%)
糖尿病	7 (2.2%)	6 (1.9%)	13 (2.1%)	2 (0.6%)
低血糖	7 (2.2%)	6 (1.9%)	13 (2.1%)	1 (0.3%)
高コレステロール血症	3 (1.0%)	4 (1.3%)	7 (1.1%)	5 (1.6%)
コントロール不良の糖尿病	6 (1.9%)	1 (0.3%)	7 (1.1%)	4 (1.3%)
高脂血症	4 (1.3%)	3 (1.0%)	7 (1.1%)	4 (1.3%)
ビタミンＤ欠乏	3 (1.0%)	3 (1.0%)	6 (1.0%)	3 (1.0%)
脱水	4 (1.3%)	1 (0.3%)	5 (0.8%)	2 (0.6%)
体液貯留	2 (0.6%)	1 (0.3%)	3 (0.5%)	4 (1.3%)
２型糖尿病	2 (0.6%)	2 (0.6%)	4 (0.6%)	3 (1.0%)
低カリウム血症	2 (0.6%)	2 (0.6%)	4 (0.6%)	1 (0.3%)
ビタミンＢ１２欠乏	0	3 (1.0%)	3 (0.5%)	2 (0.6%)
高カリウム血症	1 (0.3%)	1 (0.3%)	2 (0.3%)	2 (0.6%)
食欲減退	0	1 (0.3%)	1 (0.2%)	2 (0.6%)
低ナトリウム血症	2 (0.6%)	0	2 (0.3%)	1 (0.3%)
肥満	1 (0.3%)	2 (0.6%)	3 (0.5%)	0
アシドーシス	1 (0.3%)	0	1 (0.2%)	1 (0.3%)
糖尿病性代謝代償不全	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
痛風	0	2 (0.6%)	2 (0.3%)	0
高トリグリセリド血症	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
鉄欠乏	0	0	0	2 (0.6%)
悪液質	1 (0.3%)	0	1 (0.2%)	0
カルシウム欠乏	1 (0.3%)	0	1 (0.2%)	0
糖尿病合併症	1 (0.3%)	0	1 (0.2%)	0
糖尿病性ケトアシドーシス	1 (0.3%)	0	1 (0.2%)	0
脂質異常症	0	1 (0.3%)	1 (0.2%)	0
葉酸欠乏	0	1 (0.3%)	1 (0.2%)	0
高血糖性高浸透圧性非ケトン性症候群	1 (0.3%)	0	1 (0.2%)	0
高尿酸血症	0	0	0	1 (0.3%)
低マグネシウム血症	0	0	0	1 (0.3%)
乳酸アシドーシス	1 (0.3%)	0	1 (0.2%)	0
マグネシウム欠乏	1 (0.3%)	0	1 (0.2%)	0
栄養障害	0	1 (0.3%)	1 (0.2%)	0
代謝性アシドーシス	1 (0.3%)	0	1 (0.2%)	0
代謝性アルカローシス	0	0	0	1 (0.3%)
代謝症候群	0	1 (0.3%)	1 (0.2%)	0
ビタミンＣ欠乏	0	1 (0.3%)	1 (0.2%)	0

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.6.2-28 眼以外の有害事象の集計（GR40349試験）（続）

Non-Ocular Adverse Events through Week 56, Safety-Evaluable Population
Protocol: GR40349
Clinical Cutoff Date: 20OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Faricimab 6 mg All (N=626)	Aflibercept 2 mg Q8W (N=311)
神経系障害				
Total number of patients with at least one adverse event	40 (12.8%)	39 (12.5%)	79 (12.6%)	32 (10.3%)
Total number of events	61	49	110	41
頭痛	8 (2.6%)	8 (2.6%)	16 (2.6%)	7 (2.3%)
浮動性めまい	4 (1.3%)	4 (1.3%)	8 (1.3%)	6 (1.9%)
糖尿病性ニューロパチー	3 (1.0%)	1 (0.3%)	4 (0.6%)	5 (1.6%)
失神	4 (1.3%)	2 (0.6%)	6 (1.0%)	1 (0.3%)
脳血管発作	2 (0.6%)	3 (1.0%)	5 (0.8%)	1 (0.3%)
感覚鈍麻	1 (0.3%)	2 (0.6%)	3 (0.5%)	3 (1.0%)
片頭痛	2 (0.6%)	2 (0.6%)	4 (0.6%)	1 (0.3%)
末梢性ニューロパチー	1 (0.3%)	2 (0.6%)	3 (0.5%)	2 (0.6%)
虚血性脳卒中	3 (1.0%)	0	3 (0.5%)	1 (0.3%)
神経痛	3 (1.0%)	0	3 (0.5%)	1 (0.3%)
坐骨神経痛	1 (0.3%)	1 (0.3%)	2 (0.3%)	2 (0.6%)
頚動脈硬化症	2 (0.6%)	1 (0.3%)	3 (0.5%)	0
脳症	1 (0.3%)	0	1 (0.2%)	2 (0.6%)
腰髄神経根障害	0	2 (0.6%)	2 (0.3%)	1 (0.3%)
一過性脳虚血発作	1 (0.3%)	1 (0.3%)	2 (0.3%)	1 (0.3%)
頚動脈閉塞	1 (0.3%)	0	1 (0.2%)	1 (0.3%)
アルツハイマー型認知症	1 (0.3%)	0	1 (0.2%)	1 (0.3%)
てんかん	2 (0.6%)	0	2 (0.3%)	0
嗜眠	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
錯感覚	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
聴神経炎	0	1 (0.3%)	1 (0.2%)	0
意識変容状態	0	1 (0.3%)	1 (0.2%)	0
健忘	0	0	0	1 (0.3%)
筋萎縮性側索硬化症	0	1 (0.3%)	1 (0.2%)	0
失語症	1 (0.3%)	0	1 (0.2%)	0
運動失調	1 (0.3%)	0	1 (0.2%)	0
頚動脈狭窄	1 (0.3%)	0	1 (0.2%)	0
手根管症候群	1 (0.3%)	0	1 (0.2%)	0
大脳石灰化	1 (0.3%)	0	1 (0.2%)	0
脳出血	1 (0.3%)	0	1 (0.2%)	0
脳梗塞	1 (0.3%)	0	1 (0.2%)	0
脳血管障害	0	1 (0.3%)	1 (0.2%)	0
頚髄神経根障害	0	1 (0.3%)	1 (0.2%)	0
昏睡	1 (0.3%)	0	1 (0.2%)	0
認知症	1 (0.3%)	0	1 (0.2%)	0
顔面麻痺	1 (0.3%)	0	1 (0.2%)	0
出血性卒中	0	1 (0.3%)	1 (0.2%)	0
不全片麻痺	1 (0.3%)	0	1 (0.2%)	0
高血圧性脳症	0	1 (0.3%)	1 (0.2%)	0
低酸素性虚血性脳症	1 (0.3%)	0	1 (0.2%)	0
意識消失	0	1 (0.3%)	1 (0.2%)	0
記憶障害	1 (0.3%)	0	1 (0.2%)	0

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.6.2-28 眼以外の有害事象の集計（GR40349試験）（続）

Non-Ocular Adverse Events through Week 56, Safety-Evaluable Population
Protocol: GR40349
Clinical Cutoff Date: 20OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Faricimab 6 mg All (N=626)	Aflibercept 2 mg Q8W (N=311)
代謝性脳症	0	0	0	1 (0.3%)
部分発作	0	1 (0.3%)	1 (0.2%)	0
末梢性感覚ニューロパチー	0	1 (0.3%)	1 (0.2%)	0
ヘルペス後神経痛	1 (0.3%)	0	1 (0.2%)	0
失神寸前の状態	1 (0.3%)	0	1 (0.2%)	0
副鼻腔炎に伴う頭痛	1 (0.3%)	0	1 (0.2%)	0
中枢神経系に起因する回転性めまい	0	1 (0.3%)	1 (0.2%)	0
声帯不全麻痺	0	1 (0.3%)	1 (0.2%)	0
胃腸障害				
Total number of patients with at least one adverse event	40 (12.8%)	32 (10.2%)	72 (11.5%)	32 (10.3%)
Total number of events	60	51	111	48
悪心	9 (2.9%)	5 (1.6%)	14 (2.2%)	7 (2.3%)
嘔吐	10 (3.2%)	2 (0.6%)	12 (1.9%)	5 (1.6%)
下痢	3 (1.0%)	5 (1.6%)	8 (1.3%)	6 (1.9%)
胃食道逆流性疾患	5 (1.6%)	3 (1.0%)	8 (1.3%)	4 (1.3%)
齲歯	4 (1.3%)	3 (1.0%)	7 (1.1%)	1 (0.3%)
上腹部痛	3 (1.0%)	4 (1.3%)	7 (1.1%)	0
便秘	1 (0.3%)	2 (0.6%)	3 (0.5%)	4 (1.3%)
大腸ポリープ	1 (0.3%)	4 (1.3%)	5 (0.8%)	0
大腸炎	1 (0.3%)	2 (0.6%)	3 (0.5%)	1 (0.3%)
嚥下障害	0	2 (0.6%)	2 (0.3%)	2 (0.6%)
消化不良	1 (0.3%)	1 (0.3%)	2 (0.3%)	1 (0.3%)
胃炎	0	2 (0.6%)	2 (0.3%)	1 (0.3%)
食道炎	0	2 (0.6%)	2 (0.3%)	1 (0.3%)
膵炎	3 (1.0%)	0	3 (0.5%)	0
腹痛	0	0	0	2 (0.6%)
下腹部痛	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
腸憩室	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
食中毒	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
胃腸出血	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
血便排泄	2 (0.6%)	0	2 (0.3%)	0
腹部ヘルニア	1 (0.3%)	0	1 (0.2%)	0
痔瘻	1 (0.3%)	0	1 (0.2%)	0
肛門失禁	0	1 (0.3%)	1 (0.2%)	0
腹水	1 (0.3%)	0	1 (0.2%)	0
潰瘍性大腸炎	1 (0.3%)	0	1 (0.2%)	0
歯嚢胞	0	0	0	1 (0.3%)
糖尿病性胃不全麻痺	0	1 (0.3%)	1 (0.2%)	0
憩室	0	1 (0.3%)	1 (0.2%)	0
口内乾燥	0	0	0	1 (0.3%)
十二指腸炎	1 (0.3%)	0	1 (0.2%)	0
十二指腸胃逆流	1 (0.3%)	0	1 (0.2%)	0
鼓腸	1 (0.3%)	0	1 (0.2%)	0
消化管運動過剰	1 (0.3%)	0	1 (0.2%)	0

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.6.2-28 眼以外の有害事象の集計（GR40349試験）（続）

Non-Ocular Adverse Events through Week 56, Safety-Evaluable Population
Protocol: GR40349
Clinical Cutoff Date: 20OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Faricimab 6 mg All (N=626)	Aflibercept 2 mg Q8W (N=311)
消化器痛	0	0	0	1 (0.3%)
歯肉退縮	0	1 (0.3%)	1 (0.2%)	0
痔核	0	0	0	1 (0.3%)
血栓性痔核	0	1 (0.3%)	1 (0.2%)	0
裂孔ヘルニア	0	0	0	1 (0.3%)
イレウス	0	1 (0.3%)	1 (0.2%)	0
過敏性腸症候群	0	0	0	1 (0.3%)
閉塞性膵炎	0	1 (0.3%)	1 (0.2%)	0
慢性膵炎	1 (0.3%)	0	1 (0.2%)	0
歯痛	0	0	0	1 (0.3%)
口蓋垂炎	1 (0.3%)	0	1 (0.2%)	0
筋骨格系および結合組織障害				
Total number of patients with at least one adverse event	35 (11.2%)	30 (9.6%)	65 (10.4%)	25 (8.0%)
Total number of events	43	41	84	40
関節痛	5 (1.6%)	6 (1.9%)	11 (1.8%)	5 (1.6%)
背部痛	5 (1.6%)	5 (1.6%)	10 (1.6%)	6 (1.9%)
四肢痛	4 (1.3%)	4 (1.3%)	8 (1.3%)	5 (1.6%)
筋痙縮	3 (1.0%)	1 (0.3%)	4 (0.6%)	4 (1.3%)
変形性関節症	2 (0.6%)	2 (0.6%)	4 (0.6%)	1 (0.3%)
椎間板突出	2 (0.6%)	0	2 (0.3%)	2 (0.6%)
神経障害性関節症	3 (1.0%)	0	3 (0.5%)	1 (0.3%)
脊椎痛	2 (0.6%)	1 (0.3%)	3 (0.5%)	1 (0.3%)
関節炎	1 (0.3%)	1 (0.3%)	2 (0.3%)	1 (0.3%)
筋肉痛	2 (0.6%)	1 (0.3%)	3 (0.5%)	0
肩回旋筋腱板症候群	2 (0.6%)	1 (0.3%)	3 (0.5%)	0
滑液包炎	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
足変形	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
椎間板変性症	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
筋力低下	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
筋骨格硬直	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
頚部痛	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
多発性関節炎	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
側弯症	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
変形性脊椎症	1 (0.3%)	0	1 (0.2%)	1 (0.3%)
脊椎すべり症	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
弾発指	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
骨代謝障害	0	0	0	1 (0.3%)
外骨腫	0	1 (0.3%)	1 (0.2%)	0
椎間関節症候群	0	0	0	1 (0.3%)
関節拘縮	0	0	0	1 (0.3%)
四肢不快感	0	1 (0.3%)	1 (0.2%)	0
腰部脊柱管狭窄症	0	1 (0.3%)	1 (0.2%)	0
咀嚼障害	0	0	0	1 (0.3%)

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.6.2-28 眼以外の有害事象の集計（GR40349試験）（続）

Non-Ocular Adverse Events through Week 56, Safety-Evaluable Population
Protocol: GR40349
Clinical Cutoff Date: 20OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Faricimab 6 mg All (N=626)	Aflibercept 2 mg Q8W (N=311)
筋障害	1 (0.3%)	0	1 (0.2%)	0
筋骨格系胸痛	0	1 (0.3%)	1 (0.2%)	0
筋骨格痛	1 (0.3%)	0	1 (0.2%)	0
骨端症	0	1 (0.3%)	1 (0.2%)	0
骨減少症	1 (0.3%)	0	1 (0.2%)	0
骨粗鬆症	0	1 (0.3%)	1 (0.2%)	0
関節周囲炎	1 (0.3%)	0	1 (0.2%)	0
足底筋膜炎	1 (0.3%)	0	1 (0.2%)	0
横紋筋融解症	0	0	0	1 (0.3%)
交感神経性後頚部症候群	1 (0.3%)	0	1 (0.2%)	0
滑液嚢腫	0	1 (0.3%)	1 (0.2%)	0
腱炎	0	0	0	1 (0.3%)
傷害、中毒および処置合併症				
Total number of patients with at least one adverse event	27 (8.6%)	35 (11.2%)	62 (9.9%)	22 (7.1%)
Total number of events	36	54	90	25
転倒	10 (3.2%)	10 (3.2%)	20 (3.2%)	7 (2.3%)
挫傷	1 (0.3%)	3 (1.0%)	4 (0.6%)	3 (1.0%)
皮膚裂傷	2 (0.6%)	4 (1.3%)	6 (1.0%)	1 (0.3%)
四肢損傷	1 (0.3%)	3 (1.0%)	4 (0.6%)	1 (0.3%)
熱傷	2 (0.6%)	3 (1.0%)	5 (0.8%)	0
歯牙破折	1 (0.3%)	1 (0.3%)	2 (0.3%)	3 (1.0%)
節足動物咬傷	1 (0.3%)	2 (0.6%)	3 (0.5%)	1 (0.3%)
肋骨骨折	1 (0.3%)	1 (0.3%)	2 (0.3%)	2 (0.6%)
足骨折	1 (0.3%)	1 (0.3%)	2 (0.3%)	1 (0.3%)
靱帯断裂	1 (0.3%)	0	1 (0.2%)	2 (0.6%)
処置による疼痛	0	3 (1.0%)	3 (0.5%)	0
大腿骨骨折	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
頭部損傷	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
上腕骨骨折	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
関節損傷	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
上肢骨折	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
事故	0	1 (0.3%)	1 (0.2%)	0
術後貧血	1 (0.3%)	0	1 (0.2%)	0
足関節部骨折	1 (0.3%)	0	1 (0.2%)	0
骨挫傷	0	1 (0.3%)	1 (0.2%)	0
脳振盪	0	1 (0.3%)	1 (0.2%)	0
上顆炎	0	1 (0.3%)	1 (0.2%)	0
大腿骨頚部骨折	0	1 (0.3%)	1 (0.2%)	0
体内異物	0	1 (0.3%)	1 (0.2%)	0
転位骨折	0	0	0	1 (0.3%)
手骨折	0	1 (0.3%)	1 (0.2%)	0
股関節部骨折	0	1 (0.3%)	1 (0.2%)	0

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.6.2-28 眼以外の有害事象の集計（GR40349試験）（続）

Non-Ocular Adverse Events through Week 56, Safety-Evaluable Population
Protocol: GR40349
Clinical Cutoff Date: 20OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Faricimab 6 mg All (N=626)	Aflibercept 2 mg Q8W (N=311)
腸骨骨折	0	1 (0.3%)	1 (0.2%)	0
切開部位痛	0	1 (0.3%)	1 (0.2%)	0
関節脱臼	1 (0.3%)	0	1 (0.2%)	0
靱帯損傷	0	0	0	1 (0.3%)
靱帯捻挫	0	1 (0.3%)	1 (0.2%)	0
四肢骨折	1 (0.3%)	0	1 (0.2%)	0
四肢外傷性切断	1 (0.3%)	0	1 (0.2%)	0
口唇損傷	0	1 (0.3%)	1 (0.2%)	0
膝蓋骨骨折	0	1 (0.3%)	1 (0.2%)	0
橈骨骨折	0	0	0	1 (0.3%)
鎮静合併症	0	1 (0.3%)	1 (0.2%)	0
皮膚擦過傷	1 (0.3%)	0	1 (0.2%)	0
脊椎圧迫骨折	0	1 (0.3%)	1 (0.2%)	0
脛骨骨折	1 (0.3%)	0	1 (0.2%)	0
歯の脱臼	1 (0.3%)	0	1 (0.2%)	0
歯牙損傷	0	1 (0.3%)	1 (0.2%)	0
創離開	1 (0.3%)	0	1 (0.2%)	0
手首関節骨折	0	1 (0.3%)	1 (0.2%)	0
血管障害				
Total number of patients with at least one adverse event	27 (8.6%)	30 (9.6%)	57 (9.1%)	32 (10.3%)
Total number of events	35	35	70	38
高血圧	17 (5.4%)	18 (5.8%)	35 (5.6%)	25 (8.0%)
低血圧	1 (0.3%)	4 (1.3%)	5 (0.8%)	3 (1.0%)
血圧変動	3 (1.0%)	3 (1.0%)	6 (1.0%)	1 (0.3%)
動脈硬化症	1 (0.3%)	2 (0.6%)	3 (0.5%)	0
大動脈狭窄	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
血腫	0	0	0	2 (0.6%)
末梢動脈閉塞	1 (0.3%)	0	1 (0.2%)	1 (0.3%)
動脈瘤	1 (0.3%)	0	1 (0.2%)	0
血管硬化	1 (0.3%)	0	1 (0.2%)	0
コントロール不良の血圧	0	0	0	1 (0.3%)
深部静脈血栓症	0	0	0	1 (0.3%)
塞栓症	1 (0.3%)	0	1 (0.2%)	0
高血圧クリーゼ	0	1 (0.3%)	1 (0.2%)	0
高血圧緊急症	1 (0.3%)	0	1 (0.2%)	0
末梢動脈閉塞性疾患	0	1 (0.3%)	1 (0.2%)	0
末梢動脈狭窄	0	0	0	1 (0.3%)
末梢動脈血栓症	1 (0.3%)	0	1 (0.2%)	0
末梢冷感	0	1 (0.3%)	1 (0.2%)	0
静脈瘤	0	1 (0.3%)	1 (0.2%)	0

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.6.2-28 眼以外の有害事象の集計（GR40349試験）（続）

Non-Ocular Adverse Events through Week 56, Safety-Evaluable Population
Protocol: GR40349
Clinical Cutoff Date: 20OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Faricimab 6 mg All (N=626)	Aflibercept 2 mg Q8W (N=311)
呼吸器、胸郭および縦隔障害				
Total number of patients with at least one adverse event	29 (9.3%)	26 (8.3%)	55 (8.8%)	20 (6.4%)
Total number of events	42	43	85	26
咳嗽	8 (2.6%)	7 (2.2%)	15 (2.4%)	3 (1.0%)
胸水	3 (1.0%)	4 (1.3%)	7 (1.1%)	2 (0.6%)
鼻漏	2 (0.6%)	5 (1.6%)	7 (1.1%)	1 (0.3%)
喘息	3 (1.0%)	2 (0.6%)	5 (0.8%)	1 (0.3%)
呼吸困難	2 (0.6%)	1 (0.3%)	3 (0.5%)	2 (0.6%)
急性呼吸不全	2 (0.6%)	0	2 (0.3%)	2 (0.6%)
労作性呼吸困難	1 (0.3%)	2 (0.6%)	3 (0.5%)	1 (0.3%)
睡眠時無呼吸症候群	3 (1.0%)	1 (0.3%)	4 (0.6%)	0
慢性閉塞性肺疾患	1 (0.3%)	2 (0.6%)	3 (0.5%)	0
鼻閉	2 (0.6%)	1 (0.3%)	3 (0.5%)	0
口腔咽頭痛	2 (0.6%)	0	2 (0.3%)	1 (0.3%)
肺塞栓症	2 (0.6%)	0	2 (0.3%)	1 (0.3%)
無気肺	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
下気道うっ血	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
呼吸障害	2 (0.6%)	0	2 (0.3%)	0
呼吸不全	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
副鼻腔うっ血	2 (0.6%)	0	2 (0.3%)	0
上気道うっ血	0	2 (0.6%)	2 (0.3%)	0
無呼吸	1 (0.3%)	0	1 (0.2%)	0
気管支痙攣	0	0	0	1 (0.3%)
肺気腫	1 (0.3%)	0	1 (0.2%)	0
鼻出血	0	0	0	1 (0.3%)
喀血	0	1 (0.3%)	1 (0.2%)	0
低酸素症	0	0	0	1 (0.3%)
喉頭浮腫	0	1 (0.3%)	1 (0.2%)	0
肺嚢胞	0	1 (0.3%)	1 (0.2%)	0
鼻痂皮	1 (0.3%)	0	1 (0.2%)	0
副鼻腔分泌過多	1 (0.3%)	0	1 (0.2%)	0
咽頭障害	0	0	0	1 (0.3%)
胸膜痛	0	0	0	1 (0.3%)
誤嚥性肺炎	0	1 (0.3%)	1 (0.2%)	0
湿性咳嗽	0	1 (0.3%)	1 (0.2%)	0
肺水腫	0	0	0	1 (0.3%)
肺血管障害	1 (0.3%)	0	1 (0.2%)	0
アレルギー性鼻炎	0	0	0	1 (0.3%)
気管の炎症	0	1 (0.3%)	1 (0.2%)	0
上気道の炎症	0	0	0	1 (0.3%)

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).
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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.6.2-28 眼以外の有害事象の集計（GR40349試験）（続）

Non-Ocular Adverse Events through Week 56, Safety-Evaluable Population
Protocol: GR40349
Clinical Cutoff Date: 20OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Faricimab 6 mg All (N=626)	Aflibercept 2 mg Q8W (N=311)
心臓障害				
Total number of patients with at least one adverse event	24 (7.7%)	26 (8.3%)	50 (8.0%)	25 (8.0%)
Total number of events	41	37	78	33
うっ血性心不全	6 (1.9%)	0	6 (1.0%)	5 (1.6%)
冠動脈疾患	3 (1.0%)	5 (1.6%)	8 (1.3%)	3 (1.0%)
心房細動	3 (1.0%)	4 (1.3%)	7 (1.1%)	2 (0.6%)
急性心筋梗塞	2 (0.6%)	2 (0.6%)	4 (0.6%)	4 (1.3%)
心筋梗塞	1 (0.3%)	3 (1.0%)	4 (0.6%)	4 (1.3%)
心不全	1 (0.3%)	3 (1.0%)	4 (0.6%)	1 (0.3%)
心筋虚血	3 (1.0%)	1 (0.3%)	4 (0.6%)	1 (0.3%)
急性左室不全	0	1 (0.3%)	1 (0.2%)	2 (0.6%)
狭心症	1 (0.3%)	1 (0.3%)	2 (0.3%)	1 (0.3%)
徐脈	1 (0.3%)	2 (0.6%)	3 (0.5%)	0
心拡大	1 (0.3%)	0	1 (0.2%)	2 (0.6%)
心筋症	1 (0.3%)	2 (0.6%)	3 (0.5%)	0
頻脈	0	1 (0.3%)	1 (0.2%)	2 (0.6%)
不整脈	0	2 (0.6%)	2 (0.3%)	0
心停止	2 (0.6%)	0	2 (0.3%)	0
慢性心不全	0	2 (0.6%)	2 (0.3%)	0
冠動脈狭窄	1 (0.3%)	0	1 (0.2%)	1 (0.3%)
左室不全	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
動悸	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
洞結節機能不全	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
冠動脈硬化症	0	1 (0.3%)	1 (0.2%)	0
心房粗動	1 (0.3%)	0	1 (0.2%)	0
完全房室ブロック	0	1 (0.3%)	1 (0.2%)	0
急性心不全	1 (0.3%)	0	1 (0.2%)	0
心血管障害	0	1 (0.3%)	1 (0.2%)	0
心血管不全	0	1 (0.3%)	1 (0.2%)	0
慢性左室不全	1 (0.3%)	0	1 (0.2%)	0
冠動脈閉塞	0	0	0	1 (0.3%)
高血圧性心疾患	0	1 (0.3%)	1 (0.2%)	0
左房拡張	1 (0.3%)	0	1 (0.2%)	0
左室拡張	1 (0.3%)	0	1 (0.2%)	0
心筋炎	1 (0.3%)	0	1 (0.2%)	0
心嚢液貯留	0	0	0	1 (0.3%)
心膜炎	1 (0.3%)	0	1 (0.2%)	0
洞性徐脈	0	0	0	1 (0.3%)
心室性頻脈性不整脈	1 (0.3%)	0	1 (0.2%)	0

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Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.6.2-28 眼以外の有害事象の集計（GR40349試験）（続）

Non-Ocular Adverse Events through Week 56, Safety-Evaluable Population
Protocol: GR40349
Clinical Cutoff Date: 20OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Faricimab 6 mg All (N=626)	Aflibercept 2 mg Q8W (N=311)
腎および尿路障害				
Total number of patients with at least one adverse event	27 (8.6%)	16 (5.1%)	43 (6.9%)	28 (9.0%)
Total number of events	39	16	55	32
慢性腎臓病	8 (2.6%)	2 (0.6%)	10 (1.6%)	8 (2.6%)
急性腎障害	7 (2.2%)	3 (1.0%)	10 (1.6%)	5 (1.6%)
腎不全	5 (1.6%)	4 (1.3%)	9 (1.4%)	2 (0.6%)
糖尿病性腎症	2 (0.6%)	1 (0.3%)	3 (0.5%)	3 (1.0%)
末期腎疾患	3 (1.0%)	0	3 (0.5%)	2 (0.6%)
腎結石症	1 (0.3%)	1 (0.3%)	2 (0.3%)	2 (0.6%)
腎症	1 (0.3%)	0	1 (0.2%)	3 (1.0%)
血尿	1 (0.3%)	0	1 (0.2%)	1 (0.3%)
ミクロアルブミン尿	2 (0.6%)	0	2 (0.3%)	0
蛋白尿	1 (0.3%)	0	1 (0.2%)	1 (0.3%)
腎嚢胞	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
腎機能障害	1 (0.3%)	0	1 (0.2%)	1 (0.3%)
膀胱嚢胞	0	1 (0.3%)	1 (0.2%)	0
糖尿	1 (0.3%)	0	1 (0.2%)	0
水腎症	1 (0.3%)	0	1 (0.2%)	0
緊張性膀胱	0	0	0	1 (0.3%)
代謝性腎症	0	1 (0.3%)	1 (0.2%)	0
夜間頻尿	0	1 (0.3%)	1 (0.2%)	0
頻尿	0	0	0	1 (0.3%)
腎動脈狭窄症	0	0	0	1 (0.3%)
腎仙痛	0	1 (0.3%)	1 (0.2%)	0
尿失禁	0	0	0	1 (0.3%)
尿閉	1 (0.3%)	0	1 (0.2%)	0
尿生殖器瘻	1 (0.3%)	0	1 (0.2%)	0

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.6.2-28 眼以外の有害事象の集計（GR40349試験）（続）

Non-Ocular Adverse Events through Week 56, Safety-Evaluable Population
Protocol: GR40349
Clinical Cutoff Date: 20OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Faricimab 6 mg All (N=626)	Aflibercept 2 mg Q8W (N=311)
臨床検査				
Total number of patients with at least one adverse event	17 (5.4%)	23 (7.3%)	40 (6.4%)	21 (6.8%)
Total number of events	21	26	47	26
血中ブドウ糖増加	0	4 (1.3%)	4 (0.6%)	3 (1.0%)
血圧上昇	1 (0.3%)	2 (0.6%)	3 (0.5%)	3 (1.0%)
血中コレステロール増加	1 (0.3%)	1 (0.3%)	2 (0.3%)	3 (1.0%)
血中カリウム増加	1 (0.3%)	3 (1.0%)	4 (0.6%)	1 (0.3%)
血中尿素増加	1 (0.3%)	3 (1.0%)	4 (0.6%)	1 (0.3%)
グリコヘモグロビン増加	2 (0.6%)	1 (0.3%)	3 (0.5%)	2 (0.6%)
血中ブドウ糖変動	1 (0.3%)	2 (0.6%)	3 (0.5%)	1 (0.3%)
血中クレアチニン増加	2 (0.6%)	0	2 (0.3%)	1 (0.3%)
血中尿酸増加	0	0	0	2 (0.6%)
体重増加	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
アミラーゼ増加	0	1 (0.3%)	1 (0.2%)	0
心血管造影	0	1 (0.3%)	1 (0.2%)	0
アスパラギン酸アミノトランスフェラーゼ増加	0	1 (0.3%)	1 (0.2%)	0
細菌検査陽性	1 (0.3%)	0	1 (0.2%)	0
血中重炭酸塩減少	0	0	0	1 (0.3%)
血中カルシウム減少	1 (0.3%)	0	1 (0.2%)	0
血中クレアチン増加	0	0	0	1 (0.3%)
血中ブドウ糖減少	0	0	0	1 (0.3%)
血中鉄減少	0	1 (0.3%)	1 (0.2%)	0
血中マグネシウム減少	0	0	0	1 (0.3%)
血中カリウム減少	1 (0.3%)	0	1 (0.2%)	0
拡張期血圧上昇	0	1 (0.3%)	1 (0.2%)	0
血中テストステロン増加	0	1 (0.3%)	1 (0.2%)	0
体温上昇	0	0	0	1 (0.3%)
コンピュータ断層撮影異常	0	0	0	1 (0.3%)
駆出率減少	1 (0.3%)	0	1 (0.2%)	0
心電図Ｔ波振幅減少	1 (0.3%)	0	1 (0.2%)	0
糸球体濾過率減少	1 (0.3%)	0	1 (0.2%)	0
ヘモグロビン減少	1 (0.3%)	0	1 (0.2%)	0
ヘリコバクター検査陽性	1 (0.3%)	0	1 (0.2%)	0
Ａ型インフルエンザウイルス検査陽性	1 (0.3%)	0	1 (0.2%)	0
眼圧上昇	1 (0.3%)	0	1 (0.2%)	0
血小板数減少	0	1 (0.3%)	1 (0.2%)	0
前立腺特異性抗原増加	1 (0.3%)	0	1 (0.2%)	0
尿中赤血球	0	0	0	1 (0.3%)
トロポニン増加	0	0	0	1 (0.3%)
尿中ウロビリノーゲン増加	0	1 (0.3%)	1 (0.2%)	0
ビタミンＤ減少	0	1 (0.3%)	1 (0.2%)	0
尿中白血球陽性	1 (0.3%)	0	1 (0.2%)	0

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.6.2-28 眼以外の有害事象の集計（GR40349試験）（続）

Non-Ocular Adverse Events through Week 56, Safety-Evaluable Population
Protocol: GR40349
Clinical Cutoff Date: 20OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Faricimab 6 mg All (N=626)	Aflibercept 2 mg Q8W (N=311)
一般・全身障害および投与部位の状態				
Total number of patients with at least one adverse event	23 (7.3%)	18 (5.8%)	41 (6.5%)	17 (5.5%)
Total number of events	29	27	56	23
末梢性浮腫	3 (1.0%)	4 (1.3%)	7 (1.1%)	3 (1.0%)
無力症	4 (1.3%)	3 (1.0%)	7 (1.1%)	2 (0.6%)
胸痛	3 (1.0%)	2 (0.6%)	5 (0.8%)	4 (1.3%)
末梢腫脹	2 (0.6%)	2 (0.6%)	4 (0.6%)	4 (1.3%)
発熱	5 (1.6%)	1 (0.3%)	6 (1.0%)	2 (0.6%)
疲労	2 (0.6%)	1 (0.3%)	3 (0.5%)	4 (1.3%)
死亡	1 (0.3%)	3 (1.0%)	4 (0.6%)	0
悪寒	0	1 (0.3%)	1 (0.2%)	2 (0.6%)
疼痛	2 (0.6%)	1 (0.3%)	3 (0.5%)	0
胸部不快感	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
不快感	0	1 (0.3%)	1 (0.2%)	0
溢出	0	1 (0.3%)	1 (0.2%)	0
体温変動感	0	1 (0.3%)	1 (0.2%)	0
歩行障害	0	1 (0.3%)	1 (0.2%)	0
全身健康状態悪化	1 (0.3%)	0	1 (0.2%)	0
全身性浮腫	1 (0.3%)	0	1 (0.2%)	0
異常高熱	1 (0.3%)	0	1 (0.2%)	0
不明確な障害	1 (0.3%)	0	1 (0.2%)	0
インフルエンザ様疾患	0	1 (0.3%)	1 (0.2%)	0
注射部位損傷	0	1 (0.3%)	1 (0.2%)	0
限局性浮腫	0	1 (0.3%)	1 (0.2%)	0
倦怠感	1 (0.3%)	0	1 (0.2%)	0
腫脹	0	0	0	1 (0.3%)
評価不能の事象	1 (0.3%)	0	1 (0.2%)	0

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).
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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.6.2-28 眼以外の有害事象の集計（GR40349試験）（続）

Non-Ocular Adverse Events through Week 56, Safety-Evaluable Population
Protocol: GR40349
Clinical Cutoff Date: 20OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Faricimab 6 mg All (N=626)	Aflibercept 2 mg Q8W (N=311)
皮膚および皮下組織障害				
Total number of patients with at least one adverse event	24 (7.7%)	14 (4.5%)	38 (6.1%)	12 (3.9%)
Total number of events	32	15	47	15
糖尿病性足病変	4 (1.3%)	2 (0.6%)	6 (1.0%)	4 (1.3%)
水疱	1 (0.3%)	2 (0.6%)	3 (0.5%)	1 (0.3%)
接触皮膚炎	0	2 (0.6%)	2 (0.3%)	2 (0.6%)
そう痒症	0	2 (0.6%)	2 (0.3%)	2 (0.6%)
発疹	4 (1.3%)	0	4 (0.6%)	0
皮膚潰瘍	3 (1.0%)	1 (0.3%)	4 (0.6%)	0
皮膚嚢腫	2 (0.6%)	0	2 (0.3%)	0
皮膚炎	2 (0.6%)	0	2 (0.3%)	0
過角化	1 (0.3%)	0	1 (0.2%)	1 (0.3%)
嵌入爪	1 (0.3%)	0	1 (0.2%)	1 (0.3%)
点状出血	1 (0.3%)	0	1 (0.2%)	1 (0.3%)
酒さ	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
蕁麻疹	0	2 (0.6%)	2 (0.3%)	0
光線角化症	1 (0.3%)	0	1 (0.2%)	0
糖尿病性手関節症	1 (0.3%)	0	1 (0.2%)	0
斑状出血	0	0	0	1 (0.3%)
湿疹	1 (0.3%)	0	1 (0.2%)	0
手皮膚炎	0	1 (0.3%)	1 (0.2%)	0
内方発育毛	1 (0.3%)	0	1 (0.2%)	0
機械性蕁麻疹	1 (0.3%)	0	1 (0.2%)	0
乾癬	1 (0.3%)	0	1 (0.2%)	0
紫斑	0	0	0	1 (0.3%)
皮膚亀裂	0	1 (0.3%)	1 (0.2%)	0
皮膚病変	1 (0.3%)	0	1 (0.2%)	0
日光黒子	1 (0.3%)	0	1 (0.2%)	0
皮下気腫	1 (0.3%)	0	1 (0.2%)	0
丘疹状蕁麻疹	1 (0.3%)	0	1 (0.2%)	0
血液およびリンパ系障害				
Total number of patients with at least one adverse event	14 (4.5%)	12 (3.8%)	26 (4.2%)	18 (5.8%)
Total number of events	15	16	31	18
貧血	10 (3.2%)	10 (3.2%)	20 (3.2%)	10 (3.2%)
鉄欠乏性貧血	1 (0.3%)	1 (0.3%)	2 (0.3%)	2 (0.6%)
腎性貧血	1 (0.3%)	0	1 (0.2%)	3 (1.0%)
血小板減少症	2 (0.6%)	2 (0.6%)	4 (0.6%)	0
慢性疾患の貧血	0	0	0	1 (0.3%)
失血性貧血	1 (0.3%)	0	1 (0.2%)	0
白血球増加症	0	0	0	1 (0.3%)
好中球増加症	0	0	0	1 (0.3%)

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.6.2-28 眼以外の有害事象の集計（GR40349試験）（続）

Non-Ocular Adverse Events through Week 56, Safety-Evaluable Population
Protocol: GR40349
Clinical Cutoff Date: 20OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Faricimab 6 mg All (N=626)	Aflibercept 2 mg Q8W (N=311)
精神障害				
Total number of patients with at least one adverse event	12 (3.8%)	5 (1.6%)	17 (2.7%)	11 (3.5%)
Total number of events	13	8	21	12
うつ病	2 (0.6%)	2 (0.6%)	4 (0.6%)	3 (1.0%)
不安	1 (0.3%)	3 (1.0%)	4 (0.6%)	2 (0.6%)
不眠症	3 (1.0%)	1 (0.3%)	4 (0.6%)	2 (0.6%)
錯乱状態	1 (0.3%)	0	1 (0.2%)	1 (0.3%)
失見当識	2 (0.6%)	0	2 (0.3%)	0
激越	1 (0.3%)	0	1 (0.2%)	0
自殺既遂	0	0	0	1 (0.3%)
妄想性障害、詳細不明	1 (0.3%)	0	1 (0.2%)	0
幻視	1 (0.3%)	0	1 (0.2%)	0
気力低下	0	0	0	1 (0.3%)
精神状態変化	1 (0.3%)	0	1 (0.2%)	0
パニック発作	0	1 (0.3%)	1 (0.2%)	0
処置に対する不安	0	0	0	1 (0.3%)
季節性感情障害	0	0	0	1 (0.3%)
睡眠障害	0	1 (0.3%)	1 (0.2%)	0

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.6.2-28 眼以外の有害事象の集計（GR40349試験）（続）

Non-Ocular Adverse Events through Week 56, Safety-Evaluable Population
Protocol: GR40349
Clinical Cutoff Date: 20OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Faricimab 6 mg All (N=626)	Aflibercept 2 mg Q8W (N=311)
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）				
Total number of patients with at least one adverse event	5 (1.6%)	14 (4.5%)	19 (3.0%)	5 (1.6%)
Total number of events	7	15	22	5
基底細胞癌	1 (0.3%)	3 (1.0%)	4 (0.6%)	0
結腸腺癌	0	1 (0.3%)	1 (0.2%)	2 (0.6%)
Ｂ細胞性リンパ腫	0	1 (0.3%)	1 (0.2%)	0
乳房の良性新生物	0	1 (0.3%)	1 (0.2%)	0
胆管癌	1 (0.3%)	0	1 (0.2%)	0
膀胱癌	1 (0.3%)	0	1 (0.2%)	0
乳癌	1 (0.3%)	0	1 (0.2%)	0
慢性リンパ性白血病	0	0	0	1 (0.3%)
異形成母斑	1 (0.3%)	0	1 (0.2%)	0
平滑筋腫	0	1 (0.3%)	1 (0.2%)	0
白血病	0	1 (0.3%)	1 (0.2%)	0
新生物	0	1 (0.3%)	1 (0.2%)	0
膵癌	1 (0.3%)	0	1 (0.2%)	0
形質細胞性骨髄腫	0	1 (0.3%)	1 (0.2%)	0
腎新生物	0	1 (0.3%)	1 (0.2%)	0
皮膚癌	0	0	0	1 (0.3%)
扁平上皮癌	1 (0.3%)	0	1 (0.2%)	0
皮膚有棘細胞癌	0	1 (0.3%)	1 (0.2%)	0
移行上皮癌	0	1 (0.3%)	1 (0.2%)	0
腫瘍浸潤	0	1 (0.3%)	1 (0.2%)	0
腫瘍性血栓症	0	1 (0.3%)	1 (0.2%)	0
子宮平滑筋腫	0	0	0	1 (0.3%)
肝胆道系障害				
Total number of patients with at least one adverse event	7 (2.2%)	6 (1.9%)	13 (2.1%)	3 (1.0%)
Total number of events	11	8	19	4
胆石症	5 (1.6%)	1 (0.3%)	6 (1.0%)	0
肝硬変	1 (0.3%)	1 (0.3%)	2 (0.3%)	1 (0.3%)
急性胆嚢炎	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
脂肪肝	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
肝腫大	0	2 (0.6%)	2 (0.3%)	0
非アルコール性脂肪性肝炎	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
胆道ジスキネジア	1 (0.3%)	0	1 (0.2%)	0
慢性胆嚢炎	1 (0.3%)	0	1 (0.2%)	0
慢性肝炎	0	0	0	1 (0.3%)
黄疸	0	0	0	1 (0.3%)
門脈拡張	0	1 (0.3%)	1 (0.2%)	0

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.6.2-28 眼以外の有害事象の集計（GR40349試験）（続）

Non-Ocular Adverse Events through Week 56, Safety-Evaluable Population
Protocol: GR40349
Clinical Cutoff Date: 20OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Faricimab 6 mg All (N=626)	Aflibercept 2 mg Q8W (N=311)
耳および迷路障害				
Total number of patients with at least one adverse event	4 (1.3%)	5 (1.6%)	9 (1.4%)	4 (1.3%)
Total number of events	4	5	9	5
回転性めまい	2 (0.6%)	0	2 (0.3%)	1 (0.3%)
耳痛	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
聴力低下	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
耳鳴	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
耳閉	1 (0.3%)	0	1 (0.2%)	0
乗物酔い	0	0	0	1 (0.3%)
突発性難聴	0	1 (0.3%)	1 (0.2%)	0
前庭障害	0	1 (0.3%)	1 (0.2%)	0
生殖系および乳房障害				
Total number of patients with at least one adverse event	2 (0.6%)	6 (1.9%)	8 (1.3%)	4 (1.3%)
Total number of events	2	6	8	4
良性前立腺肥大症	1 (0.3%)	1 (0.3%)	2 (0.3%)	3 (1.0%)
腺筋症	0	1 (0.3%)	1 (0.2%)	0
勃起不全	1 (0.3%)	0	1 (0.2%)	0
卵巣嚢胞	0	1 (0.3%)	1 (0.2%)	0
骨盤内嚢胞	0	0	0	1 (0.3%)
前立腺炎	0	1 (0.3%)	1 (0.2%)	0
前立腺腫大	0	1 (0.3%)	1 (0.2%)	0
陰部そう痒症	0	1 (0.3%)	1 (0.2%)	0
内分泌障害				
Total number of patients with at least one adverse event	2 (0.6%)	4 (1.3%)	6 (1.0%)	2 (0.6%)
Total number of events	2	5	7	2
甲状腺機能低下症	1 (0.3%)	3 (1.0%)	4 (0.6%)	2 (0.6%)
自己免疫性甲状腺炎	0	1 (0.3%)	1 (0.2%)	0
甲状腺腫	0	1 (0.3%)	1 (0.2%)	0
続発性副甲状腺機能亢進症	1 (0.3%)	0	1 (0.2%)	0
免疫系障害				
Total number of patients with at least one adverse event	3 (1.0%)	1 (0.3%)	4 (0.6%)	3 (1.0%)
Total number of events	3	1	4	3
季節性アレルギー	0	1 (0.3%)	1 (0.2%)	2 (0.6%)
過敏症	2 (0.6%)	0	2 (0.3%)	0
造影剤アレルギー	0	0	0	1 (0.3%)
造影剤反応	1 (0.3%)	0	1 (0.2%)	0

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.6.2-28 眼以外の有害事象の集計（GR40349試験）（続）

Non-Ocular Adverse Events through Week 56, Safety-Evaluable Population
Protocol: GR40349
Clinical Cutoff Date: 20OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Faricimab 6 mg All (N=626)	Aflibercept 2 mg Q8W (N=311)
外科および内科処置				
Total number of patients with at least one adverse event	1 (0.3%)	2 (0.6%)	3 (0.5%)	0
Total number of events	1	2	3	0
関節固定術	0	1 (0.3%)	1 (0.2%)	0
胆嚢切除	1 (0.3%)	0	1 (0.2%)	0
外科的脊椎固定	0	1 (0.3%)	1 (0.2%)	0

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).
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[5.3.5.3-nAMD-1 t_ae_NOCUL_W56_SE_20OCT2020_40349を改変]

表 2.7.6.2-29 試験眼の副作用の集計（GR40349試験）

Ocular Adverse Events Related to Study Treatment in the Study Eye through Week 56, Safety-Evaluable Population
Protocol: GR40349
Clinical Cutoff Date: 20OCT2020

MedDRA Preferred Term	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Faricimab 6 mg All (N=626)	Aflibercept 2 mg Q8W (N=311)
Total number of patients with at least one adverse event	11 (3.5%)	8 (2.6%)	19 (3.0%)	5 (1.6%)
Total number of events	15	13	28	7
眼圧上昇	5 (1.6%)	1 (0.3%)	6 (1.0%)	1 (0.3%)
ぶどう膜炎	1 (0.3%)	3 (1.0%)	4 (0.6%)	0
虹彩炎	0	2 (0.6%)	2 (0.3%)	1 (0.3%)
硝子体浮遊物	2 (0.6%)	0	2 (0.3%)	1 (0.3%)
硝子体炎	1 (0.3%)	0	1 (0.2%)	1 (0.3%)
白内障	0	1 (0.3%)	1 (0.2%)	0
脈絡網膜炎	0	1 (0.3%)	1 (0.2%)	0
結膜出血	0	0	0	1 (0.3%)
角膜浮腫	0	1 (0.3%)	1 (0.2%)	0
糖尿病性網膜浮腫	1 (0.3%)	0	1 (0.2%)	0
眼痛	1 (0.3%)	0	1 (0.2%)	0
角膜後面沈着物	0	1 (0.3%)	1 (0.2%)	0
角膜ぶどう膜炎	0	1 (0.3%)	1 (0.2%)	0
黄斑線維症	1 (0.3%)	0	1 (0.2%)	0
高眼圧症	0	1 (0.3%)	1 (0.2%)	0

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

[5.3.5.1-DME-2 t_ae_pt_SOCUL_SREL_W56_SE_20OCT2020_40349を改変]

表 2.7.6.2-30 非試験眼の副作用の集計（GR40349試験）

Ocular Adverse Events in the Fellow Eye related to Fellow Eye Treatment through Week 56, Safety-Evaluable Population
Protocol: GR40349
Clinical Cutoff Date: 20OCT2020

MedDRA Preferred Term	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Aflibercept 2 mg Q8W (N=311)
Total number of patients with at least one adverse event	3 (1.0%)	3 (1.0%)	6 (1.9%)
Total number of events	3	4	7
結膜出血	1 (0.3%)	1 (0.3%)	1 (0.3%)
眼圧上昇	1 (0.3%)	1 (0.3%)	1 (0.3%)
硝子体浮遊物	1 (0.3%)	0	1 (0.3%)
眼内炎	0	1 (0.3%)	0
眼刺激	0	0	1 (0.3%)
眼そう痒症	0	0	1 (0.3%)
黄斑円孔	0	0	1 (0.3%)
硝子体炎	0	0	1 (0.3%)

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

[5.3.5.1-DME-2 PR11341_t_ae_pt_FOCUL_FREL_W56_SE_20OCT2020_40349を改変]

表 2.7.6.2-31 眼以外の副作用の集計（GR40349試験）

Non-Ocular Adverse Events Related to Study Treatment through Week 56, Safety-Evaluable Population
Protocol: GR40349
Clinical Cutoff Date: 20OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=313)	Faricimab 6 mg PTI (N=313)	Faricimab 6 mg All run (N=626)	Aflibercept 2 mg Q8W (N=311)
Total number of patients with at least one adverse event	3 (1.0%)	1 (0.3%)	4 (0.6%)	0
Overall total number of events	3	1	4	0
血管障害				
Total number of patients with at least one adverse event	1 (0.3%)	0	1 (0.2%)	0
Total number of events	1	0	1	0
高血圧	1 (0.3%)	0	1 (0.2%)	0
耳および迷路障害				
Total number of patients with at least one adverse event	0	1 (0.3%)	1 (0.2%)	0
Total number of events	0	1	1	0
突発性難聴	0	1 (0.3%)	1 (0.2%)	0
神経系障害				
Total number of patients with at least one adverse event	1 (0.3%)	0	1 (0.2%)	0
Total number of events	1	0	1	0
虚血性脳卒中	1 (0.3%)	0	1 (0.2%)	0
精神障害				
Total number of patients with at least one adverse event	1 (0.3%)	0	1 (0.2%)	0
Total number of events	1	0	1	0
幻視	1 (0.3%)	0	1 (0.2%)	0

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

Program: root/clinical_studies/RO6867461/CDT70122/GR40349/data_analysis/CTD_Yosemite/prod/program/t_ae.sas
Output: root/clinical_studies/RO6867461/CDT70122/GR40349/data_analysis/CTD_Yosemite/prod/output/t_ae_NOCUL_SREL_W56_SE_dme.out
27JAN2021 14:27 Page 1 of 1

[5.3.5.3-nAMD-1 t_ae_NOCUL_SREL_W56_SE_dme を再掲]

表 2.7.6.2-32 試験眼の有害事象の集計（GR40398試験）

Ocular Adverse Events in the Study Eye through Week 56, Safety-Evaluable Population
Protocol: GR40398
Clinical Cutoff Date: 19OCT2020

MedDRA Preferred Term	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Faricimab 6 mg All (N=636)	Aflibercept 2 mg Q8W (N=314)
Total number of patients with at least one adverse event	137 (43.2%)	119 (37.3%)	256 (40.3%)	113 (36.0%)
Total number of events	250	211	461	181
結膜出血	26 (8.2%)	16 (5.0%)	42 (6.6%)	19 (6.1%)
白内障	18 (5.7%)	15 (4.7%)	33 (5.2%)	13 (4.1%)
ドライアイ	14 (4.4%)	11 (3.4%)	25 (3.9%)	7 (2.2%)
硝子体剥離	13 (4.1%)	7 (2.2%)	20 (3.1%)	11 (3.5%)
眼圧上昇	13 (4.1%)	9 (2.8%)	22 (3.5%)	8 (2.5%)
硝子体浮遊物	15 (4.7%)	7 (2.2%)	22 (3.5%)	8 (2.5%)
眼痛	4 (1.3%)	8 (2.5%)	12 (1.9%)	10 (3.2%)
投薬過誤	5 (1.6%)	9 (2.8%)	14 (2.2%)	4 (1.3%)
結膜炎	6 (1.9%)	6 (1.9%)	12 (1.9%)	4 (1.3%)
眼瞼炎	9 (2.8%)	4 (1.3%)	13 (2.0%)	1 (0.3%)
皮質白内障	3 (0.9%)	8 (2.5%)	11 (1.7%)	2 (0.6%)
糖尿病性網膜浮腫	4 (1.3%)	5 (1.6%)	9 (1.4%)	3 (1.0%)
点状角膜炎	5 (1.6%)	4 (1.3%)	9 (1.4%)	2 (0.6%)
眼そう痒症	5 (1.6%)	1 (0.3%)	6 (0.9%)	3 (1.0%)
嚢下白内障	4 (1.3%)	4 (1.3%)	8 (1.3%)	0
糖尿病網膜症	2 (0.6%)	4 (1.3%)	6 (0.9%)	2 (0.6%)
眼刺激	3 (0.9%)	1 (0.3%)	4 (0.6%)	4 (1.3%)
後嚢部混濁	5 (1.6%)	1 (0.3%)	6 (0.9%)	2 (0.6%)
核性白内障	4 (1.3%)	3 (0.9%)	7 (1.1%)	0
霧視	1 (0.3%)	0	1 (0.2%)	6 (1.9%)
硝子体出血	2 (0.6%)	3 (0.9%)	5 (0.8%)	2 (0.6%)
角膜擦過傷	2 (0.6%)	3 (0.9%)	5 (0.8%)	1 (0.3%)
網膜滲出物	1 (0.3%)	3 (0.9%)	4 (0.6%)	2 (0.6%)
網膜出血	2 (0.6%)	3 (0.9%)	5 (0.8%)	1 (0.3%)
異物感	4 (1.3%)	0	4 (0.6%)	2 (0.6%)

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.6.2-32 試験眼の有害事象の集計（GR40398試験）（続）

Ocular Adverse Events in the Study Eye through Week 56, Safety-Evaluable Population
Protocol: GR40398
Clinical Cutoff Date: 19OCT2020

MedDRA Preferred Term	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Faricimab 6 mg All (N=636)	Aflibercept 2 mg Q8W (N=314)
アレルギー性結膜炎	3 (0.9%)	1 (0.3%)	4 (0.6%)	1 (0.3%)
角膜炎	1 (0.3%)	3 (0.9%)	4 (0.6%)	1 (0.3%)
黄斑線維症	1 (0.3%)	0	1 (0.2%)	4 (1.3%)
眼充血	4 (1.3%)	1 (0.3%)	5 (0.8%)	0
高眼圧症	0	4 (1.3%)	4 (0.6%)	1 (0.3%)
視力障害	2 (0.6%)	2 (0.6%)	4 (0.6%)	1 (0.3%)
嚢胞様黄斑浮腫	2 (0.6%)	1 (0.3%)	3 (0.5%)	1 (0.3%)
麦粒腫	0	2 (0.6%)	2 (0.3%)	2 (0.6%)
流涙増加	1 (0.3%)	3 (0.9%)	4 (0.6%)	0
一過性視力低下	2 (0.6%)	1 (0.3%)	3 (0.5%)	1 (0.3%)
アデノウイルス結膜炎	1 (0.3%)	1 (0.3%)	2 (0.3%)	1 (0.3%)
角膜障害	1 (0.3%)	1 (0.3%)	2 (0.3%)	1 (0.3%)
角膜びらん	2 (0.6%)	0	2 (0.3%)	1 (0.3%)
眼内炎	2 (0.6%)	0	2 (0.3%)	1 (0.3%)
眼の異物感	1 (0.3%)	1 (0.3%)	2 (0.3%)	1 (0.3%)
緑内障	1 (0.3%)	1 (0.3%)	2 (0.3%)	1 (0.3%)
虹彩炎	2 (0.6%)	0	2 (0.3%)	1 (0.3%)
光視症	2 (0.6%)	1 (0.3%)	3 (0.5%)	0
潰瘍性角膜炎	2 (0.6%)	1 (0.3%)	3 (0.5%)	0

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.6.2-32 試験眼の有害事象の集計（GR40398試験）（続）

Ocular Adverse Events in the Study Eye through Week 56, Safety-Evaluable Population
Protocol: GR40398
Clinical Cutoff Date: 19OCT2020

MedDRA Preferred Term	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Faricimab 6 mg All (N=636)	Aflibercept 2 mg Q8W (N=314)
霰粒腫	0	0	0	2 (0.6%)
結膜浮腫	0	2 (0.6%)	2 (0.3%)	0
ウイルス性結膜炎	2 (0.6%)	0	2 (0.3%)	0
角膜上皮欠損	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
角膜刺激	2 (0.6%)	0	2 (0.3%)	0
眼瞼皮膚弛緩症	2 (0.6%)	0	2 (0.3%)	0
眼瞼浮腫	0	2 (0.6%)	2 (0.3%)	0
眼瞼そう痒症	2 (0.6%)	0	2 (0.3%)	0
眼内異物	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
充血	0	2 (0.6%)	2 (0.3%)	0
瞼板腺炎	0	2 (0.6%)	2 (0.3%)	0
眼部不快感	0	2 (0.6%)	2 (0.3%)	0
疼痛	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
視野欠損	0	0	0	2 (0.6%)
硝子体網膜牽引症候群	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
硝子体混濁	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
眼の異常感	1 (0.3%)	0	1 (0.2%)	0
動脈瘤	0	1 (0.3%)	1 (0.2%)	0
眼瞼痙攣	1 (0.3%)	0	1 (0.2%)	0
灼熱感	0	1 (0.3%)	1 (0.2%)	0
眼部化学熱傷	0	0	0	1 (0.3%)
結膜障害	0	1 (0.3%)	1 (0.2%)	0
結膜充血	0	1 (0.3%)	1 (0.2%)	0
細菌性結膜炎	0	0	0	1 (0.3%)
角膜ジストロフィー	0	0	0	1 (0.3%)
角膜浮腫	1 (0.3%)	0	1 (0.2%)	0
糖尿病性眼病変	0	1 (0.3%)	1 (0.2%)	0
斑状出血	0	1 (0.3%)	1 (0.2%)	0

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.6.2-32 試験眼の有害事象の集計（GR40398試験）（続）

Ocular Adverse Events in the Study Eye through Week 56, Safety-Evaluable Population
Protocol: GR40398
Clinical Cutoff Date: 19OCT2020

MedDRA Preferred Term	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Faricimab 6 mg All (N=636)	Aflibercept 2 mg Q8W (N=314)
眼瞼湿疹	0	0	0	1 (0.3%)
眼瞼内反	1 (0.3%)	0	1 (0.2%)	0
上強膜炎	1 (0.3%)	0	1 (0.2%)	0
紅斑	0	0	0	1 (0.3%)
血液溢出	1 (0.3%)	0	1 (0.2%)	0
眼のアレルギー	0	0	0	1 (0.3%)
眼挫傷	0	0	0	1 (0.3%)
眼脂	0	1 (0.3%)	1 (0.2%)	0
眼出血	0	1 (0.3%)	1 (0.2%)	0
眼部腫脹	0	1 (0.3%)	1 (0.2%)	0
眼瞼下垂	1 (0.3%)	0	1 (0.2%)	0
緑内障性視神経乳頭萎縮	0	1 (0.3%)	1 (0.2%)	0
星状硝子体症	1 (0.3%)	0	1 (0.2%)	0
低眼圧	1 (0.3%)	0	1 (0.2%)	0
インフルエンザ	1 (0.3%)	0	1 (0.2%)	0
内方発育毛	0	1 (0.3%)	1 (0.2%)	0
注射部位出血	0	0	0	1 (0.3%)
虹彩毛様体炎	0	1 (0.3%)	1 (0.2%)	0
虹彩癒着	0	0	0	1 (0.3%)
細菌性角膜炎	0	0	0	1 (0.3%)
ウイルス性角膜炎	0	0	0	1 (0.3%)
黄斑嚢胞	1 (0.3%)	0	1 (0.2%)	0
黄斑浮腫	0	0	0	1 (0.3%)
マイボーム腺機能不全	1 (0.3%)	0	1 (0.2%)	0
神経血管コンフリクト	0	1 (0.3%)	1 (0.2%)	0
開放隅角緑内障	0	1 (0.3%)	1 (0.2%)	0
視神経萎縮	1 (0.3%)	0	1 (0.2%)	0
視神経乳頭障害	1 (0.3%)	0	1 (0.2%)	0

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.6.2-32 試験眼の有害事象の集計（GR40398試験）（続）

Ocular Adverse Events in the Study Eye through Week 56, Safety-Evaluable Population
Protocol: GR40398
Clinical Cutoff Date: 19OCT2020

MedDRA Preferred Term	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Faricimab 6 mg All (N=636)	Aflibercept 2 mg Q8W (N=314)
眼窩周囲痛	0	0	0	1 (0.3%)
羞明	0	0	0	1 (0.3%)
瞼裂斑	0	1 (0.3%)	1 (0.2%)	0
瞳孔不同	0	0	0	1 (0.3%)
化膿性肉芽腫	0	0	0	1 (0.3%)
網膜血管瘤	0	0	0	1 (0.3%)
網膜動脈塞栓症	0	0	0	1 (0.3%)
網膜嚢胞	0	1 (0.3%)	1 (0.2%)	0
網膜変性	0	0	0	1 (0.3%)
網膜血管新生	0	1 (0.3%)	1 (0.2%)	0
網膜裂孔	0	1 (0.3%)	1 (0.2%)	0
網膜肥厚	0	1 (0.3%)	1 (0.2%)	0
網膜静脈閉塞	0	1 (0.3%)	1 (0.2%)	0
高血圧性網膜症	0	0	0	1 (0.3%)
眼瞼腫脹	0	0	0	1 (0.3%)
ぶどう膜炎	0	1 (0.3%)	1 (0.2%)	0
視力低下	0	1 (0.3%)	1 (0.2%)	0
角膜生体染色陽性	1 (0.3%)	0	1 (0.2%)	0
硝子体癒着	0	0	0	1 (0.3%)
硝子体炎	1 (0.3%)	0	1 (0.2%)	0

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

[5.3.5.1-DME-3 t_ae_pt_SOCUL_W56_SE_19OCT2020_40398を改変]

表 2.7.6.2-33 非試験眼の有害事象の集計（GR40398試験）

Ocular Adverse Events in the Fellow Eye through Week 56, Safety-Evaluable Population
Protocol: GR40398
Clinical Cutoff Date: 19OCT2020

MedDRA Preferred Term	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Faricimab 6 mg All (N=636)	Aflibercept 2 mg Q8W (N=314)
Total number of patients with at least one adverse event	128 (40.4%)	91 (28.5%)	219 (34.4%)	105 (33.4%)
Total number of events	216	150	366	170
糖尿病性網膜浮腫	25 (7.9%)	18 (5.6%)	43 (6.8%)	14 (4.5%)
白内障	20 (6.3%)	10 (3.1%)	30 (4.7%)	12 (3.8%)
ドライアイ	10 (3.2%)	8 (2.5%)	18 (2.8%)	7 (2.2%)
硝子体剥離	7 (2.2%)	4 (1.3%)	11 (1.7%)	11 (3.5%)
結膜出血	7 (2.2%)	5 (1.6%)	12 (1.9%)	7 (2.2%)
糖尿病網膜症	6 (1.9%)	2 (0.6%)	8 (1.3%)	9 (2.9%)
硝子体出血	8 (2.5%)	3 (0.9%)	11 (1.7%)	6 (1.9%)
結膜炎	8 (2.5%)	2 (0.6%)	10 (1.6%)	6 (1.9%)
網膜出血	4 (1.3%)	9 (2.8%)	13 (2.0%)	3 (1.0%)
眼圧上昇	6 (1.9%)	5 (1.6%)	11 (1.7%)	4 (1.3%)
硝子体浮遊物	0	6 (1.9%)	6 (0.9%)	8 (2.5%)
眼瞼炎	8 (2.5%)	3 (0.9%)	11 (1.7%)	1 (0.3%)
皮質白内障	3 (0.9%)	6 (1.9%)	9 (1.4%)	3 (1.0%)
黄斑浮腫	2 (0.6%)	4 (1.3%)	6 (0.9%)	4 (1.3%)
点状角膜炎	5 (1.6%)	4 (1.3%)	9 (1.4%)	1 (0.3%)
眼そう痒症	3 (0.9%)	3 (0.9%)	6 (0.9%)	3 (1.0%)
後嚢部混濁	3 (0.9%)	2 (0.6%)	5 (0.8%)	4 (1.3%)
網膜滲出物	2 (0.6%)	2 (0.6%)	4 (0.6%)	5 (1.6%)
眼痛	2 (0.6%)	1 (0.3%)	3 (0.5%)	5 (1.6%)
嚢下白内障	4 (1.3%)	3 (0.9%)	7 (1.1%)	0
嚢胞様黄斑浮腫	3 (0.9%)	1 (0.3%)	4 (0.6%)	3 (1.0%)
網膜血管新生	2 (0.6%)	1 (0.3%)	3 (0.5%)	4 (1.3%)
角膜擦過傷	1 (0.3%)	3 (0.9%)	4 (0.6%)	2 (0.6%)
黄斑線維症	4 (1.3%)	2 (0.6%)	6 (0.9%)	0
霧視	1 (0.3%)	1 (0.3%)	2 (0.3%)	4 (1.3%)
アレルギー性結膜炎	3 (0.9%)	1 (0.3%)	4 (0.6%)	1 (0.3%)

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.6.2-33 非試験眼の有害事象の集計（GR40398試験）（続）

Ocular Adverse Events in the Fellow Eye through Week 56, Safety-Evaluable Population
Protocol: GR40398
Clinical Cutoff Date: 19OCT2020

MedDRA Preferred Term	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Faricimab 6 mg All (N=636)	Aflibercept 2 mg Q8W (N=314)
核性白内障	2 (0.6%)	2 (0.6%)	4 (0.6%)	0
虹彩炎	3 (0.9%)	1 (0.3%)	4 (0.6%)	0
流涙増加	1 (0.3%)	2 (0.6%)	3 (0.5%)	1 (0.3%)
眼充血	4 (1.3%)	0	4 (0.6%)	0
視力低下	0	3 (0.9%)	3 (0.5%)	1 (0.3%)
アデノウイルス結膜炎	1 (0.3%)	0	1 (0.2%)	2 (0.6%)
ウイルス性結膜炎	2 (0.6%)	0	2 (0.3%)	0
角膜上皮欠損	1 (0.3%)	0	1 (0.2%)	1 (0.3%)
角膜びらん	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
眼瞼皮膚弛緩症	2 (0.6%)	0	2 (0.3%)	0
眼出血	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
眼刺激	0	0	0	2 (0.6%)
眼瞼痛	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
眼瞼下垂	2 (0.6%)	0	2 (0.3%)	0
緑内障	1 (0.3%)	0	1 (0.2%)	1 (0.3%)
角膜炎	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
血管新生	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
高眼圧症	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
疼痛	2 (0.6%)	0	2 (0.3%)	0
光視症	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
網膜血管瘤	1 (0.3%)	0	1 (0.2%)	1 (0.3%)
硝子体混濁	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
眼の異常感	1 (0.3%)	0	1 (0.2%)	0
前嚢破裂	0	1 (0.3%)	1 (0.2%)	0
動脈硬化症	1 (0.3%)	0	1 (0.2%)	0
一過性失明	0	0	0	1 (0.3%)
霰粒腫	0	1 (0.3%)	1 (0.2%)	0
眼部化学熱傷	0	0	0	1 (0.3%)

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.6.2-33 非試験眼の有害事象の集計（GR40398試験）（続）

Ocular Adverse Events in the Fellow Eye through Week 56, Safety-Evaluable Population
Protocol: GR40398
Clinical Cutoff Date: 19OCT2020

MedDRA Preferred Term	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Faricimab 6 mg All (N=636)	Aflibercept 2 mg Q8W (N=314)
脈絡膜血管新生	0	1 (0.3%)	1 (0.2%)	0
結膜浮腫	0	1 (0.3%)	1 (0.2%)	0
細菌性結膜炎	0	0	0	1 (0.3%)
角膜ジストロフィー	0	0	0	1 (0.3%)
角膜瘢痕	1 (0.3%)	0	1 (0.2%)	0
皮膚嚢腫	1 (0.3%)	0	1 (0.2%)	0
糖尿病性眼病変	0	0	0	1 (0.3%)
不快感	0	0	0	1 (0.3%)
薬物過敏症	1 (0.3%)	0	1 (0.2%)	0
斑状出血	1 (0.3%)	0	1 (0.2%)	0
上強膜炎	1 (0.3%)	0	1 (0.2%)	0
紅斑	0	0	0	1 (0.3%)
眼のアレルギー	0	0	0	1 (0.3%)
眼の母斑	0	0	0	1 (0.3%)
眼瞼縁痂皮	1 (0.3%)	0	1 (0.2%)	0
眼瞼浮腫	0	1 (0.3%)	1 (0.2%)	0
眼瞼そう痒症	1 (0.3%)	0	1 (0.2%)	0
眼内異物	1 (0.3%)	0	1 (0.2%)	0
グレア	1 (0.3%)	0	1 (0.2%)	0
緑内障性視神経乳頭萎縮	0	1 (0.3%)	1 (0.2%)	0
半盲	1 (0.3%)	0	1 (0.2%)	0
麦粒腫	1 (0.3%)	0	1 (0.2%)	0
星状硝子体症	0	0	0	1 (0.3%)
第３脳神経麻痺	1 (0.3%)	0	1 (0.2%)	0
眼内レンズ挿入	1 (0.3%)	0	1 (0.2%)	0
虹彩毛様体炎	0	0	0	1 (0.3%)
細菌性角膜炎	0	0	0	1 (0.3%)
ウイルス性角膜炎	0	0	0	1 (0.3%)

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.6.2-33 非試験眼の有害事象の集計（GR40398試験）（続）

Ocular Adverse Events in the Fellow Eye through Week 56, Safety-Evaluable Population
Protocol: GR40398
Clinical Cutoff Date: 19OCT2020

MedDRA Preferred Term	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Faricimab 6 mg All (N=636)	Aflibercept 2 mg Q8W (N=314)
水晶体混濁	0	1 (0.3%)	1 (0.2%)	0
黄斑円孔	1 (0.3%)	0	1 (0.2%)	0
黄斑肥厚	0	0	0	1 (0.3%)
黄斑症	1 (0.3%)	0	1 (0.2%)	0
瞼板腺炎	0	1 (0.3%)	1 (0.2%)	0
神経血管コンフリクト	0	1 (0.3%)	1 (0.2%)	0
視神経乳頭ドルーゼン	1 (0.3%)	0	1 (0.2%)	0
視神経乳頭出血	0	1 (0.3%)	1 (0.2%)	0
眼窩周囲血腫	1 (0.3%)	0	1 (0.2%)	0
点状出血	1 (0.3%)	0	1 (0.2%)	0
羞明	0	0	0	1 (0.3%)
処置による疼痛	0	0	0	1 (0.3%)
そう痒症	1 (0.3%)	0	1 (0.2%)	0
網膜変性	0	1 (0.3%)	1 (0.2%)	0
網膜肥厚	0	1 (0.3%)	1 (0.2%)	0
網膜血管障害	0	0	0	1 (0.3%)
高血圧性網膜症	0	0	0	1 (0.3%)
異物感	1 (0.3%)	0	1 (0.2%)	0
網膜下液	1 (0.3%)	0	1 (0.2%)	0
牽引性網膜剥離	1 (0.3%)	0	1 (0.2%)	0
一過性視力低下	1 (0.3%)	0	1 (0.2%)	0
視力障害	1 (0.3%)	0	1 (0.2%)	0
硝子体網膜牽引症候群	0	1 (0.3%)	1 (0.2%)	0
硝子体癒着	0	0	0	1 (0.3%)

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

[5.3.5.1-DME-3 t_ae_pt_FOCUL_W56_SE_19OCT2020_40398を改変]

表 2.7.6.2-34 眼以外の有害事象の集計（GR40398試験）

Non-Ocular Adverse Events through Week 56, Safety-Evaluable Population
Protocol: GR40398
Clinical Cutoff Date: 19OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Faricimab 6 mg All (N=636)	Aflibercept 2 mg Q8W (N=314)
Total number of patients with at least one adverse event	189 (59.6%)	175 (54.9%)	364 (57.2%)	187 (59.6%)
Overall total number of events	641	514	1155	563
感染症および寄生虫症				
Total number of patients with at least one adverse event	86 (27.1%)	75 (23.5%)	161 (25.3%)	102 (32.5%)
Total number of events	140	107	247	157
上咽頭炎	23 (7.3%)	22 (6.9%)	45 (7.1%)	31 (9.9%)
尿路感染	7 (2.2%)	11 (3.4%)	18 (2.8%)	21 (6.7%)
蜂巣炎	8 (2.5%)	3 (0.9%)	11 (1.7%)	11 (3.5%)
インフルエンザ	4 (1.3%)	9 (2.8%)	13 (2.0%)	9 (2.9%)
肺炎	9 (2.8%)	7 (2.2%)	16 (2.5%)	4 (1.3%)
気管支炎	8 (2.5%)	7 (2.2%)	15 (2.4%)	4 (1.3%)
副鼻腔炎	7 (2.2%)	5 (1.6%)	12 (1.9%)	5 (1.6%)
上気道感染	7 (2.2%)	5 (1.6%)	12 (1.9%)	4 (1.3%)
下気道感染	5 (1.6%)	1 (0.3%)	6 (0.9%)	2 (0.6%)
敗血症	6 (1.9%)	0	6 (0.9%)	1 (0.3%)
帯状疱疹	1 (0.3%)	4 (1.3%)	5 (0.8%)	1 (0.3%)
限局性感染	1 (0.3%)	1 (0.3%)	2 (0.3%)	4 (1.3%)
骨髄炎	2 (0.6%)	1 (0.3%)	3 (0.5%)	3 (1.0%)
耳感染	1 (0.3%)	3 (0.9%)	4 (0.6%)	1 (0.3%)
膀胱炎	2 (0.6%)	1 (0.3%)	3 (0.5%)	1 (0.3%)
ウイルス性胃腸炎	2 (0.6%)	0	2 (0.3%)	2 (0.6%)
鼻炎	1 (0.3%)	1 (0.3%)	2 (0.3%)	2 (0.6%)
ＣＯＶＩＤ－１９	0	1 (0.3%)	1 (0.2%)	2 (0.6%)
糖尿病性足感染	3 (0.9%)	0	3 (0.5%)	0
壊疽	1 (0.3%)	2 (0.6%)	3 (0.5%)	0
気道感染	2 (0.6%)	0	2 (0.3%)	1 (0.3%)
歯感染	2 (0.6%)	0	2 (0.3%)	1 (0.3%)
ウイルス感染	2 (0.6%)	0	2 (0.3%)	1 (0.3%)
四肢膿瘍	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
急性副鼻腔炎	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
憩室炎	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
中耳炎	0	0	0	2 (0.6%)
咽頭炎	0	0	0	2 (0.6%)
レンサ球菌性咽頭炎	1 (0.3%)	0	1 (0.2%)	1 (0.3%)
ブドウ球菌感染	0	0	0	2 (0.6%)
気管炎	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
顎膿瘍	0	0	0	1 (0.3%)
ダニ皮膚炎	1 (0.3%)	0	1 (0.2%)	0
肛門膿瘍	1 (0.3%)	0	1 (0.2%)	0
細菌性関節炎	0	0	0	1 (0.3%)
異型肺炎	1 (0.3%)	0	1 (0.2%)	0
菌血症	1 (0.3%)	0	1 (0.2%)	0

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.6.2-34 眼以外の有害事象の集計（GR40398試験）（続）

Non-Ocular Adverse Events through Week 56, Safety-Evaluable Population
Protocol: GR40398
Clinical Cutoff Date: 19OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Faricimab 6 mg All (N=636)	Aflibercept 2 mg Q8W (N=314)
ＣＯＶＩＤ－１９肺炎	1 (0.3%)	0	1 (0.2%)	0
壊疽性蜂巣炎	1 (0.3%)	0	1 (0.2%)	0
コロナウイルス感染	0	0	0	1 (0.3%)
糖尿病性壊疽	0	0	0	1 (0.3%)
感染性下痢	0	1 (0.3%)	1 (0.2%)	0
心内膜炎	0	0	0	1 (0.3%)
大腸菌性敗血症	0	0	0	1 (0.3%)
毛包炎	1 (0.3%)	0	1 (0.2%)	0
真菌性鼻炎	0	1 (0.3%)	1 (0.2%)	0
胆嚢蓄膿	0	0	0	1 (0.3%)
胃腸炎	0	0	0	1 (0.3%)
細菌性胃腸炎	0	1 (0.3%)	1 (0.2%)	0
感染性嚢腫	0	0	0	1 (0.3%)
感染性皮膚潰瘍	0	1 (0.3%)	1 (0.2%)	0
伝染性単核症	1 (0.3%)	0	1 (0.2%)	0
感染性血栓症	0	0	0	1 (0.3%)
腎感染	0	1 (0.3%)	1 (0.2%)	0
迷路炎	1 (0.3%)	0	1 (0.2%)	0
肺膿瘍	0	0	0	1 (0.3%)
鼻ヘルペス	0	1 (0.3%)	1 (0.2%)	0
爪真菌症	1 (0.3%)	0	1 (0.2%)	0
口腔カンジダ症	0	0	0	1 (0.3%)
口腔ヘルペス	1 (0.3%)	0	1 (0.2%)	0
急性中耳炎	0	0	0	1 (0.3%)
歯周炎	1 (0.3%)	0	1 (0.2%)	0
腹膜炎	0	0	0	1 (0.3%)
ブドウ球菌性肺炎	1 (0.3%)	0	1 (0.2%)	0
術後膿瘍	0	0	0	1 (0.3%)
歯髄炎	0	0	0	1 (0.3%)
穿刺部位感染	0	1 (0.3%)	1 (0.2%)	0
腎盂腎炎	1 (0.3%)	0	1 (0.2%)	0
ＲＳウイルス気管支炎	0	0	0	1 (0.3%)
ライノウイルス感染	0	1 (0.3%)	1 (0.2%)	0
敗血症性凝固異常	0	1 (0.3%)	1 (0.2%)	0
敗血症性ショック	0	0	0	1 (0.3%)
皮膚感染	1 (0.3%)	0	1 (0.2%)	0
皮下組織膿瘍	0	0	0	1 (0.3%)
外陰部炎	0	0	0	1 (0.3%)
創傷感染	1 (0.3%)	0	1 (0.2%)	0

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.6.2-34 眼以外の有害事象の集計（GR40398試験）（続）

Non-Ocular Adverse Events through Week 56, Safety-Evaluable Population
Protocol: GR40398
Clinical Cutoff Date: 19OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Faricimab 6 mg All (N=636)	Aflibercept 2 mg Q8W (N=314)
胃腸障害				
Total number of patients with at least one adverse event	39 (12.3%)	32 (10.0%)	71 (11.2%)	24 (7.6%)
Total number of events	55	47	102	39
悪心	7 (2.2%)	7 (2.2%)	14 (2.2%)	8 (2.5%)
嘔吐	8 (2.5%)	3 (0.9%)	11 (1.7%)	5 (1.6%)
下痢	7 (2.2%)	2 (0.6%)	9 (1.4%)	2 (0.6%)
胃食道逆流性疾患	2 (0.6%)	5 (1.6%)	7 (1.1%)	4 (1.3%)
便秘	4 (1.3%)	3 (0.9%)	7 (1.1%)	2 (0.6%)
胃炎	3 (0.9%)	3 (0.9%)	6 (0.9%)	1 (0.3%)
上腹部痛	3 (0.9%)	1 (0.3%)	4 (0.6%)	1 (0.3%)
消化不良	1 (0.3%)	3 (0.9%)	4 (0.6%)	1 (0.3%)
腹痛	2 (0.6%)	0	2 (0.3%)	2 (0.6%)
齲歯	2 (0.6%)	1 (0.3%)	3 (0.5%)	1 (0.3%)
嚥下障害	1 (0.3%)	0	1 (0.2%)	3 (1.0%)
歯痛	1 (0.3%)	1 (0.3%)	2 (0.3%)	2 (0.6%)
痔核	1 (0.3%)	2 (0.6%)	3 (0.5%)	0
胃排出不全	3 (0.9%)	0	3 (0.5%)	0
大腸炎	1 (0.3%)	0	1 (0.2%)	1 (0.3%)
食中毒	1 (0.3%)	0	1 (0.2%)	1 (0.3%)
胃ポリープ	0	2 (0.6%)	2 (0.3%)	0
裂孔ヘルニア	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
腹部ヘルニア	0	1 (0.3%)	1 (0.2%)	0
下腹部痛	1 (0.3%)	0	1 (0.2%)	0
裂肛	0	1 (0.3%)	1 (0.2%)	0
慢性胃炎	0	1 (0.3%)	1 (0.2%)	0
十二指腸ポリープ	0	1 (0.3%)	1 (0.2%)	0
十二指腸炎	0	0	0	1 (0.3%)
小腸炎	0	1 (0.3%)	1 (0.2%)	0
びらん性食道炎	0	1 (0.3%)	1 (0.2%)	0
びらん性胃炎	1 (0.3%)	0	1 (0.2%)	0
胃腸異形成	0	0	0	1 (0.3%)
胃腸出血	0	1 (0.3%)	1 (0.2%)	0
歯肉腫脹	0	1 (0.3%)	1 (0.2%)	0
血便排泄	0	0	0	1 (0.3%)
腸管ポリープ	0	0	0	1 (0.3%)
過敏性腸症候群	1 (0.3%)	0	1 (0.2%)	0
非感染性唾液腺炎	1 (0.3%)	0	1 (0.2%)	0
食道炎	0	1 (0.3%)	1 (0.2%)	0
口腔瘻	1 (0.3%)	0	1 (0.2%)	0
直腸出血	0	1 (0.3%)	1 (0.2%)	0
逆流性胃炎	1 (0.3%)	0	1 (0.2%)	0
埋伏歯	0	1 (0.3%)	1 (0.2%)	0
上部消化管出血	0	1 (0.3%)	1 (0.2%)	0

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.6.2-34 眼以外の有害事象の集計（GR40398試験）（続）

Non-Ocular Adverse Events through Week 56, Safety-Evaluable Population
Protocol: GR40398
Clinical Cutoff Date: 19OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Faricimab 6 mg All (N=636)	Aflibercept 2 mg Q8W (N=314)
筋骨格系および結合組織障害				
Total number of patients with at least one adverse event	41 (12.9%)	22 (6.9%)	63 (9.9%)	31 (9.9%)
Total number of events	52	28	80	38
関節痛	9 (2.8%)	5 (1.6%)	14 (2.2%)	6 (1.9%)
背部痛	11 (3.5%)	4 (1.3%)	15 (2.4%)	3 (1.0%)
変形性関節症	2 (0.6%)	3 (0.9%)	5 (0.8%)	5 (1.6%)
四肢痛	2 (0.6%)	3 (0.9%)	5 (0.8%)	4 (1.3%)
筋肉痛	4 (1.3%)	1 (0.3%)	5 (0.8%)	0
椎間板突出	2 (0.6%)	1 (0.3%)	3 (0.5%)	1 (0.3%)
筋痙縮	1 (0.3%)	1 (0.3%)	2 (0.3%)	2 (0.6%)
頚部痛	2 (0.6%)	0	2 (0.3%)	2 (0.6%)
関節炎	1 (0.3%)	2 (0.6%)	3 (0.5%)	0
肩回旋筋腱板症候群	0	2 (0.6%)	2 (0.3%)	1 (0.3%)
筋力低下	1 (0.3%)	0	1 (0.2%)	1 (0.3%)
筋骨格硬直	2 (0.6%)	0	2 (0.3%)	0
神経障害性関節症	2 (0.6%)	0	2 (0.3%)	0
骨減少症	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
リウマチ性多発筋痛	2 (0.6%)	0	2 (0.3%)	0
脊椎痛	0	0	0	2 (0.6%)
関節障害	0	0	0	1 (0.3%)
滑液包炎	1 (0.3%)	0	1 (0.2%)	0
慢性腎臓病に伴う骨ミネラル代謝異常	1 (0.3%)	0	1 (0.2%)	0
尾骨痛	1 (0.3%)	0	1 (0.2%)	0
デュプイトラン拘縮	0	0	0	1 (0.3%)
足変形	0	0	0	1 (0.3%)
椎間板変性症	0	0	0	1 (0.3%)
関節滲出液	0	0	0	1 (0.3%)
四肢腫瘤	1 (0.3%)	0	1 (0.2%)	0
運動性低下	0	0	0	1 (0.3%)
筋拘縮	0	1 (0.3%)	1 (0.2%)	0
筋骨格系胸痛	0	1 (0.3%)	1 (0.2%)	0
骨粗鬆症	0	0	0	1 (0.3%)
関節周囲炎	0	0	0	1 (0.3%)
足底筋膜炎	0	1 (0.3%)	1 (0.2%)	0
乾癬性関節症	1 (0.3%)	0	1 (0.2%)	0
側弯症	1 (0.3%)	0	1 (0.2%)	0
変形性脊椎症	0	1 (0.3%)	1 (0.2%)	0
脊椎炎	1 (0.3%)	0	1 (0.2%)	0
腱炎	1 (0.3%)	0	1 (0.2%)	0
弾発指	1 (0.3%)	0	1 (0.2%)	0

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.6.2-34 眼以外の有害事象の集計（GR40398試験）（続）

Non-Ocular Adverse Events through Week 56, Safety-Evaluable Population
Protocol: GR40398
Clinical Cutoff Date: 19OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Faricimab 6 mg All (N=636)	Aflibercept 2 mg Q8W (N=314)
代謝および栄養障害				
Total number of patients with at least one adverse event	31 (9.8%)	35 (11.0%)	66 (10.4%)	24 (7.6%)
Total number of events	40	50	90	36
高脂血症	7 (2.2%)	7 (2.2%)	14 (2.2%)	5 (1.6%)
低血糖	2 (0.6%)	6 (1.9%)	8 (1.3%)	4 (1.3%)
高カリウム血症	5 (1.6%)	1 (0.3%)	6 (0.9%)	3 (1.0%)
高コレステロール血症	3 (0.9%)	4 (1.3%)	7 (1.1%)	1 (0.3%)
痛風	2 (0.6%)	2 (0.6%)	4 (0.6%)	3 (1.0%)
２型糖尿病	3 (0.9%)	2 (0.6%)	5 (0.8%)	2 (0.6%)
脱水	1 (0.3%)	2 (0.6%)	3 (0.5%)	3 (1.0%)
糖尿病	4 (1.3%)	2 (0.6%)	6 (0.9%)	0
脂質異常症	0	6 (1.9%)	6 (0.9%)	0
高血糖	0	5 (1.6%)	5 (0.8%)	1 (0.3%)
ビタミンＤ欠乏	1 (0.3%)	1 (0.3%)	2 (0.3%)	2 (0.6%)
コントロール不良の糖尿病	1 (0.3%)	1 (0.3%)	2 (0.3%)	1 (0.3%)
低ナトリウム血症	1 (0.3%)	2 (0.6%)	3 (0.5%)	0
糖尿病性ケトアシドーシス	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
糖尿病性代謝代償不全	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
体液貯留	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
高尿酸血症	2 (0.6%)	0	2 (0.3%)	0
マグネシウム欠乏	2 (0.6%)	0	2 (0.3%)	0
アシドーシス	1 (0.3%)	0	1 (0.2%)	0
糖尿病性末端器官損傷	0	0	0	1 (0.3%)
高リン酸塩血症	0	0	0	1 (0.3%)
高トリグリセリド血症	1 (0.3%)	0	1 (0.2%)	0
低カリウム血症	0	1 (0.3%)	1 (0.2%)	0
低マグネシウム血症	1 (0.3%)	0	1 (0.2%)	0
血液量減少症	0	1 (0.3%)	1 (0.2%)	0
乳酸アシドーシス	0	1 (0.3%)	1 (0.2%)	0
代謝性アシドーシス	0	1 (0.3%)	1 (0.2%)	0
肥満	0	1 (0.3%)	1 (0.2%)	0
１型糖尿病	0	0	0	1 (0.3%)
ビタミンＢ１２欠乏	1 (0.3%)	0	1 (0.2%)	0

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.6.2-34 眼以外の有害事象の集計（GR40398試験）（続）

Non-Ocular Adverse Events through Week 56, Safety-Evaluable Population
Protocol: GR40398
Clinical Cutoff Date: 19OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Faricimab 6 mg All (N=636)	Aflibercept 2 mg Q8W (N=314)
神経系障害				
Total number of patients with at least one adverse event	34 (10.7%)	30 (9.4%)	64 (10.1%)	23 (7.3%)
Total number of events	51	42	93	34
頭痛	16 (5.0%)	9 (2.8%)	25 (3.9%)	5 (1.6%)
浮動性めまい	2 (0.6%)	2 (0.6%)	4 (0.6%)	6 (1.9%)
糖尿病性ニューロパチー	4 (1.3%)	3 (0.9%)	7 (1.1%)	0
坐骨神経痛	1 (0.3%)	5 (1.6%)	6 (0.9%)	0
末梢性ニューロパチー	1 (0.3%)	1 (0.3%)	2 (0.3%)	2 (0.6%)
失神	0	2 (0.6%)	2 (0.3%)	2 (0.6%)
脳血管発作	1 (0.3%)	1 (0.3%)	2 (0.3%)	1 (0.3%)
片頭痛	2 (0.6%)	1 (0.3%)	3 (0.5%)	0
一過性脳虚血発作	2 (0.6%)	1 (0.3%)	3 (0.5%)	0
平衡障害	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
頚動脈硬化症	0	2 (0.6%)	2 (0.3%)	0
手根管症候群	1 (0.3%)	0	1 (0.2%)	1 (0.3%)
脳梗塞	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
代謝性脳症	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
多発ニューロパチー	1 (0.3%)	0	1 (0.2%)	1 (0.3%)
失神寸前の状態	0	2 (0.6%)	2 (0.3%)	0
下肢静止不能症候群	0	2 (0.6%)	2 (0.3%)	0
痙攣発作	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
健忘	0	1 (0.3%)	1 (0.2%)	0
無嗅覚	0	0	0	1 (0.3%)
馬尾症候群	1 (0.3%)	0	1 (0.2%)	0
脳出血	1 (0.3%)	0	1 (0.2%)	0
頚髄神経根障害	0	0	0	1 (0.3%)
脳症	1 (0.3%)	0	1 (0.2%)	0
顔面麻痺	1 (0.3%)	0	1 (0.2%)	0
ギラン・バレー症候群	0	1 (0.3%)	1 (0.2%)	0
頭部不快感	0	0	0	1 (0.3%)
過眠症	1 (0.3%)	0	1 (0.2%)	0
ラクナ脳卒中	0	1 (0.3%)	1 (0.2%)	0
意識消失	0	0	0	1 (0.3%)
不全単麻痺	0	0	0	1 (0.3%)
脊髄症	1 (0.3%)	0	1 (0.2%)	0
神経圧迫	0	1 (0.3%)	1 (0.2%)	0
錯感覚	1 (0.3%)	0	1 (0.2%)	0
パーキンソン病	0	0	0	1 (0.3%)
神経周囲嚢胞	0	0	0	1 (0.3%)
梨状筋症候群	0	0	0	1 (0.3%)
脳卒中後てんかん	0	0	0	1 (0.3%)
副鼻腔炎に伴う頭痛	0	1 (0.3%)	1 (0.2%)	0
傾眠	1 (0.3%)	0	1 (0.2%)	0
脊髄圧迫	0	0	0	1 (0.3%)
振戦	1 (0.3%)	0	1 (0.2%)	0

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.6.2-34 眼以外の有害事象の集計（GR40398試験）（続）

Non-Ocular Adverse Events through Week 56, Safety-Evaluable Population
Protocol: GR40398
Clinical Cutoff Date: 19OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Faricimab 6 mg All (N=636)	Aflibercept 2 mg Q8W (N=314)
傷害、中毒および処置合併症				
Total number of patients with at least one adverse event	36 (11.4%)	20 (6.3%)	56 (8.8%)	33 (10.5%)
Total number of events	55	28	83	43
転倒	14 (4.4%)	8 (2.5%)	22 (3.5%)	10 (3.2%)
足骨折	5 (1.6%)	0	5 (0.8%)	1 (0.3%)
四肢損傷	1 (0.3%)	1 (0.3%)	2 (0.3%)	4 (1.3%)
肋骨骨折	2 (0.6%)	1 (0.3%)	3 (0.5%)	2 (0.6%)
皮膚擦過傷	3 (0.9%)	0	3 (0.5%)	2 (0.6%)
大腿骨頚部骨折	1 (0.3%)	1 (0.3%)	2 (0.3%)	2 (0.6%)
肉離れ	1 (0.3%)	2 (0.6%)	3 (0.5%)	1 (0.3%)
皮膚裂傷	2 (0.6%)	1 (0.3%)	3 (0.5%)	1 (0.3%)
節足動物咬傷	0	1 (0.3%)	1 (0.2%)	2 (0.6%)
頭部損傷	1 (0.3%)	0	1 (0.2%)	2 (0.6%)
動物咬傷	0	2 (0.6%)	2 (0.3%)	0
足関節部骨折	0	0	0	2 (0.6%)
手骨折	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
靱帯捻挫	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
鼻部損傷	2 (0.6%)	0	2 (0.3%)	0
過量投与	0	0	0	2 (0.6%)
交通事故	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
歯牙破折	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
創傷	1 (0.3%)	0	1 (0.2%)	1 (0.3%)
手首関節骨折	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
動物による引っかき傷	1 (0.3%)	0	1 (0.2%)	0
動静脈瘻部位合併症	1 (0.3%)	0	1 (0.2%)	0
節足動物刺傷	1 (0.3%)	0	1 (0.2%)	0
骨挫傷	0	0	0	1 (0.3%)
骨亀裂	0	1 (0.3%)	1 (0.2%)	0
軟骨損傷	0	0	0	1 (0.3%)
胸部損傷	1 (0.3%)	0	1 (0.2%)	0
脳振盪	1 (0.3%)	0	1 (0.2%)	0
挫傷	1 (0.3%)	0	1 (0.2%)	0
頭蓋脳損傷	1 (0.3%)	0	1 (0.2%)	0
耳部損傷	1 (0.3%)	0	1 (0.2%)	0
顔面骨骨折	0	1 (0.3%)	1 (0.2%)	0
大腿骨骨折	0	0	0	1 (0.3%)
転位骨折	1 (0.3%)	0	1 (0.2%)	0
尾骨骨折	1 (0.3%)	0	1 (0.2%)	0
関節脱臼	1 (0.3%)	0	1 (0.2%)	0
関節損傷	1 (0.3%)	0	1 (0.2%)	0
四肢骨折	1 (0.3%)	0	1 (0.2%)	0
口唇損傷	1 (0.3%)	0	1 (0.2%)	0

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Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.6.2-34 眼以外の有害事象の集計（GR40398試験）（続）

Non-Ocular Adverse Events through Week 56, Safety-Evaluable Population
Protocol: GR40398
Clinical Cutoff Date: 19OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Faricimab 6 mg All (N=636)	Aflibercept 2 mg Q8W (N=314)
投薬過誤	0	1 (0.3%)	1 (0.2%)	0
爪裂離	0	0	0	1 (0.3%)
骨盤骨折	0	1 (0.3%)	1 (0.2%)	0
処置後炎症	0	1 (0.3%)	1 (0.2%)	0
処置による疼痛	0	0	0	1 (0.3%)
脊椎圧迫骨折	0	0	0	1 (0.3%)
上肢骨折	0	1 (0.3%)	1 (0.2%)	0
血管障害				
Total number of patients with at least one adverse event	22 (6.9%)	33 (10.3%)	55 (8.6%)	24 (7.6%)
Total number of events	29	39	68	28
高血圧	15 (4.7%)	19 (6.0%)	34 (5.3%)	12 (3.8%)
低血圧	3 (0.9%)	2 (0.6%)	5 (0.8%)	2 (0.6%)
血管脆弱化	2 (0.6%)	2 (0.6%)	4 (0.6%)	1 (0.3%)
高血圧クリーゼ	0	2 (0.6%)	2 (0.3%)	1 (0.3%)
末梢血管障害	1 (0.3%)	2 (0.6%)	3 (0.5%)	0
静脈虚脱	0	2 (0.6%)	2 (0.3%)	1 (0.3%)
血圧変動	1 (0.3%)	0	1 (0.2%)	1 (0.3%)
深部静脈血栓症	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
高血圧切迫症	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
静脈炎	0	2 (0.6%)	2 (0.3%)	0
大動脈瘤	1 (0.3%)	0	1 (0.2%)	0
大動脈硬化症	0	1 (0.3%)	1 (0.2%)	0
大動脈狭窄	0	1 (0.3%)	1 (0.2%)	0
動脈閉塞性疾患	0	1 (0.3%)	1 (0.2%)	0
動脈硬化症	1 (0.3%)	0	1 (0.2%)	0
四肢壊死	0	1 (0.3%)	1 (0.2%)	0
頚静脈血栓症	1 (0.3%)	0	1 (0.2%)	0
リンパ浮腫	0	0	0	1 (0.3%)
起立性低血圧	0	0	0	1 (0.3%)
末梢動脈閉塞性疾患	1 (0.3%)	0	1 (0.2%)	0
末梢性虚血	0	1 (0.3%)	1 (0.2%)	0
末梢静脈疾患	1 (0.3%)	0	1 (0.2%)	0
末梢循環不良	0	1 (0.3%)	1 (0.2%)	0
ショック	0	0	0	1 (0.3%)
鎖骨下静脈血栓症	1 (0.3%)	0	1 (0.2%)	0
血栓性静脈炎	0	0	0	1 (0.3%)
血管閉塞	0	0	0	1 (0.3%)
静脈破裂	0	0	0	1 (0.3%)

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Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.6.2-34 眼以外の有害事象の集計（GR40398試験）（続）

Non-Ocular Adverse Events through Week 56, Safety-Evaluable Population
Protocol: GR40398
Clinical Cutoff Date: 19OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Faricimab 6 mg All (N=636)	Aflibercept 2 mg Q8W (N=314)
呼吸器、胸郭および縦隔障害				
Total number of patients with at least one adverse event	29 (9.1%)	27 (8.5%)	56 (8.8%)	18 (5.7%)
Total number of events	35	38	73	23
咳嗽	11 (3.5%)	14 (4.4%)	25 (3.9%)	7 (2.2%)
呼吸困難	4 (1.3%)	5 (1.6%)	9 (1.4%)	4 (1.3%)
急性呼吸不全	0	2 (0.6%)	2 (0.3%)	2 (0.6%)
胸水	1 (0.3%)	2 (0.6%)	3 (0.5%)	1 (0.3%)
鼻漏	3 (0.9%)	1 (0.3%)	4 (0.6%)	0
喘息	1 (0.3%)	1 (0.3%)	2 (0.3%)	1 (0.3%)
鼻出血	1 (0.3%)	1 (0.3%)	2 (0.3%)	1 (0.3%)
低酸素症	0	2 (0.6%)	2 (0.3%)	1 (0.3%)
口腔咽頭痛	2 (0.6%)	0	2 (0.3%)	1 (0.3%)
肺水腫	2 (0.6%)	1 (0.3%)	3 (0.5%)	0
慢性閉塞性肺疾患	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
発声障害	2 (0.6%)	0	2 (0.3%)	0
鼻閉	2 (0.6%)	0	2 (0.3%)	0
肺腫瘤	1 (0.3%)	0	1 (0.2%)	1 (0.3%)
アレルギー性鼻炎	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
上気道の炎症	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
肺障害	0	1 (0.3%)	1 (0.2%)	0
湿性咳嗽	0	0	0	1 (0.3%)
肺線維症	0	1 (0.3%)	1 (0.2%)	0
呼吸停止	1 (0.3%)	0	1 (0.2%)	0
呼吸不全	1 (0.3%)	0	1 (0.2%)	0
睡眠時無呼吸症候群	0	0	0	1 (0.3%)
頻呼吸	0	1 (0.3%)	1 (0.2%)	0

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.6.2-34 眼以外の有害事象の集計（GR40398試験）（続）

Non-Ocular Adverse Events through Week 56, Safety-Evaluable Population
Protocol: GR40398
Clinical Cutoff Date: 19OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Faricimab 6 mg All (N=636)	Aflibercept 2 mg Q8W (N=314)
心臓障害				
Total number of patients with at least one adverse event	23 (7.3%)	20 (6.3%)	43 (6.8%)	15 (4.8%)
Total number of events	31	36	67	20
うっ血性心不全	6 (1.9%)	4 (1.3%)	10 (1.6%)	2 (0.6%)
心房細動	4 (1.3%)	2 (0.6%)	6 (0.9%)	2 (0.6%)
心不全	1 (0.3%)	2 (0.6%)	3 (0.5%)	4 (1.3%)
狭心症	1 (0.3%)	3 (0.9%)	4 (0.6%)	2 (0.6%)
冠動脈疾患	1 (0.3%)	4 (1.3%)	5 (0.8%)	1 (0.3%)
心筋梗塞	3 (0.9%)	1 (0.3%)	4 (0.6%)	2 (0.6%)
頻脈	1 (0.3%)	3 (0.9%)	4 (0.6%)	0
急性心筋梗塞	0	1 (0.3%)	1 (0.2%)	2 (0.6%)
心停止	2 (0.6%)	1 (0.3%)	3 (0.5%)	0
虚血性心筋症	0	3 (0.9%)	3 (0.5%)	0
不安定狭心症	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
冠動脈硬化症	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
左室肥大	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
心筋虚血	1 (0.3%)	0	1 (0.2%)	1 (0.3%)
急性冠動脈症候群	0	1 (0.3%)	1 (0.2%)	0
大動脈弁狭窄	0	1 (0.3%)	1 (0.2%)	0
不整脈	0	1 (0.3%)	1 (0.2%)	0
心房粗動	1 (0.3%)	0	1 (0.2%)	0
脚ブロック	1 (0.3%)	0	1 (0.2%)	0
右脚ブロック	0	1 (0.3%)	1 (0.2%)	0
急性心不全	0	0	0	1 (0.3%)
慢性心不全	1 (0.3%)	0	1 (0.2%)	0
心細動	1 (0.3%)	0	1 (0.2%)	0
心拡大	0	1 (0.3%)	1 (0.2%)	0
慢性左室不全	1 (0.3%)	0	1 (0.2%)	0
うっ血性心筋症	0	0	0	1 (0.3%)
僧帽弁閉鎖不全症	0	1 (0.3%)	1 (0.2%)	0
右房拡張	0	1 (0.3%)	1 (0.2%)	0
右室不全	1 (0.3%)	0	1 (0.2%)	0
洞性頻脈	1 (0.3%)	0	1 (0.2%)	0
心内膜下虚血	1 (0.3%)	0	1 (0.2%)	0
上室性頻脈	1 (0.3%)	0	1 (0.2%)	0
三尖弁閉鎖不全症	0	1 (0.3%)	1 (0.2%)	0

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Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.6.2-34 眼以外の有害事象の集計（GR40398試験）（続）

Non-Ocular Adverse Events through Week 56, Safety-Evaluable Population
Protocol: GR40398
Clinical Cutoff Date: 19OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Faricimab 6 mg All (N=636)	Aflibercept 2 mg Q8W (N=314)
一般・全身障害および投与部位の状態				
Total number of patients with at least one adverse event	20 (6.3%)	15 (4.7%)	35 (5.5%)	16 (5.1%)
Total number of events	28	18	46	19
末梢性浮腫	4 (1.3%)	5 (1.6%)	9 (1.4%)	3 (1.0%)
発熱	2 (0.6%)	4 (1.3%)	6 (0.9%)	5 (1.6%)
末梢腫脹	5 (1.6%)	0	5 (0.8%)	3 (1.0%)
疲労	4 (1.3%)	2 (0.6%)	6 (0.9%)	1 (0.3%)
胸痛	2 (0.6%)	2 (0.6%)	4 (0.6%)	2 (0.6%)
無力症	2 (0.6%)	2 (0.6%)	4 (0.6%)	0
歩行障害	2 (0.6%)	0	2 (0.3%)	0
疼痛	1 (0.3%)	0	1 (0.2%)	1 (0.3%)
石灰沈着症	1 (0.3%)	0	1 (0.2%)	0
胸部不快感	1 (0.3%)	0	1 (0.2%)	0
顔面浮腫	0	1 (0.3%)	1 (0.2%)	0
高体温症	0	1 (0.3%)	1 (0.2%)	0
炎症	1 (0.3%)	0	1 (0.2%)	0
インフルエンザ様疾患	1 (0.3%)	0	1 (0.2%)	0
倦怠感	0	0	0	1 (0.3%)
多臓器機能不全症候群	0	1 (0.3%)	1 (0.2%)	0
壊死	1 (0.3%)	0	1 (0.2%)	0
軟部組織の炎症	1 (0.3%)	0	1 (0.2%)	0
顔面腫脹	0	0	0	1 (0.3%)
治療不成功	0	0	0	1 (0.3%)

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For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.6.2-34 眼以外の有害事象の集計（GR40398試験）（続）

Non-Ocular Adverse Events through Week 56, Safety-Evaluable Population
Protocol: GR40398
Clinical Cutoff Date: 19OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Faricimab 6 mg All (N=636)	Aflibercept 2 mg Q8W (N=314)
臨床検査				
Total number of patients with at least one adverse event	17 (5.4%)	12 (3.8%)	29 (4.6%)	23 (7.3%)
Total number of events	21	13	34	30
血中ブドウ糖増加	2 (0.6%)	1 (0.3%)	3 (0.5%)	4 (1.3%)
血圧上昇	1 (0.3%)	2 (0.6%)	3 (0.5%)	4 (1.3%)
グリコヘモグロビン増加	3 (0.9%)	2 (0.6%)	5 (0.8%)	2 (0.6%)
血中クレアチニン増加	2 (0.6%)	0	2 (0.3%)	2 (0.6%)
血中ブドウ糖変動	1 (0.3%)	1 (0.3%)	2 (0.3%)	1 (0.3%)
血中尿酸増加	2 (0.6%)	0	2 (0.3%)	1 (0.3%)
アラニンアミノトランスフェラーゼ増加	2 (0.6%)	0	2 (0.3%)	0
血中鉄減少	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
血中カリウム増加	0	2 (0.6%)	2 (0.3%)	0
血中尿素増加	0	0	0	2 (0.6%)
尿中ブドウ糖陽性	1 (0.3%)	0	1 (0.2%)	1 (0.3%)
前立腺特異性抗原増加	1 (0.3%)	1 (0.3%)	2 (0.3%)	0
白血球数増加	1 (0.3%)	0	1 (0.2%)	1 (0.3%)
アスパラギン酸アミノトランスフェラーゼ増加	1 (0.3%)	0	1 (0.2%)	0
血中コレステロール増加	0	0	0	1 (0.3%)
血中クレアチニン異常	0	0	0	1 (0.3%)
収縮期血圧上昇	0	0	0	1 (0.3%)
血中ナトリウム減少	1 (0.3%)	0	1 (0.2%)	0
血中尿酸異常	0	0	0	1 (0.3%)
心臓負荷試験異常	0	1 (0.3%)	1 (0.2%)	0
凝固時間延長	0	0	0	1 (0.3%)
駆出率減少	0	0	0	1 (0.3%)
フィブリンＤダイマー増加	0	1 (0.3%)	1 (0.2%)	0
ヘモグロビン減少	0	0	0	1 (0.3%)
心拍数増加	0	0	0	1 (0.3%)
肝酵素上昇	1 (0.3%)	0	1 (0.2%)	0
臨床検査異常	0	0	0	1 (0.3%)
脂質増加	0	1 (0.3%)	1 (0.2%)	0
尿検査異常	0	0	0	1 (0.3%)
ビタミンＢ１２増加	0	0	0	1 (0.3%)
体重増加	0	0	0	1 (0.3%)

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.6.2-34 眼以外の有害事象の集計（GR40398試験）（続）

Non-Ocular Adverse Events through Week 56, Safety-Evaluable Population
Protocol: GR40398
Clinical Cutoff Date: 19OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Faricimab 6 mg All (N=636)	Aflibercept 2 mg Q8W (N=314)
腎および尿路障害				
Total number of patients with at least one adverse event	21 (6.6%)	8 (2.5%)	29 (4.6%)	15 (4.8%)
Total number of events	26	11	37	25
慢性腎臓病	8 (2.5%)	2 (0.6%)	10 (1.6%)	3 (1.0%)
急性腎障害	3 (0.9%)	3 (0.9%)	6 (0.9%)	5 (1.6%)
糖尿病性腎症	3 (0.9%)	0	3 (0.5%)	1 (0.3%)
末期腎疾患	3 (0.9%)	1 (0.3%)	4 (0.6%)	0
腎不全	2 (0.6%)	1 (0.3%)	3 (0.5%)	1 (0.3%)
腎機能障害	1 (0.3%)	1 (0.3%)	2 (0.3%)	2 (0.6%)
腎嚢胞	1 (0.3%)	0	1 (0.2%)	2 (0.6%)
腎症	1 (0.3%)	0	1 (0.2%)	1 (0.3%)
頻尿	0	0	0	2 (0.6%)
蛋白尿	1 (0.3%)	0	1 (0.2%)	1 (0.3%)
尿路の炎症	1 (0.3%)	0	1 (0.2%)	1 (0.3%)
高窒素血症	1 (0.3%)	0	1 (0.2%)	0
膀胱壁肥厚	1 (0.3%)	0	1 (0.2%)	0
尿路結石	0	0	0	1 (0.3%)
腎結石症	0	1 (0.3%)	1 (0.2%)	0
腎動脈の動脈硬化症	0	1 (0.3%)	1 (0.2%)	0
腎仙痛	0	0	0	1 (0.3%)
尿道狭窄	0	1 (0.3%)	1 (0.2%)	0

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.6.2-34 眼以外の有害事象の集計（GR40398試験）（続）

Non-Ocular Adverse Events through Week 56, Safety-Evaluable Population
Protocol: GR40398
Clinical Cutoff Date: 19OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Faricimab 6 mg All (N=636)	Aflibercept 2 mg Q8W (N=314)
皮膚および皮下組織障害				
Total number of patients with at least one adverse event	15 (4.7%)	15 (4.7%)	30 (4.7%)	13 (4.1%)
Total number of events	16	18	34	19
皮膚潰瘍	4 (1.3%)	3 (0.9%)	7 (1.1%)	4 (1.3%)
発疹	3 (0.9%)	1 (0.3%)	4 (0.6%)	1 (0.3%)
糖尿病性足病変	0	2 (0.6%)	2 (0.3%)	2 (0.6%)
そう痒症	1 (0.3%)	1 (0.3%)	2 (0.3%)	2 (0.6%)
水疱	0	1 (0.3%)	1 (0.2%)	2 (0.6%)
皮膚炎	0	2 (0.6%)	2 (0.3%)	1 (0.3%)
接触皮膚炎	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
光線角化症	0	1 (0.3%)	1 (0.2%)	0
脱毛症	0	0	0	1 (0.3%)
血管浮腫	0	0	0	1 (0.3%)
蝶形皮疹	1 (0.3%)	0	1 (0.2%)	0
褥瘡性潰瘍	1 (0.3%)	0	1 (0.2%)	0
皮膚嚢腫	0	1 (0.3%)	1 (0.2%)	0
アレルギー性皮膚炎	0	1 (0.3%)	1 (0.2%)	0
アトピー性皮膚炎	1 (0.3%)	0	1 (0.2%)	0
糖尿病性潰瘍	1 (0.3%)	0	1 (0.2%)	0
皮膚乾燥	0	1 (0.3%)	1 (0.2%)	0
過角化	0	1 (0.3%)	1 (0.2%)	0
内方発育毛	1 (0.3%)	0	1 (0.2%)	0
硬化性苔癬	0	0	0	1 (0.3%)
爪床の炎症	1 (0.3%)	0	1 (0.2%)	0
紅斑性皮疹	0	0	0	1 (0.3%)
酒さ	0	1 (0.3%)	1 (0.2%)	0
皮膚灼熱感	1 (0.3%)	0	1 (0.2%)	0
皮膚病変	1 (0.3%)	0	1 (0.2%)	0
血液およびリンパ系障害				
Total number of patients with at least one adverse event	14 (4.4%)	10 (3.1%)	24 (3.8%)	12 (3.8%)
Total number of events	16	11	27	17
貧血	10 (3.2%)	4 (1.3%)	14 (2.2%)	10 (3.2%)
血小板減少症	3 (0.9%)	0	3 (0.5%)	1 (0.3%)
白血球増加症	0	2 (0.6%)	2 (0.3%)	0
小球性貧血	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
巨赤芽球性貧血	0	1 (0.3%)	1 (0.2%)	0
溶血性尿毒症症候群	1 (0.3%)	0	1 (0.2%)	0
鉄欠乏性貧血	0	1 (0.3%)	1 (0.2%)	0
リンパ節炎	0	0	0	1 (0.3%)
リンパ節症	1 (0.3%)	0	1 (0.2%)	0
微小血管症性溶血性貧血	1 (0.3%)	0	1 (0.2%)	0
汎血球減少症	0	1 (0.3%)	1 (0.2%)	0
脾腫	0	1 (0.3%)	1 (0.2%)	0

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.6.2-34 眼以外の有害事象の集計（GR40398試験）（続）

Non-Ocular Adverse Events through Week 56, Safety-Evaluable Population
Protocol: GR40398
Clinical Cutoff Date: 19OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Faricimab 6 mg All (N=636)	Aflibercept 2 mg Q8W (N=314)
良性、悪性および詳細不明の新生物（嚢胞およびポリープを含む）				
Total number of patients with at least one adverse event	9 (2.8%)	4 (1.3%)	13 (2.0%)	8 (2.5%)
Total number of events	11	5	16	8
腺癌	0	0	0	1 (0.3%)
基底細胞癌	1 (0.3%)	0	1 (0.2%)	0
副腎の良性新生物	0	1 (0.3%)	1 (0.2%)	0
甲状腺の良性新生物	0	0	0	1 (0.3%)
腎臓の良性新生物	1 (0.3%)	0	1 (0.2%)	0
膀胱癌	1 (0.3%)	0	1 (0.2%)	0
膀胱移行上皮癌第２期	0	0	0	1 (0.3%)
結腸癌	0	1 (0.3%)	1 (0.2%)	0
骨血管腫	1 (0.3%)	0	1 (0.2%)	0
ヘアリー細胞白血病	0	1 (0.3%)	1 (0.2%)	0
平滑筋腫	1 (0.3%)	0	1 (0.2%)	0
脂肪腫	0	1 (0.3%)	1 (0.2%)	0
肺の悪性新生物	1 (0.3%)	0	1 (0.2%)	0
新生物	0	0	0	1 (0.3%)
皮膚の新生物	0	0	0	1 (0.3%)
膵癌	0	0	0	1 (0.3%)
リンパ腫性乳頭状嚢胞腺腫	1 (0.3%)	0	1 (0.2%)	0
前立腺癌	1 (0.3%)	0	1 (0.2%)	0
腎膨大細胞腫	0	0	0	1 (0.3%)
脂漏性角化症	1 (0.3%)	0	1 (0.2%)	0
舌の良性新生物	0	0	0	1 (0.3%)
子宮平滑筋腫	1 (0.3%)	0	1 (0.2%)	0
精神障害				
Total number of patients with at least one adverse event	7 (2.2%)	4 (1.3%)	11 (1.7%)	9 (2.9%)
Total number of events	7	4	11	9
不眠症	2 (0.6%)	1 (0.3%)	3 (0.5%)	2 (0.6%)
不安	1 (0.3%)	0	1 (0.2%)	3 (1.0%)
うつ病	1 (0.3%)	0	1 (0.2%)	3 (1.0%)
激越	1 (0.3%)	0	1 (0.2%)	0
不安障害	0	1 (0.3%)	1 (0.2%)	0
錯乱状態	0	1 (0.3%)	1 (0.2%)	0
譫妄	0	1 (0.3%)	1 (0.2%)	0
精神状態変化	1 (0.3%)	0	1 (0.2%)	0
気分変化	0	0	0	1 (0.3%)
精神生理性不眠症	1 (0.3%)	0	1 (0.2%)	0

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.6.2-34 眼以外の有害事象の集計（GR40398試験）（続）

Non-Ocular Adverse Events through Week 56, Safety-Evaluable Population
Protocol: GR40398
Clinical Cutoff Date: 19OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Faricimab 6 mg All (N=636)	Aflibercept 2 mg Q8W (N=314)
生殖系および乳房障害				
Total number of patients with at least one adverse event	6 (1.9%)	3 (0.9%)	9 (1.4%)	6 (1.9%)
Total number of events	7	3	10	6
良性前立腺肥大症	2 (0.6%)	3 (0.9%)	5 (0.8%)	1 (0.3%)
勃起不全	2 (0.6%)	0	2 (0.3%)	1 (0.3%)
卵巣嚢胞	1 (0.3%)	0	1 (0.2%)	1 (0.3%)
前立腺腫大	1 (0.3%)	0	1 (0.2%)	1 (0.3%)
閉経期症状	1 (0.3%)	0	1 (0.2%)	0
膣出血	0	0	0	1 (0.3%)
外陰膣そう痒症	0	0	0	1 (0.3%)
耳および迷路障害				
Total number of patients with at least one adverse event	8 (2.5%)	1 (0.3%)	9 (1.4%)	2 (0.6%)
Total number of events	8	1	9	2
聴力低下	2 (0.6%)	0	2 (0.3%)	1 (0.3%)
回転性めまい	2 (0.6%)	1 (0.3%)	3 (0.5%)	0
耳鳴	2 (0.6%)	0	2 (0.3%)	0
片耳難聴	1 (0.3%)	0	1 (0.2%)	0
耳閉	0	0	0	1 (0.3%)
メニエール病	1 (0.3%)	0	1 (0.2%)	0
肝胆道系障害				
Total number of patients with at least one adverse event	4 (1.3%)	4 (1.3%)	8 (1.3%)	4 (1.3%)
Total number of events	4	4	8	4
胆嚢炎	0	2 (0.6%)	2 (0.3%)	1 (0.3%)
脂肪肝	1 (0.3%)	1 (0.3%)	2 (0.3%)	1 (0.3%)
胆管狭窄	0	0	0	1 (0.3%)
慢性胆嚢炎	1 (0.3%)	0	1 (0.2%)	0
胆石症	0	1 (0.3%)	1 (0.2%)	0
高ビリルビン血症	1 (0.3%)	0	1 (0.2%)	0
過形成性胆嚢症	1 (0.3%)	0	1 (0.2%)	0
肝障害	0	0	0	1 (0.3%)
免疫系障害				
Total number of patients with at least one adverse event	2 (0.6%)	7 (2.2%)	9 (1.4%)	1 (0.3%)
Total number of events	3	7	10	1
季節性アレルギー	1 (0.3%)	4 (1.3%)	5 (0.8%)	0
過敏症	1 (0.3%)	1 (0.3%)	2 (0.3%)	1 (0.3%)
アナフィラキシー反応	0	1 (0.3%)	1 (0.2%)	0
造影剤アレルギー	0	1 (0.3%)	1 (0.2%)	0

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

表 2.7.6.2-34 眼以外の有害事象の集計（GR40398試験）（続）

Non-Ocular Adverse Events through Week 56, Safety-Evaluable Population
Protocol: GR40398
Clinical Cutoff Date: 19OCT2020

MedDRA System Organ Class MedDRA Preferred Term	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Faricimab 6 mg All (N=636)	Aflibercept 2 mg Q8W (N=314)
内分泌障害				
Total number of patients with at least one adverse event	2 (0.6%)	3 (0.9%)	5 (0.8%)	3 (1.0%)
Total number of events	2	3	5	3
甲状腺機能低下症	1 (0.3%)	2 (0.6%)	3 (0.5%)	1 (0.3%)
副甲状腺機能亢進症	0	1 (0.3%)	1 (0.2%)	0
副腎過形成	1 (0.3%)	0	1 (0.2%)	0
甲状腺機能亢進症	0	0	0	1 (0.3%)
原発性性腺機能低下	0	0	0	1 (0.3%)
眼障害				
Total number of patients with at least one adverse event	2 (0.6%)	1 (0.3%)	3 (0.5%)	1 (0.3%)
Total number of events	2	1	3	1
複視	1 (0.3%)	0	1 (0.2%)	0
眼痛	0	0	0	1 (0.3%)
羞明	1 (0.3%)	0	1 (0.2%)	0
閃輝暗点	0	1 (0.3%)	1 (0.2%)	0
外科および内科処置				
Total number of patients with at least one adverse event	1 (0.3%)	0	1 (0.2%)	1 (0.3%)
Total number of events	1	0	1	1
手根管除圧	0	0	0	1 (0.3%)
中足骨切除	1 (0.3%)	0	1 (0.2%)	0
先天性、家族性および遺伝性障害				
Total number of patients with at least one adverse event	1 (0.3%)	0	1 (0.2%)	0
Total number of events	1	0	1	0
皮様嚢腫	1 (0.3%)	0	1 (0.2%)	0

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).
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[5.3.5.3-nAMD-1 t_ae_NOCUL_W56_SE_19OCT2020_40398を改変]

表 2.7.6.2-35 試験眼の副作用の集計（GR40398試験）

Ocular Adverse Events Related to Study Treatment in the Study Eye through Week 56, Safety-Evaluable Population
Protocol: GR40398
Clinical Cutoff Date: 19OCT2020

MedDRA Preferred Term	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Faricimab 6 mg All (N=636)	Aflibercept 2 mg Q8W (N=314)
Total number of patients with at least one adverse event	8 (2.5%)	8 (2.5%)	16 (2.5%)	14 (4.5%)
Total number of events	8	9	17	14
硝子体浮遊物	4 (1.3%)	1 (0.3%)	5 (0.8%)	3 (1.0%)
眼圧上昇	2 (0.6%)	2 (0.6%)	4 (0.6%)	3 (1.0%)
白内障	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
角膜炎	0	1 (0.3%)	1 (0.2%)	1 (0.3%)
高眼圧症	0	2 (0.6%)	2 (0.3%)	0
結膜出血	0	0	0	1 (0.3%)
角膜擦過傷	1 (0.3%)	0	1 (0.2%)	0
糖尿病性網膜浮腫	0	0	0	1 (0.3%)
眼痛	0	0	0	1 (0.3%)
眼部不快感	0	1 (0.3%)	1 (0.2%)	0
霧視	0	0	0	1 (0.3%)
視力障害	0	0	0	1 (0.3%)
硝子体剥離	0	0	0	1 (0.3%)
硝子体炎	1 (0.3%)	0	1 (0.2%)	0

MedDRA = Medical Dictionary for Regulatory Activities; PTI = Personalized Treatment Interval (from Q4W up to Q16W).
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

[5.3.5.1-DME-3 t_ae_pt_SOCUL_SREL_W56_SE_19OCT2020_40398を改変]

表 2.7.6.2-36 非試験眼の副作用の集計（GR40398試験）

Ocular Adverse Events in the Fellow Eye related to Fellow Eye Treatment through Week 56, Safety-Evaluable Population
Protocol: GR40398
Clinical Cutoff Date: 19OCT2020

MedDRA Preferred Term	Faricimab 6 mg Q8W (N=317)	Faricimab 6 mg PTI (N=319)	Aflibercept 2 mg Q8W (N=314)
Total number of patients with at least one adverse event	7 (2.2%)	3 (0.9%)	7 (2.2%)
Total number of events	8	3	8
結膜出血	3 (0.9%)	0	0
眼圧上昇	1 (0.3%)	1 (0.3%)	1 (0.3%)
白内障	1 (0.3%)	0	1 (0.3%)
眼痛	0	0	2 (0.6%)
虹彩炎	1 (0.3%)	0	0
角膜炎	0	1 (0.3%)	0
流涙増加	1 (0.3%)	0	0
黄斑線維症	0	1 (0.3%)	0
疼痛	1 (0.3%)	0	0
霧視	0	0	1 (0.3%)
硝子体剥離	0	0	1 (0.3%)
硝子体浮遊物	0	0	1 (0.3%)
硝子体出血	0	0	1 (0.3%)

AE = Adverse Event, MedDRA = Medical Dictionary for Regulatory Activities.
Investigator text for AEs encoded using MedDRA version 23.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Includes AEs with onset up to Day 405 (last day of Week 56 analysis visit window).

[5.3.5.1-DME-3 PR11341_t_ae_pt_FOCUL_FREL_W56_SE_19OCT2020_40398を改変]