目次

2.6.4 薬物動態試験の概要文 3
2.6.4.1 まとめ 3
2.6.4.2 分析法 4
2.6.4.3 吸収 5
2.6.4.4 分布 6
2.6.4.5 代謝 6
2.6.4.6 排泄 6
2.6.4.7 薬物動態学的薬物相互作用 6
2.6.4.8 その他の薬物動態試験 6
2.6.4.9 考察及び結論 6
2.6.4.10 図表 6
2.6.4.11 参考文献 6
2.6.5 薬物動態試験概要表 1

略号一覧表

略号又は略称	名称及び内容
AUC	area under the serum concentration-time curve（血清中濃度－時間曲線下面積）
AUC_{∞}	area under the serum concentration-time curve from time zero to infinite time（0時間から無限大時間までの血清中濃度－時間曲線下面積）
CL	total body clearance（全身クリアランス）
C_{max}	maximum serum concentration（最高血清中濃度）
ELISA	enzyme-linked immunosorbent assay（酵素結合免疫吸着測定法）
Ig	immunoglobulin（免疫グロブリン）
$t_{1/2}$	elimination half-life（消失半減期）
V_z	volume of distribution at the terminal phase（最終相における分布容積）

2.6.4 薬物動態試験の概要文

2.6.4.1 まとめ

ダラツムマブ（遺伝子組換え）は CD38 に特異的に結合するヒト免疫グロブリン G1κ（IgG1κ）モノクローナル抗体である。ダラツムマブは，ヒト以外ではチンパンジーの CD38 のみに結合し，マウス，ラット，ウサギ，ブタ，カニクイザル及びアカゲザルの CD38 には結合しなかった【CTD 2.6.2.1.1.1 参照】。このため，非臨床薬物動態はチンパンジーを用いて評価したが，チンパンジーは絶滅危惧種であり，実験に使用可能な動物数は非常に限られているため，独立した薬物動態試験は実施せず，6 週間反復静脈内投与毒性試験の一環として実施した少数例のトキシコキネティクスデータを用いて評価した。

雌雄チンパンジーにダラツムマブを週 1 回 6 週間反復静脈内投与したとき，ダラツムマブの最高血清中濃度（C_{max}）及び血清中濃度－時間曲線下面積（AUC）は 5～25 mg/kg の範囲で用量の増加とともに増加し，全身クリアランス（CL）は減少する傾向が認められた。また，消失半減期（$t_{1/2}$）は用量及び投与回数の増加に伴い延長した。

抗ダラツムマブ抗体は，試験期間中検出されなかった。

2.6.4.2 分析法

2.6.4.2.1 血清中ダラツムマブ濃度

【評価資料 4.2.2.1.1】

チンパンジーの血清中ダラツムマブ濃度は，バリデーションされた酵素結合免疫吸着測定法（ELISA）で測定した。定量下限は，ダラツムマブを含む血清を 100 倍希釈したとき 21.538 ng/mL，及び 40 倍希釈したとき 22.973 ng/mL であった。

2.6.4.2.2 抗ダラツムマブ抗体

【評価資料 4.2.2.1.2】

チンパンジーの血清中抗ダラツムマブ抗体の産生を評価するために，バリデーションされた ELISA を用いた。なお，血清中ダラツムマブ濃度が 10 μg/mL 以上のとき，ダラツムマブの $F(ab')_2$ フラグメントと抗ダラツムマブ抗体との結合が 30%以上干渉を受ける可能性がある。

2.6.4.3 吸収

【評価資料 4.2.3.2.2】

雌雄チンパンジー（1 例/性/群）にダラツムマブを 5 又は 25 mg/kg の用量で週 1 回 6 週間反復静脈内投与したときの個体ごとの薬物動態パラメータ及び抗ダラツムマブ抗体検出に関する結果を【CTD 2.6.5.4 参照】に示す。なお，5 mg/kg 投与群（30 分間の持続静脈内投与）では，雄は 6 回投与したが，雌（個体番号 95A015）は 2 回目投与後に本薬剤投与と関連性のない損傷により投与を中止したため，別の雌（個体番号 92A016）を試験に供した。しかし，この雌は 1 回目投与の 1.5 時間後，サイトカイン放出反応により死亡したため，その薬物動態は評価しなかった。また，25 mg/kg 投与群では，雌雄ともに 6 回投与したが，サイトカインの過剰放出を防ぐために 1 回目投与の 24 時間前にダラツムマブを 10 mg の用量で静脈内投与した後，1 回目は 1 時間の持続静脈内投与，2 回目以降は 30 分間の持続静脈内投与を行った。

5 mg/kg 投与群の雄及び雌における 1 回目投与後の $t_{1/2}$ はそれぞれ 38 及び 36 時間，0 時間から無限大時間までの血清中濃度－時間曲線下面積（AUC_{∞}）はそれぞれ 2246 及び 2966 μg·h/mL，最終相における分布容積（V_z）はそれぞれ 122.7 及び 86.7 mL/kg であった。また，雄では投与回数が増えるにつれて $t_{1/2}$ は延長し，曝露量は増加した。

25 mg/kg 投与群の雄及び雌における 1 回目投与後の $t_{1/2}$ はそれぞれ 103 及び 135 時間，AUC_{∞} はそれぞれ 40463 及び 74458 μg·h/mL，V_z はそれぞれ 91.4 及び 65.6 mL/kg であった。また，雌雄とも投与回数が増えるにつれ $t_{1/2}$ は延長し，曝露量は増加した。

C_{max} 及び AUC は 5～25 mg/kg の範囲では用量の増加とともに増加し，CL は減少及び $t_{1/2}$ は延長する傾向が認められた。なお，各投与群とも雌雄 1 例ずつのため，性差について結論づけることはできなかった。

抗ダラツムマブ抗体は，試験期間中検出されなかった。

2.6.4.4 分布

ダラツムマブはヒト IgG であることから，他の内因性 IgG と同様に，組織移行性は低いと考えられる。

2.6.4.5 代謝

ダラツムマブはヒト IgG であることから，生体内では他の内因性 IgG と同様に小ペプチド及びアミノ酸に分解されると考えられる。

2.6.4.6 排泄

ダラツムマブは生体内で小ペプチド及びアミノ酸に分解された後，排泄又は再利用されると考えられる。

2.6.4.7 薬物動態学的薬物相互作用

該当資料なし

2.6.4.8 その他の薬物動態試験

該当資料なし

2.6.4.9 考察及び結論

雌雄チンパンジーにダラツムマブを週 1 回 6 週間反復静脈内投与したとき，C_{max} 及び AUC は 5～25 mg/kg の範囲では用量の増加とともに増加した。また，CL は減少及び $t_{1/2}$ は延長する傾向が認められたことから，血清中ダラツムマブ濃度が高いとき，ダラツムマブの消失は飽和すると考えられる。

抗ダラツムマブ抗体は，試験期間中検出されなかった。

2.6.4.10 図表

表は概要表中に記載した。

2.6.4.11 参考文献

該当資料なし

2.6.5 薬物動態試験概要表

2.6.5.1 薬物動態試験：一覧表

Test Article: Daratumumab

Type of Study	Test System	Route (Vehicle/Formulation)	GLP	Test Facility	Study No. Location in CTD
Absorption Repeat-Dose Toxicity Study (6 weeks [weekly] + 91 or 105 day recovery) [a] with TK and ADA analysis	Chimpanzee (Group 1: 1 M/2 F [b]; Group 2: 1 M/1 F)	IV (30 min. infusion) [c] IV (30 min.-1 h infusion) [d] (Vehicle: 25 mM sodium acetate, 60 mM sodium chloride, 140 mM mannitol, 0.006% polysorbate 20, pH 5.5; Daratumumab: 21.1 mg/mL in sterile pyrogen free 0.9% NaCl [125 mL dilution])	Yes	[redacted]	8754-0701/ 4.2.3.2.2

[a] The treatment period was followed by a recovery period of 105 and 91 days for low (5 mg/kg) and high (25 mg/kg) dose animals, respectively.

[b] On Study Day 15, female No. 95A015 had a non-drug-related accident and treatment was discontinued. She was replaced by another female chimpanzee; that replacement animal (No. 92A016), however, died approximately 1.5 h after the Study Day 7 infusion of 5 mg/kg daratumumab. As only limited TK samples (from pre-dose to terminal [ie, approximately 1.5 h post-dose]) were obtained for No. 92A016, data for that animal are not provided here.

[c] Animals assigned to Group 1 were administered the vehicle on Day 0, followed by a 5 mg/kg IV infusion (30 min.) of daratumumab on Day 7; dosing occurred weekly for 6 weeks until Day 42.

[d] Animals assigned to Group 2 were administered the vehicle on Day 7. In order to prevent exaggerated cytokine release, animals received a 10 mg pre-dose of daratumumab via IV injection on Day 21, followed by a 25 mg/kg IV infusion (1 h) of daratumumab administered 24 h later on Day 22; infusion (30 min.) occurred weekly for 6 weeks until Day 56.

ADA = anti-drug antibody; F = female; GLP = Good Laboratory Practice; IV = intravenous; M = male; No. = number; TK = toxicokinetics

2.6.5.2 分析方法及びバリデーション試験

Test Article: Daratumumab

Study No. Supported by Validation Report	Test System	Matrix	Analysis Method	LLOQ [a]	Analyte Measured	Study No. of Applicable Validation Report	Location in CTD
8754-0701	Chimpanzee	serum	ELISA [b]	21.538 ng/mL (1% CS); [c] 22.973 ng/mL (2.5% CS) [c]	Daratumumab	BKV00009 [d, g]	4.2.2.1
8754-0701	Chimpanzee	serum	ELISA [e]	0.303 AU [f]	Antibodies to Daratumumab	BKV00005 [d, g]	4.2.2.1

[a] LLOQ unless otherwise noted.
[b] The ELISA method was used for the determination of daratumumab levels in chimpanzee serum.
[c] The LLOQ for each matrix is defined by its LOD, which is expressed as a concentration of daratumumab; the LODs are shown for the assay in a 1% (100-fold) and 2.5% (40-fold) CS matrix, respectively.
[d] The validation method was conducted according to GLPs.
[e] The ELISA method was used for the detection of antibodies directed against daratumumab F(ab')$_2$ fragments in chimpanzee serum.
[f] The NCO determination established for the ELISA method used in ADA analysis is shown.
[g] The assay conditions were defined based on the assay optimization work performed at Charles River Laboratories, Preclinical Services, Nevada, Mod4.2.2.1/BKV00004.

AU = absorbance units; CS = pooled chimpanzee serum; ELISA = enzyme-linked immunosorbent assay; GLP = Good Laboratory Practice; LLOQ = lower limit of quantification; LOD = limit of detection; NCO = negative cut off

2.6.5.3 薬物動態試験：単回投与後の吸収

該当資料なし

2.6.5.4 薬物動態試験：反復投与後の吸収

Test Article: Daratumumab

Study No./Location in CTD	**8754-0701/4.2.3.2.2**
Species	Chimpanzee
Feeding Condition	Fed
Vehicle/Formulation	Vehicle: 25 mM sodium acetate, 60 mM sodium chloride, 140 mM mannitol, 0.006% polysorbate 20, pH 5.5 Daratumumab: 21.1 mg/mL in sterile pyrogen free 0.9% NaCl (125 mL dilution)
Sample	Serum
Assay (PK)	ELISA
Analyte	Daratumumab
Duration of Dosing	6 weeks [a]
Route	IV (vehicle: 30 min. infusion; daratumumab: 30 min.–1 h infusion) [b, c]
Sex (M/F)/Number of Animals	1/sex/group
Pharmacokinetic Parameters [d]	

Dose (mg/kg/week)	Study Day [d]	Dosing Day [d]	Animal ID No.	Sex	C_{max} (µg/mL)	AUC_t [e] (µg·h/mL)	AUC_∞ (µg·h/mL)	AUC_{corr} [f] (µg·h/mL)	$AUC_{\%Extrap}$ [g] (%)	$t_{1/2}$ (h)	V_z (mL/kg)	CL (mL/h/kg)
0→5 [b,h]	7	0	95A015 [h]	F	86	2,799	2,966	-	5.6	36	86.7	1.69
	7	0	96A009	M	100	2,185	2,246	-	2.7	38	122.7	2.23
	21	14	96A009	M	129	11,309	15,836	14,506	28.6	88	43.8 [i]	0.34 [i]
	42	35	96A009	M	129	21,450	23,171	14,929	7.4	132	63.8 [i]	0.33 [i]
0→25 [c]	22	0	96A015	M	612	25,885	40,463	-	36.0	103	91.4	0.62
	22	0	96A017	F	778	39,158	74,458	-	47.4	135	65.6	0.34
	35	14	96A015	M	630	39,995	96,676	34,711	58.6	231	240.0 [i]	0.72 [i]
	35	14	96A017	F	599	62,112	215,145	73,347	71.1	335	164.7 [i]	0.34 [i]
	56	35	96A015	M	695	146,729	319,583	9,747	54.1	596	2,205.3 [i]	2.56 [i]
	56	35	96A017	F	967	201,462	364,102	43,254	44.7	461	384.4 [i]	0.58 [i]

[a] The treatment period was followed by a recovery period of 105 and 91 days for low (5 mg/kg) and high (25 mg/kg) dose animals, respectively.

[b] Animals assigned to Group 1 were administered the vehicle on Day 0, followed by a 5 mg/kg IV infusion (30 min.) of daratumumab on Day 7; dosing occurred weekly for 6 weeks until Day 42.

[c] Animals assigned to Group 2 were administered the vehicle on Day 7. In order to prevent exaggerated cytokine release, animals received a 10 mg pre-dose of daratumumab via IV injection on Day 21, followed by a 25 mg/kg IV infusion (1 h) of daratumumab administered 24 h later on Day 22; infusion (30 min.) occurred weekly for 6 weeks until Day 56.

[d] The actual day of dosing (Study Day) is shown, followed by the standardized Dosing Day (standardized dosing days = 0, 7, 14, 21, 28, and 35). Days correspond to the first, third, and sixth doses. Blood samples were collected for serum prior to infusion and 0.58, 2, 3.5, 6.5, 24, 48, and 144 or 168 h after initiation of the first, third, and sixth doses. Additional blood samples were collected after the sixth infusion in Group 1 (96, 240, 360, 528, 2016, 2184, 2352, and 2520 h) and Group 2 (96, 240, 360, 528, 1680, 1848, 2016, and 2184 h). Due to the low number of animals, individual animal data is shown.

[e] In Group 1, the last quantifiable PK sample was collected 168 h after the first and third dose, and 528 h after the sixth dose. In Group 2, the last quantifiable PK sample was collected 144 h after the first dose, 168 h after the third dose, and 528 h after the sixth dose. These time points were considered “t” for the respective calculations of AUC_t.

[f] $AUC_{corr} = AUC\text{-}C(0)/\lambda_z$

[g] $AUC_{\%Extrap}$ exceeded 50% for Animal No. 96A015 on Study Days 35 and 56 and Animal No. 96A017 on Day 35; AUC, V_z, and CL should be evaluated with some reservation.

[h] On Study Day 15, female No. 95A015 had a non-drug-related accident and treatment was discontinued. She was replaced by another female chimpanzee; that replacement animal (No. 92A016), however, died approximately 1.5 h after the Study Day 7 initial 5 mg/kg infusion of daratumumab. As only limited PK samples (from pre-dose to terminal [ie, approximately 1.5 h post-dose]) were obtained for No. 92A016, data for that animal are not provided here.

[i] Calculated from AUC_{corr}.

AUC_{corr} = AUC corrected by subtracting rest area from previous dosing; AUC_t = area under the serum concentration-time curve from time zero to time t; AUC_∞ = area under the serum concentration-time curve from time zero to infinite time; $AUC_{\%Extrap}$ = extrapolated AUC as percentage of total AUC; CL = total body clearance; C_{max} = maximum serum concentration; ELISA = enzyme-linked immunosorbent assay; F = female; ID = identification; IV = intravenous; M = male; No. = number; PK = pharmacokinetics; $t_{1/2}$ = elimination half-life; V_z = volume of distribution at the terminal phase; - = not calculated/ not applicable

(Continued)

2.6.5.4 薬物動態試験：反復投与後の吸収（続き）

Test Article: Daratumumab

Study No./Location in CTD	**8754-0701/4.2.3.2.2**				
Sample	Serum				
Assay (ADA)	ELISA				
Analyte	Antibodies to daratumumab				
Dose (mg/kg/week)	0→5			0→25	
No. of Animals	M:1	F:2 [a]		M:1	F:1
Animal ID No.	96A009	95A015	92A016	96A015	96A017
ADA Response [b]					
ADA Positive Animals [c]	0/3			0/2	

Additional Information: Data from a 6-week repeat-dose toxicology study with a recovery period of 105 or 91 days for low (5 mg/kg) and high (25 mg/kg) dose animals.

[a] Data are for animal No. 95A015 and No. 92A016, which received 2 or 1 IV infusions of daratumumab, respectively. On Study Day 15, animal No. 95A015 had a non-drug related accident and treatment was discontinued, although the animal remained on study. It was replaced by animal No. 92A016, which received only 1 dose of daratumumab, and died approximately 1.5 h after the first dose.

[b] Blood samples were collected from all animals (except for 95A015 and 92A016) for the detection of anti-daratumumab antibodies in serum pre-dose and prior to the fourth and sixth doses, and on Study Days 71, 98, 126, 133, 140 and 147 from Group 1 animals, and Study Days 85, 112, 126, 133, 140, and 147 from Group 2 animals.

[c] Noted as the number of ADA positive animals/the total number of animals tested per dose group. No animals exhibited a positive ADA response to daratumumab; all samples were below the NCO.

ADA = anti-drug antibody; ELISA = enzyme-linked immunosorbent assay; F = female; ID = identification; IV = intravenous; M = male; NCO = negative cut off

2.6.5.5 薬物動態試験：組織分布

該当資料なし

2.6.5.6 薬物動態試験：血漿たん白結合

該当資料なし

2.6.5.7 薬物動態試験：妊娠又は授乳動物における試験

該当資料なし

2.6.5.8 薬物動態試験：その他の分布試験

該当資料なし

2.6.5.9 薬物動態試験：*In vitro* における代謝

該当資料なし

2.6.5.10 薬物動態試験：*In vivo* における代謝

該当資料なし

2.6.5.11 薬物動態試験：推定代謝経路

該当資料なし

2.6.5.12　薬物動態試験：薬物代謝酵素の誘導／阻害

該当資料なし

2.6.5.13　薬物動態試験：尿・糞中排泄

該当資料なし

2.6.5.14　薬物動態試験：胆汁中排泄

該当資料なし

2.6.5.15　薬物動態試験：薬物相互作用

該当資料なし

2.6.5.16　薬物動態試験：その他

該当資料なし