表 2.7.6.28-12　日本人集団を含むグローバル集団の治験中に発現した器官別大分類及び基本語別の有害事象（中間解析対象集団）（続き）

器官別大分類 基本語	20110233 親試験から移行 Part A EvoMab (N = 8) n (%)	20110233 親試験から移行 Part B EvoMab (N = 30) n (%)	20110233 親試験から移行 Part B プラセボ (N = 16) n (%)	20110271 非親試験/その他親試験から移行 組入れ時アフェレーシス (N = 50) n (%)	20110271 非親試験/その他親試験から移行 組入れ時非アフェレーシス (N = 138) n (%)	20110271 非親試験/その他親試験から移行 合計 (N = 188) n (%)	合計 (N = 242) n (%)
一般・全身障害および投与部位の状態（続き）							
医療機器合併症	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
非心臓性胸痛	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
浮腫	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
ポリープ	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
血管穿刺部位内出血	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)	1 (0.4)
血管穿刺部位出血	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)	1 (0.4)
免疫系障害	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)	1 (0.4)
季節性アレルギー	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)	1 (0.4)
感染症および寄生虫症	5 (62.5)	6 (20.0)	4 (25.0)	14 (28.0)	30 (21.7)	44 (23.4)	59 (24.4)

データカットオフ [redacted]年[redacted]月[redacted]日

EvoMab = evolocumab (AMG 145)、N = 20110271 試験に組み入れ投与した被験者数

MedDRA 17.0 版でコード化

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表 2.7.6.28-12　日本人集団を含むグローバル集団の治験中に発現した器官別大分類及び基本語別の有害事象（中間解析対象集団）（続き）

器官別大分類 基本語	20110233 親試験から移行 Part A EvoMab (N = 8) n (%)	 Part B EvoMab (N = 30) n (%)	 Part B プラセボ (N = 16) n (%)	20110271 非親試験/その他親試験から移行 組入れ時アフェレーシス (N = 50) n (%)	 組入れ時非アフェレーシス (N = 138) n (%)	 合計 (N = 188) n (%)	 合計 (N = 242) n (%)
感染症および寄生虫症（続き）							
鼻咽頭炎	1 (12.5)	1 (3.3)	1 (6.3)	5 (10.0)	13 (9.4)	18 (9.6)	21 (8.7)
上気道感染	2 (25.0)	0 (0.0)	1 (6.3)	1 (2.0)	7 (5.1)	8 (4.3)	11 (4.5)
インフルエンザ	0 (0.0)	3 (10.0)	1 (6.3)	3 (6.0)	2 (1.4)	5 (2.7)	9 (3.7)
胃腸炎	0 (0.0)	1 (3.3)	2 (12.5)	1 (2.0)	3 (2.2)	4 (2.1)	7 (2.9)
気管支炎	1 (12.5)	0 (0.0)	1 (6.3)	1 (2.0)	0 (0.0)	1 (0.5)	3 (1.2)
肺炎	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	2 (1.4)	3 (1.6)	3 (1.2)
歯膿瘍	0 (0.0)	0 (0.0)	1 (6.3)	1 (2.0)	1 (0.7)	2 (1.1)	3 (1.2)
咽頭炎	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	1 (0.7)	2 (1.1)	2 (0.8)
尿路感染	0 (0.0)	1 (3.3)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	2 (0.8)
動静脈瘻部位感染	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
蜂巣炎	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)

データカットオフ [redacted]年[redacted]月[redacted]日

EvoMab = evolocumab (AMG 145)、N = 20110271 試験に組み入れ投与した被験者数

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表 2.7.6.28-12　日本人集団を含むグローバル集団の治験中に発現した器官別大分類及び基本語別の有害事象（中間解析対象集団）（続き）

器官別大分類 基本語	20110233 親試験から移行			20110271 非親試験/その他親試験から移行			
	Part A EvoMab (N = 8) n (%)	Part B EvoMab (N = 30) n (%)	Part B プラセボ (N = 16) n (%)	組入れ時アフェレーシス (N = 50) n (%)	組入れ時非アフェレーシス (N = 138) n (%)	合計 (N = 188) n (%)	合計 (N = 242) n (%)
感染症および寄生虫症（続き）							
結膜炎	0 (0.0)	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
膀胱炎	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)	1 (0.4)
感染性湿疹	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
ウイルス性消化管感染	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
切開部位膿瘍	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
口腔ヘルペス	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)	1 (0.4)
副鼻腔炎	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
皮膚感染	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)	1 (0.4)
足部白癬	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
ウイルス性上気道感染	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
傷害、中毒および処置合併症	1 (12.5)	1 (3.3)	0 (0.0)	4 (8.0)	9 (6.5)	13 (6.9)	15 (6.2)

データカットオフ [redacted]年[redacted]月[redacted]日

EvoMab = evolocumab (AMG 145)、N = 20110271 試験に組み入れ投与した被験者数

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表 2.7.6.28-12　日本人集団を含むグローバル集団の治験中に発現した器官別大分類及び基本語別の有害事象（中間解析対象集団）（続き）

器官別大分類 基本語	20110233 親試験から移行			20110271 非親試験/その他親試験から移行			
	Part A EvoMab (N = 8) n (%)	Part B EvoMab (N = 30) n (%)	Part B プラセボ (N = 16) n (%)	組入れ時アフェレーシス (N = 50) n (%)	組入れ時非アフェレーシス (N = 138) n (%)	合計 (N = 188) n (%)	合計 (N = 242) n (%)
傷害、中毒および処置合併症（続き）							
挫傷	1 (12.5)	0 (0.0)	0 (0.0)	1 (2.0)	1 (0.7)	2 (1.1)	3 (1.2)
上顎炎	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.4)	2 (1.1)	2 (0.8)
裂傷	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	1 (0.7)	2 (1.1)	2 (0.8)
動静脈瘻閉塞	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)	1 (0.4)
動静脈瘻血栓症	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)	1 (0.4)
転倒	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
手骨折	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
肉離れ	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
処置による疼痛	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
サンバーン	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)	1 (0.4)
腱損傷	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
外傷性関節障害	0 (0.0)	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)

データカットオフ [redacted]年[redacted]月[redacted]日

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表 2.7.6.28-12　日本人集団を含むグローバル集団の治験中に発現した器官別大分類及び基本語別の有害事象（中間解析対象集団）（続き）

器官別大分類 基本語	20110233 親試験から移行			20110271 非親試験/その他親試験から移行			
	Part A EvoMab (N = 8) n (%)	Part B EvoMab (N = 30) n (%)	Part B プラセボ (N = 16) n (%)	組入れ時アフェレーシス (N = 50) n (%)	組入れ時非アフェレーシス (N = 138) n (%)	合計 (N = 188) n (%)	合計 (N = 242) n (%)
臨床検査	0 (0.0)	3 (10.0)	1 (6.3)	6 (12.0)	5 (3.6)	11 (5.9)	15 (6.2)
頚動脈内膜中膜肥厚度増加	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.0)	3 (2.2)	5 (2.7)	5 (2.1)
血中クレアチンホスホキナーゼ増加	0 (0.0)	3 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.2)
アラニンアミノトランスフェラーゼ増加	0 (0.0)	0 (0.0)	1 (6.3)	1 (2.0)	0 (0.0)	1 (0.5)	2 (0.8)
アスパラギン酸アミノトランスフェラーゼ増加	0 (0.0)	0 (0.0)	1 (6.3)	1 (2.0)	0 (0.0)	1 (0.5)	2 (0.8)
血中重炭酸塩減少	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)	1 (0.4)
血中鉄減少	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
血中亜鉛減少	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)	1 (0.4)
肝機能検査異常	0 (0.0)	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
血小板数減少	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)	1 (0.4)

データカットオフ [redacted]年[redacted]月[redacted]日

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器官別大分類 基本語	20110233 親試験から移行			20110271 非親試験/その他親試験から移行			
	Part A EvoMab (N = 8) n (%)	Part B EvoMab (N = 30) n (%)	Part B プラセボ (N = 16) n (%)	組入れ時アフェレーシス (N = 50) n (%)	組入れ時非アフェレーシス (N = 138) n (%)	合計 (N = 188) n (%)	合計 (N = 242) n (%)
臨床検査（続き）							
プロトロンビン時間延長	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
ビタミンD減少	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)	1 (0.4)
代謝および栄養障害	0 (0.0)	0 (0.0)	3 (18.8)	0 (0.0)	2 (1.4)	2 (1.1)	5 (2.1)
耐糖能障害	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.4)	2 (1.1)	2 (0.8)
痛風	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
高血糖	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
鉄欠乏	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
筋骨格系および結合組織障害	1 (12.5)	0 (0.0)	2 (12.5)	12 (24.0)	24 (17.4)	36 (19.1)	39 (16.1)

データカットオフ [redacted]年[redacted]月[redacted]日.

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	Part A EvoMab (N = 8) n (%)	Part B EvoMab (N = 30) n (%)	Part B プラセボ (N = 16) n (%)	組入れ時アフェレーシス (N = 50) n (%)	組入れ時非アフェレーシス (N = 138) n (%)	合計 (N = 188) n (%)	合計 (N = 242) n (%)
筋骨格系および結合組織障害（続き）							
筋肉痛	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.0)	6 (4.3)	8 (4.3)	8 (3.3)
背部痛	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.0)	4 (2.9)	6 (3.2)	6 (2.5)
筋痙縮	0 (0.0)	0 (0.0)	0 (0.0)	3 (6.0)	3 (2.2)	6 (3.2)	6 (2.5)
関節痛	0 (0.0)	0 (0.0)	1 (6.3)	1 (2.0)	3 (2.2)	4 (2.1)	5 (2.1)
腱炎	1 (12.5)	0 (0.0)	1 (6.3)	0 (0.0)	3 (2.2)	3 (1.6)	5 (2.1)
四肢痛	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.0)	2 (1.4)	4 (2.1)	4 (1.7)
頚部痛	0 (0.0)	0 (0.0)	0 (0.0)	3 (6.0)	0 (0.0)	3 (1.6)	3 (1.2)
筋骨格痛	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	1 (0.7)	2 (1.1)	2 (0.8)
滑液包炎	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
側腹部痛	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
椎間板圧迫	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
関節硬直	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
筋肉疲労	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)

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データカットオフ [redacted]年[redacted]月[redacted]日.

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	Part A EvoMab (N = 8) n (%)	Part B EvoMab (N = 30) n (%)	Part B プラセボ (N = 16) n (%)	組入れ時アフェレーシス (N = 50) n (%)	組入れ時非アフェレーシス (N = 138) n (%)	合計 (N = 188) n (%)	合計 (N = 242) n (%)
筋骨格系および結合組織障害（続き）							
筋骨格硬直	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
頚部腫瘤	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
骨粗鬆症	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
顎痛	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)	1 (0.4)
重感	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)	1 (0.4)
変形性脊椎症	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
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）	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	2 (1.4)	2 (1.1)	3 (1.2)
脂肪腫	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	1 (0.7)	1 (0.5)	2 (0.8)
皮膚乳頭腫	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)

データカットオフ [redacted]年[redacted]月[redacted]日.

EvoMab = evolocumab (AMG 145)、N = 20110271 試験に組み入れ投与した被験者数

MedDRA 17.0 版でコード化

有害事象の要約には臨床評価項目と判定された事象は含まれない。

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表 2.7.6.28-12　日本人集団を含むグローバル集団の治験中に発現した器官別大分類及び基本語別の有害事象（中間解析対象集団）（続き）

器官別大分類 基本語	20110233 親試験から移行			20110271 非親試験/その他親試験から移行			
	Part A EvoMab (N = 8) n (%)	Part B EvoMab (N = 30) n (%)	Part B プラセボ (N = 16) n (%)	組入れ時アフェレーシス (N = 50) n (%)	組入れ時非アフェレーシス (N = 138) n (%)	合計 (N = 188) n (%)	合計 (N = 242) n (%)
神経系障害	1 (12.5)	4 (13.3)	2 (12.5)	13 (26.0)	12 (8.7)	25 (13.3)	32 (13.2)
頭痛	1 (12.5)	1 (3.3)	0 (0.0)	4 (8.0)	7 (5.1)	11 (5.9)	13 (5.4)
浮動性めまい	0 (0.0)	1 (3.3)	0 (0.0)	2 (4.0)	3 (2.2)	5 (2.7)	6 (2.5)
嗜眠	0 (0.0)	0 (0.0)	0 (0.0)	4 (8.0)	1 (0.7)	5 (2.7)	5 (2.1)
失神寸前の状態	0 (0.0)	0 (0.0)	1 (6.3)	1 (2.0)	2 (1.4)	3 (1.6)	4 (1.7)
片頭痛	0 (0.0)	1 (3.3)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)	2 (0.8)
錯感覚	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.0)	0 (0.0)	2 (1.1)	2 (0.8)
頚動脈閉塞	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)	1 (0.4)
手根管症候群	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
感覚鈍麻	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)	1 (0.4)
記憶障害	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
神経痛	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)	1 (0.4)
下肢静止不能症候群	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
緊張性頭痛	0 (0.0)	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)

データカットオフ [redacted]年[redacted]月[redacted]日.

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[redacted]

表 2.7.6.28-12　日本人集団を含むグローバル集団の治験中に発現した器官別大分類及び基本語別の有害事象（中間解析対象集団）（続き）

器官別大分類 基本語	20110233 親試験から移行 Part A EvoMab (N = 8) n (%)	 Part B EvoMab (N = 30) n (%)	 Part B プラセボ (N = 16) n (%)	20110271 非親試験/その他親試験から移行 組入れ時アフェレーシス (N = 50) n (%)	 組入れ時非アフェレーシス (N = 138) n (%)	 合計 (N = 188) n (%)	 合計 (N = 242) n (%)
神経系障害（続き）							
一過性脳虚血発作	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
精神障害	1 (12.5)	2 (6.7)	0 (0.0)	1 (2.0)	4 (2.9)	5 (2.7)	8 (3.3)
不眠症	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.2)	3 (1.6)	3 (1.2)
不安	1 (12.5)	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.8)
抑うつ気分	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)	1 (0.4)
悪夢	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
パニック発作	0 (0.0)	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
腎および尿路障害	1 (12.5)	0 (0.0)	1 (6.3)	1 (2.0)	2 (1.4)	3 (1.6)	5 (2.1)
血尿	1 (12.5)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)	2 (0.8)
排尿困難	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)

データカットオフ [redacted]年[redacted]月[redacted]日

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表 2.7.6.28-12　日本人集団を含むグローバル集団の治験中に発現した器官別大分類及び基本語別の有害事象（中間解析対象集団）（続き）

器官別大分類 基本語	20110233 親試験から移行 Part A EvoMab (N = 8) n (%)	20110233 親試験から移行 Part B EvoMab (N = 30) n (%)	20110233 親試験から移行 Part B プラセボ (N = 16) n (%)	20110271 非親試験/その他親試験から移行 組入れ時アフェレーシス (N = 50) n (%)	20110271 非親試験/その他親試験から移行 組入れ時非アフェレーシス (N = 138) n (%)	20110271 非親試験/その他親試験から移行 合計 (N = 188) n (%)	合計 (N = 242) n (%)
腎および尿路障害（続き）							
夜間頻尿	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
頻尿	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
生殖系および乳房障害	0 (0.0)	0 (0.0)	1 (6.3)	3 (6.0)	2 (1.4)	5 (2.7)	6 (2.5)
月経困難症	0 (0.0)	0 (0.0)	1 (6.3)	1 (2.0)	0 (0.0)	1 (0.5)	2 (0.8)
乳房嚢胞	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)	1 (0.4)
乳房痛	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
月経過多	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)	1 (0.4)
子宮脱	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
呼吸器、胸郭および縦隔障害	1 (12.5)	0 (0.0)	0 (0.0)	5 (10.0)	6 (4.3)	11 (5.9)	12 (5.0)

データカットオフ [redacted]年[redacted]月[redacted]日

EvoMab = evolocumab (AMG 145)、N = 20110271 試験に組み入れ投与した被験者数

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表 2.7.6.28-12　日本人集団を含むグローバル集団の治験中に発現した器官別大分類及び基本語別の有害事象（中間解析対象集団）（続き）

器官別大分類 基本語	20110233 親試験から移行 Part A EvoMab (N = 8) n (%)	20110233 親試験から移行 Part B EvoMab (N = 30) n (%)	20110233 親試験から移行 Part B プラセボ (N = 16) n (%)	20110271 非親試験/その他親試験から移行 組入れ時アフェレーシス (N = 50) n (%)	20110271 非親試験/その他親試験から移行 組入れ時非アフェレーシス (N = 138) n (%)	20110271 非親試験/その他親試験から移行 合計 (N = 188) n (%)	合計 (N = 242) n (%)
呼吸器、胸郭および縦隔障害　（続き）							
咳嗽	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.0)	2 (1.4)	4 (2.1)	4 (1.7)
口腔咽頭痛	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.0)	1 (0.7)	3 (1.6)	3 (1.2)
喘息	1 (12.5)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)	2 (0.8)
鼻出血	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.4)	2 (1.1)	2 (0.8)
呼吸困難	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
鼻閉	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
アレルギー性鼻炎	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)	1 (0.4)
鼻漏	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)	1 (0.4)
皮膚および皮下組織障害	0 (0.0)	2 (6.7)	1 (6.3)	5 (10.0)	11 (8.0)	16 (8.5)	19 (7.9)
発疹	0 (0.0)	1 (3.3)	0 (0.0)	3 (6.0)	1 (0.7)	4 (2.1)	5 (2.1)
脱毛症	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.2)	3 (1.6)	3 (1.2)

データカットオフ [redacted]年[redacted]月[redacted]日.

EvoMab = evolocumab (AMG 145)、N = 20110271 試験に組み入れ投与した被験者数

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表 2.7.6.28-12　日本人集団を含むグローバル集団の治験中に発現した器官別大分類及び基本語別の有害事象（中間解析対象集団）（続き）

器官別大分類 基本語	20110233 親試験から移行			20110271 非親試験/その他親試験から移行			
	Part A EvoMab (N = 8) n (%)	Part B EvoMab (N = 30) n (%)	Part B プラセボ (N = 16) n (%)	組入れ時アフェレーシス (N = 50) n (%)	組入れ時非アフェレーシス (N = 138) n (%)	合計 (N = 188) n (%)	合計 (N = 242) n (%)
皮膚および皮下組織障害（続き）							
多汗症	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	2 (1.4)	3 (1.6)	3 (1.2)
そう痒症	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	1 (0.7)	2 (1.1)	2 (0.8)
蕁麻疹	0 (0.0)	1 (3.3)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)	2 (0.8)
ざ瘡	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
接触性皮膚炎	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
薬疹	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
斑状出血	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
湿疹	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
紅斑	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)	1 (0.4)
爪破損	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
全身性そう痒症	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
皮膚病変	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
皮膚腫瘤	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)

データカットオフ [redacted]年[redacted]月[redacted]日

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[redacted]

表 2.7.6.28-12　日本人集団を含むグローバル集団の治験中に発現した器官別大分類及び基本語別の有害事象（中間解析対象集団）（続き）

器官別大分類 基本語	20110233 親試験から移行			20110271 非親試験/その他親試験から移行			
	Part A EvoMab (N = 8) n (%)	Part B EvoMab (N = 30) n (%)	Part B プラセボ (N = 16) n (%)	組入れ時アフェレーシス (N = 50) n (%)	組入れ時非アフェレーシス (N = 138) n (%)	合計 (N = 188) n (%)	合計 (N = 242) n (%)
皮膚および皮下組織障害（続き）							
黄色板腫	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)	1 (0.4)
社会環境	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.4)	2 (1.1)	2 (0.8)
元タバコ使用者	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
タバコ使用者	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
血管障害	1 (12.5)	1 (3.3)	1 (6.3)	1 (2.0)	4 (2.9)	5 (2.7)	8 (3.3)
高血圧	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	2 (0.8)
大動脈狭窄	0 (0.0)	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
潮紅	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
血腫	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)	1 (0.4)
低血圧	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
起立性低血圧	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)

データカットオフ [redacted]年[redacted]月[redacted]日

EvoMab = evolocumab (AMG 145)、N =20110271 試験に組み入れ投与した被験者数

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[redacted]

表 2.7.6.28-12　日本人集団を含むグローバル集団のに発現した器官別大分類及び基本語別の有害事象（中間解析対象集団）（続き）

器官別大分類 基本語	20110233 親試験から移行 Part A EvoMab (N = 8) n (%)	 Part B EvoMab (N = 30) n (%)	 Part B プラセボ (N = 16) n (%)	20110271 非親試験/その他親試験から移行 組入れ時アフェレーシス (N = 50) n (%)	 組入れ時非アフェレーシス (N = 138) n (%)	 合計 (N = 188) n (%)	 合計 (N = 242) n (%)
血管障害（続き）							
末梢動脈解離	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)

データカットオフ [redacted]年[redacted]月[redacted]日
EvoMab=Evolocumab (AMG 145)、N = 20110271 試験に組み入れ投与した被験者数
MedDRA 17.0 版でコード化
有害事象の要約には臨床評価項目と判定された事象は含まれない。

[redacted]

表 2.7.6.28-13　日本人集団の治験中に発現した器官別大分類及び基本語別の有害事象　20110271 試験

器官別大分類 基本語	重症 FH 合計 (N = 1) n (%)	HoFH の日本人 組入れ時アフェレーシス (N = 5) n (%)	HoFH の日本人 組入れ時非アフェレーシス (N = 2) n (%)	HoFH の日本人 合計 (N = 7) n (%)	合計 (N = 8) n (%)
有害事象発現例	1(100.0)	5 (100.0)	2 (100.0)	7 (100.0)	8(100.0)
血液およびリンパ系障害	0 (0.0)	1 (20.0)	0 (0.0)	1 (14.3)	1(12.5)
貧血	0 (0.0)	1 (20.0)	0 (0.0)	1 (14.3)	1(12.5)
心臓障害	0 (0.0)	1 (20.0)	0 (0.0)	1 (14.3)	1(12.5)
心筋虚血	0 (0.0)	1 (20.0)	0 (0.0)	1 (14.3)	1(12.5)
胃腸障害	1(100.0)	1 (20.0)	0 (0.0)	1 (14.3)	2(25.0)
下痢	0 (0.0)	1 (20.0)	0 (0.0)	1 (14.3)	1(12.5)
舌炎	1(100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1(12.5)
感染症および寄生虫症	0 (0.0)	3 (60.0)	0 (0.0)	3 (42.9)	3(37.5)
鼻咽頭炎	0 (0.0)	2 (40.0)	0 (0.0)	2 (28.6)	2(25.0)
インフルエンザ	0 (0.0)	1 (20.0)	0 (0.0)	1 (14.3)	1(12.5)
口腔ヘルペス	0 (0.0)	1 (20.0)	0 (0.0)	1 (14.3)	1(12.5)
臨床検査	1(100.0)	2 (40.0)	2 (100.0)	4 (57.1)	5(62.5)
頚動脈内膜中膜肥厚度増加	1(100.0)	2 (40.0)	2 (100.0)	4 (57.1)	5(62.5)
神経系障害	0 (0.0)	2 (40.0)	0 (0.0)	2 (28.6)	2(25.0)
浮動性めまい	0 (0.0)	1 (20.0)	0 (0.0)	1 (14.3)	1(12.5)
感覚鈍麻	0 (0.0)	1 (20.0)	0 (0.0)	1 (14.3)	1(12.5)
皮膚および皮下組織障害	1(100.0)	0 (0.0)	1 (50.0)	1 (14.3)	2(25.0)

表 2.7.6.28-13　日本人集団の治験中に発現した器官別大分類及び基本語別の有害事象　20110271 試験（続き）

器官別大分類 基本語	重症 FH 合計 (N = 1) n (%)	HoFH の日本人 組入れ時アフェレーシス (N = 5) n (%)	HoFH の日本人 組入れ時非アフェレーシス (N = 2) n (%)	HoFH の日本人 合計 (N = 7) n (%)	合計 (N = 8) n (%)
皮膚および皮下組織障害（続き）					
湿疹	0 (0.0)	0 (0.0)	1 (50.0)	1 (14.3)	1(12.5)
多汗症	1(100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1(12.5)
一般・全身障害および投与部位の状態	1(100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1(12.5)
倦怠感	1(100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1(12.5)
発熱	1(100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1(12.5)
筋骨格系および結合組織障害	1(100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1(12.5)
筋痙縮	1(100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1(12.5)
筋肉痛	1(100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1(12.5)
頚部腫瘤	1(100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1(12.5)
呼吸器、胸郭および縦隔障害	1(100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1(12.5)
鼻閉	1(100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1(12.5)

データカットオフ [redacted]年[redacted]月[redacted]日
N = 20110271 試験に組み入れ投与した日本人 HoFH 被験者数、HoFH=家族性高コレステロール血症ホモ接合体、EvoMab=Evolocumab (AMG 145)
MedDRA 17.0 版でコード化

[redacted]

2.6.1.3　主な有害事象

中間解析対象集団で最も多く認められた有害事象は、鼻咽頭炎（8.7%）、頭痛（5.4%）、上気道感染（4.5%）、注射部位紅斑（4.1%）、インフルエンザ（3.7%）及び筋肉痛（3.3%）であった。

HoFH 中間解析対象集団及び重症 FH 中間解析対象集団で最も多く認められた有害事象は、中間解析対象集団で認められた有害事象と類似していた。中間解析対象集団の 5 例（2.1%）に頚動脈内膜中膜肥厚度増加の有害事象が認められ、その内訳は、HoFH 中間解析対象集団が 4 例（4.0%）、重症 FH 中間解析対象集団が 1 例（0.7%）であった。これらの各有害事象はグレード 1 で非重篤であ

り、全FH被験者に対して超音波検査を年1回定期的に実施している単一の実施医療機関の治験担当医師より報告された。

2.6.1.4　治験薬投与と関連のある有害事象

日本人集団を含むグローバル集団：

日本人集団を含むグローバル集団の器官別大分類及び基本語別の治験薬投与と関連のある有害事象を表2.7.6.28-14に示す。

日本人集団を含むグローバル集団の43例（17.8%）に治験薬投与と関連のある有害事象が1件以上認められた。最も多く認められた治験薬投与と関連のある有害事象は注射部位紅斑（3.3%）であった。

日本人集団：

日本人集団の器官別大分類及び基本語別の治験薬投与と関連のある有害事象を表2.7.6.28-15に示す。

日本人集団8例のうち、HoFH被験者の4例及び重症FHの1例に治験薬投与と関連のある有害事象が1件以上認められた。最も多く認められた治験薬投与と関連のある有害事象は頚動脈内膜中膜肥厚度増加5例（62.5%）であった。

このうち、重篤な有害事象として日本人HoFH被験者の1例（[redacted]）に心筋虚血が認められた。試験開始から約8カ月後及び前回のevolocumab 420 mg投与から約2カ月後、不安定狭心症の既往を有する61歳の男性にグレード3の心筋虚血が認められた。本被験者は心筋虚血のため入院し、経皮的冠動脈インターベンションが行われステントが装着された。心筋虚血は4日以内に回復した。

表 2.7.6.28-14　日本人集団を含むグローバル集団の治験薬投与と関連のある器官別大分類及び基本語別の有害事象（中間解析対象集団）

	20110233 親試験から移行			20110271 非親試験/その他親試験から移行			
器官別大分類 基本語	Part A EvoMab (N = 8) n (%)	Part B EvoMab (N = 30) n (%)	Part B プラセボ (N = 16) n (%)	組入れ時アフェレーシス (N = 50) n (%)	組入れ時非アフェレーシス (N = 138) n (%)	合計 (N = 188) n (%)	合計 (N = 242) n (%)
有害事象発現例	0 (0.0)	2 (6.7)	2 (12.5)	17 (34.0)	22 (15.9)	39 (20.7)	43 (17.8)
血液およびリンパ系障害	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)	1 (0.4)
貧血	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)	1 (0.4)
心臓障害	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)	1 (0.4)
心筋虚血	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)	1 (0.4)
胃腸障害	0 (0.0)	0 (0.0)	1 (6.3)	4 (8.0)	3 (2.2)	7 (3.7)	8 (3.3)
下痢	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	1 (0.7)	2 (1.1)	2 (0.8)

データカットオフ [redacted]年[redacted]月[redacted]日

EvoMab = evolocumab (AMG 145)、N = 20110271 試験に組み入れ投与した被験者数

MedDRA 17.0 版でコード化

[redacted]

表 2.7.6.28-14　日本人集団を含むグローバル集団の治験薬投与と関連のある器官別大分類及び基本語別の有害事象（中間解析対象集団）（続き）

器官別大分類 基本語	20110233 親試験から移行			20110271 非親試験/その他親試験から移行			
	Part A EvoMab (N = 8) n (%)	Part B EvoMab (N = 30) n (%)	Part B プラセボ (N = 16) n (%)	組入れ時アフェレーシス (N = 50) n (%)	組入れ時非アフェレーシス (N = 138) n (%)	合計 (N = 188) n (%)	合計 (N = 242) n (%)
胃腸障害（続き）							
悪心	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.0)	0 (0.0)	2 (1.1)	2 (0.8)
腹部膨満	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)	1 (0.4)
腹痛	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
便習慣変化	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
便秘	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)	1 (0.4)
放屁	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
一般・全身障害および投与部位の状態	0 (0.0)	0 (0.0)	1 (6.3)	9 (18.0)	8 (5.8)	17 (9.0)	18 (7.4)
注射部位紅斑	0 (0.0)	0 (0.0)	0 (0.0)	6 (12.0)	2 (1.4)	8 (4.3)	8 (3.3)
注射部位内出血	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.0)	2 (1.4)	4 (2.1)	4 (1.7)
注射部位疼痛	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.0)	2 (1.4)	4 (2.1)	4 (1.7)

データカットオフ [redacted]年[redacted]月[redacted]日

EvoMab = evolocumab (AMG 145)、 N = 20110271 試験に組み入れ投与した被験者数

MedDRA 17.0 版でコード化

[redacted]

表 2.7.6.28-14　日本人集団を含むグローバル集団の治験薬投与と関連のある器官別大分類及び基本語別の有害事象（中間解析対象集団）（続き）

器官別大分類 基本語	20110233 親試験から移行 Part A EvoMab (N = 8) n (%)	20110233 親試験から移行 Part B EvoMab (N = 30) n (%)	20110233 親試験から移行 Part B プラセボ (N = 16) n (%)	20110271 非親試験/その他親試験から移行 組入れ時アフェレーシス (N = 50) n (%)	20110271 非親試験/その他親試験から移行 組入れ時非アフェレーシス (N = 138) n (%)	20110271 非親試験/その他親試験から移行 合計 (N = 188) n (%)	合計 (N = 242) n (%)
一般・全身障害および投与部位の状態（続き）							
無力症	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.4)	2 (1.1)	2 (0.8)
疲労	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.4)	2 (1.1)	2 (0.8)
注射部位そう痒感	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	1 (0.7)	2 (1.1)	2 (0.8)
注射部位腫脹	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.0)	0 (0.0)	2 (1.1)	2 (0.8)
硬結	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)	1 (0.4)
インフルエンザ様疾患	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)	1 (0.4)
注射部位出血	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
注射部位硬結	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)	1 (0.4)
注射部位結節	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)	1 (0.4)
注射部位反応	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)	1 (0.4)
医療機器合併症	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
臨床検査	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.0)	3 (2.2)	5 (2.7)	5 (2.1)

データカットオフ [redacted]年[redacted]月[redacted]日

EvoMab = evolocumab (AMG 145)、N = 20110271 試験に組み入れ投与した被験者数

MedDRA 17.0 版でコード化

[redacted]

表 2.7.6.28-14　日本人集団を含むグローバル集団の治験薬投与と関連のある器官別大分類及び基本語別の有害事象（中間解析対象集団）（続き）

器官別大分類 基本語	20110233 親試験から移行 Part A EvoMab (N = 8) n (%)	20110233 親試験から移行 Part B EvoMab (N = 30) n (%)	20110233 親試験から移行 Part B プラセボ (N = 16) n (%)	20110271 非親試験/その他親試験から移行 組入れ時アフェレーシス (N = 50) n (%)	20110271 非親試験/その他親試験から移行 組入れ時非アフェレーシス (N = 138) n (%)	20110271 非親試験/その他親試験から移行 合計 (N = 188) n (%)	合計 (N = 242) n (%)
臨床検査（続き）							
頚動脈内膜中膜肥厚度増加	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.0)	3 (2.2)	5 (2.7)	5 (2.1)
筋骨格系および結合組織障害	0 (0.0)	0 (0.0)	0 (0.0)	5 (10.0)	5 (3.6)	10 (5.3)	10 (4.1)
筋痙縮	0 (0.0)	0 (0.0)	0 (0.0)	3 (6.0)	2 (1.4)	5 (2.7)	5 (2.1)
筋肉痛	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	1 (0.7)	2 (1.1)	2 (0.8)
関節硬直	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
四肢痛	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
重感	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)	1 (0.4)
神経系障害	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.0)	4 (2.9)	6 (3.2)	6 (2.5)

データカットオフ [redacted]年[redacted]月[redacted]日

EvoMab = evolocumab (AMG 145)、 N = 20110271 試験に組み入れ投与した被験者数

MedDRA 17.0 版でコード化

[redacted]

表 2.7.6.28-14　日本人集団を含むグローバル集団の治験薬投与と関連のある器官別大分類及び基本語別の有害事象（中間解析対象集団）（続き）

器官別大分類 基本語	20110233 親試験から移行 Part A EvoMab (N = 8) n (%)	20110233 親試験から移行 Part B EvoMab (N = 30) n (%)	20110233 親試験から移行 Part B プラセボ (N = 16) n (%)	20110271 非親試験/その他親試験から移行 組入れ時アフェレーシス (N = 50) n (%)	20110271 非親試験/その他親試験から移行 組入れ時非アフェレーシス (N = 138) n (%)	20110271 非親試験/その他親試験から移行 合計 (N = 188) n (%)	合計 (N = 242) n (%)
神経系障害（続き）							
頭痛	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.0)	3 (2.2)	5 (2.7)	5 (2.1)
浮動性めまい	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.4)	2 (1.1)	2 (0.8)
嗜眠	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	1 (0.7)	2 (1.1)	2 (0.8)
記憶障害	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
精神障害	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
不眠症	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
呼吸器、胸郭および縦隔障害	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
口腔咽頭痛	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
皮膚および皮下組織障害	0 (0.0)	2 (6.7)	0 (0.0)	2 (4.0)	4 (2.9)	6 (3.2)	8 (3.3)

データカットオフ [redacted]年[redacted]月[redacted]日

EvoMab = evolocumab (AMG 145)、 N = 20110271 試験に組み入れ投与した被験者数

MedDRA 17.0 版でコード化

[redacted]

表 2.7.6.28-14　日本人集団を含むグローバル集団の治験薬投与と関連のある器官別大分類及び基本語別の有害事象（中間解析対象集団）（続き）

器官別大分類 基本語	20110233 親試験から移行 Part A EvoMab (N = 8) n (%)	20110233 親試験から移行 Part B EvoMab (N = 30) n (%)	20110233 親試験から移行 Part B プラセボ (N = 16) n (%)	20110271 非親試験/その他親試験から移行 組入れ時アフェレーシス (N = 50) n (%)	20110271 非親試験/その他親試験から移行 組入れ時非アフェレーシス (N = 138) n (%)	20110271 非親試験/その他親試験から移行 合計 (N = 188) n (%)	合計 (N = 242) n (%)
皮膚および皮下組織障害（続き）							
脱毛症	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.4)	2 (1.1)	2 (0.8)
そう痒症	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	1 (0.7)	2 (1.1)	2 (0.8)
発疹	0 (0.0)	1 (3.3)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)	2 (0.8)
蕁麻疹	0 (0.0)	1 (3.3)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)	2 (0.8)
紅斑	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)	1 (0.4)
多汗症	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)	1 (0.4)
全身性そう痒症	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
血管障害	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)
潮紅	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.5)	1 (0.4)

データカットオフ [redacted]年[redacted]月[redacted]日

EvoMab = evolocumab (AMG 145)、N = 20110271 試験に組み入れ投与した被験者数

MedDRA 17.0 版でコード化

[redacted]

表 2.7.6.28-15　日本人集団の治験薬投与と関連のある器官別大分類及び基本語別の有害事象
Study 20110271

器官別大分類 基本語	重症 FH 合計 (N = 1) n (%)	HoFH 日本人 組入れ時アフェレーシス (N = 5) n (%)	HoFH 日本人 組入れ時非アフェレーシス (N = 2) n (%)	HoFH 日本人 合計 (N = 7) n (%)	合計 (N = 8) n (%)
有害事象発現例	1(100.0)	3(60.0)	2 (100.0)	5 (71.4)	6(75.0)
血液およびリンパ系障害	0 (0.0)	1 (20.0)	0 (0.0)	1 (14.3)	1(12.5)
貧血	0 (0.0)	1 (20.0)	0 (0.0)	1 (14.3)	1(12.5)
心臓障害	0 (0.0)	1 (20.0)	0 (0.0)	1 (14.3)	1(12.5)
心筋虚血	0 (0.0)	1 (20.0)	0 (0.0)	1 (14.3)	1(12.5)
臨床検査	1(100.0)	2 (40.0)	2 (100.0)	4 (57.1)	5(62.5)
頚動脈内膜中膜肥厚度増加	1(100.0)	2 (40.0)	2 (100.0)	4 (57.1)	5(62.5)

データカットオフ　[redacted]年[redacted]月[redacted]日
N = 20110271 試験に組み入れ投与した日本人 HoFH 被験者数、HoFH=家族性高コレステロール血症ホモ接合体、EvoMab=Evolocumab (AMG 145)
MedDRA 17.0 版でコード化

[redacted]

2.6.1.5　医療機器と関連のある有害事象

医療機器を 1 回以上使用した中間解析対象集団の 207 例のうち、14 例に医療機器と関連のある有害事象が認められた。複数の被験者に認められた医療機器と関連のある有害事象は、注射部位内出血（5 例）、注射部位紅斑（3 例）、注射部位血腫（3 例）及び注射部位出血（2 例）であった。治験中に発現した医療機器関連の有害事象が認められた被験者のうち、5 例が HoFH、9 例が重症 FH であり、医療機器関連の有害事象に重篤な有害事象及びグレード 3 以上の有害事象は認められなかった。

2.6.1.6　有害事象による投与中止

中間解析対象集団の 2 例が有害事象により evolocumab の投与を中止し、その内訳は、HoFH 中間解析対象集団及び重症 FH 中間解析対象集団の各 1 例であった。いずれも非重篤であった。アトルバスタチンを併用していた 1 例（HoFH 中間解析対象集団の被験者 [redacted]）は、グレード 3 の発疹により、Day 212 に evolocumab の投与を中止し、治験担当医師により evolocumab と関連がある

と判断された。この発疹は消失した。甲状腺機能低下症の既往歴を有し、ピタバスタチンを併用していた別の1例（重症FH中間解析対象集団の日本人被験者[redacted]）は、Day 64からDay 71の間に発現し、それぞれグレード1又は2の舌炎、多汗症、倦怠感、筋痙縮、筋肉痛、鼻閉及び発熱の有害事象によりevolocumabの投与を中止し、治験担当医師によりevolocumabと関連なしと判断された。いずれの被験者でも、ベースライン時又はOLE試験中に抗evolocumab抗体の所見は認められなかった。

2.6.1.7　死に至った有害事象

本試験において中間解析のデータカットオフ日までに死亡は認められなかった。

2.6.1.8　重篤な有害事象

日本人集団を含むグローバル集団の中間解析対象集団の13例（5.4%）に14件の重篤な有害事象が認められた。重篤な有害事象のうち11件はHoFH中間解析対象集団の10例に認められ、その内訳は、1例に2件の重篤な有害事象（大動脈狭窄及び冠動脈疾患）と、狭心症、大動脈弁疾患、動静脈瘻血栓症、頚動脈閉塞、胸痛、冠動脈閉塞、血尿、心筋虚血及び非心臓性胸痛が各1例であった。重篤な有害事象のうち3件は重症FH中間解析対象集団の3例に認められ、その内訳は、狭心症、大腸炎及び子宮脱が各1例であった。大動脈弁関連の有害事象が認められた2例には大動脈弁疾患の既往歴があり、同様に、冠疾患関連の有害事象が認められた被験者には冠疾患の既往の病理学的所見があった。治験担当医師は、心筋虚血の重篤な有害事象はevolocumabと関連があり、医療機器と関連なしと判断した。ほかの治験中に発現した重篤な有害事象については、治験担当医師はいずれもevolocumabと関連なし又は医療機器と関連なしと判断した。

重篤な有害事象のうち2件（冠動脈閉塞及び非心臓性胸痛）は青年被験者に認められた。いずれの重篤な有害事象も治験薬の曝露期間中に認められた。

重篤な有害事象のうち、日本人被験者に認められた有害事象は、心筋虚血 1 例（上述）であった。

2.6.1.9　心血管系評価項目であると判定された事象

全死亡、心血管系疾患に起因する死亡、心筋梗塞、不安定狭心症のための入院、冠動脈血行再建、脳卒中、一過性脳虚血発作及び心不全のための入院の事象については、独立した臨床事象評価委員会（CEC）による判定を行った。中間解析対象集団の3例（1.2%）に心血管系評価項目と明確に判定された事象が認められ、その内訳は、HoFH被験者が2例、重症FH被験者が1例であった。3例すべてが経皮的冠動脈インターベンションを受けていた。冠動脈以外の血行再建は1例（被験者[redacted]）に認められた。冠動脈以外の血行再建についてはCECによる判定は行わなかった。心血管系疾患に起因する死亡は認められなかった。

2.6.2　臨床検査値の評価

治験薬投与と関連のある臨床的に重要な臨床検査値の異常は認められなかった。OLE の 36 週時に、HoFH 被験者 2 例に ULN の 10 倍を超える CK 値上昇が認められた。両被験者は CK 値上昇直前に激しい身体活動を行っていた。2 例はいずれも evolocumab 投与が継続され、次回評価時の CK 値は ULN の 5 倍未満であった。また、これらの被験者のうち 1 例では、OLE の 48 週時に ULN の 5 倍を超える CK 値上昇が認められたが、evolocumab 投与が継続され、次回評価時に消失した。

HoFH 被験者 4 例に、いずれかのベースライン後来院時に ULN の 3 倍を超える ALT 又は AST が認められ、そのうち 3 例では Day 1 に ALT 又は AST の上昇が認められ、1 例では Day 1 の ALT 及び AST は正常であった。これらの各被験者では、ALT 又は AST の上昇は次回評価時に ULN の 3 倍未満に戻った。いずれの来院時にも、ALT 又は AST が ULN の 3 倍超かつ総ビリルビンが ULN の 2 倍超又は INR が 1.5 超であった被験者はいなかった。

その他の臨床検査値がベースライン時のグレード 0～2 からベースライン後にグレード 3～4 となった被験者は、INR 上昇が認められた 4 例と、血糖値増加、好中球数減少及び白血球数減少が認められた各 1 例であった。

2.6.3　抗 evolocumab 抗体産生の状況

3 例で抗 evolocumab 抗体が陽性であり、このうち 2 例はベースライン時に陽性であった。いずれの被験者も中和抗体は陰性であった。これらの被験者のうち、OLE 試験中に有害事象が発現した被験者は認められなかった。

3.　結論

合計 242 例を本長期 OLE 試験の中間解析（データカットオフ日：[redacted]年[redacted]月[redacted]日）の対象とし、その内訳は、HoFH 被験者が 100 例、重症 FH 被験者が 142 例であった。このうち、日本人被験者は 8 例で、HoFH 被験者が 7 例、重症 FH 被験者が 1 例であった。データカットオフの時点で、OLE 試験における evolocumab の総曝露量は 124.6 患者年であり、その内訳は、HoFH 被験者が 73.9 患者年、重症 FH 被験者が 50.6 患者年であった。

中間解析により、HoFH 被験者（アフェレーシス療法の実施にかかわらず）及び重症 FH 被験者を対象としたほかの脂質低下療法（スタチン、エゼチミブ等）併用下の evolocumab 420 mg QM 又は 420 mg Q2W の長期投与（25.0 カ月まで）について、以下の結論が裏付けられた。

- evolocumab の長期投与により、非アフェレーシス HoFH 被験者では約 20%～30%、アフェレーシス HoFH 被験者では約 10%～20%、重症 FH 被験者では約 40%～50%の LDL-C 低下が維持された。非アフェレーシス HoFH 被験者とアフェレーシス HoFH 被験者の間に認められた差は、これら 2 集団におけるベースライン時の遺伝子型及び疾患重症度の差異によるものと考えられる。

- その他の脂質パラメータ（総コレステロール、ApoB 及び non-HDL-C、総コレステロール／HDL-C 比及び ApoB/ApoA1 比）の変化についても、HoFH 被験者又は重症 FH 被験者において、evolocumab の長期投与により安定した改善が認められた。
- HoFH 青年被験者（12 歳以上 18 歳未満）における LDL-C の低下及びその他の脂質パラメータの変化は、HoFH 被験者集団全体での変化と類似していた。
- HoFH 被験者において QM から Q2W に投与頻度を上げたところ、LDL-C が更に約 6%～8%低下し、その他の脂質パラメータにも更なる改善が認められた。
- 非結合型 evolocumab の薬物動態パラメータは用法・用量（QM 又は Q2W）と一致し、血清中非結合型 evolocumab 濃度がアフェレーシス治療中に約 15%～30%低下したことから、アフェレーシス被験者におけるより頻度の高い Q2W 投与の使用が支持された。
- QM 及び Q2W の両投与法により、血清中 PCSK9 濃度が著しく低下した。
- 本試験ではこれまでに臨床的に重要な治験薬投与と関連のある有害事象又は臨床検査値異常は認められず、本試験でこれまでに認められた重篤な有害事象は、HoFH 被験者及び重症 FH 被験者での発現が予測された事象であった。
- 抗 evolocumab 抗体の産生が認められたのは 3 例のみであり、中和抗体又は有害事象との関連はなかった。
- AI/pen を用いた evolocumab の投与は、その使用目的及び使用条件に関して安全かつ有効であった。

本長期投与試験の中間解析結果から、evolocumab の QM 投与又は Q2W 投与は HoFH 被験者又は重症 FH 被験者において良好なベネフィット・リスクプロファイルを示し、LDL-C の低下を維持することが明らかとなった。

4. 有害事象の叙述

4.1 死亡、重篤な有害事象及び投与中止に至った有害事象の症例一覧

死亡、重篤な有害事象及び投与中止に至った有害事象を表 2.7.6.28-16 に要約する。

表 2.7.6.28-16　死亡、重篤な有害事象及び投与中止に至った有害事象の要約

番号	被験者 ID	理由			MedDRA 基本語
		死亡	その他の重篤な有害事象	投与中止に至った有害事象	
1	[redacted]		X		胸痛
2	[redacted]		X		大動脈狭窄、冠動脈疾患
3	[redacted]		X		狭心症
4	[redacted]		X		冠動脈閉塞
5	[redacted]		X		非心臓性胸痛
6	[redacted]		X		大動脈弁疾患
7	[redacted]		X		狭心症
8	[redacted]		X		動静脈瘻血栓症
9	[redacted]		X		子宮脱
10	[redacted]		X		血尿
11	[redacted]		X		大腸炎
12	[redacted]		X		頚動脈閉塞
13	[redacted]		X		心筋虚血
14	[redacted]			X	発疹
15	[redacted]			X	舌炎、多汗症、倦怠感、筋痙縮、筋肉痛、鼻閉、発熱

AE =有害事象、MedDRA = ICH 国際医薬用語集

4.2 重篤な有害事象の叙述

重篤な有害事象の叙述は、下記に示す。

被験者番号：[redacted]
治療： evolocumab SC Q2W 420 mg
報告：心筋虚血

被験者[redacted]は61歳のアジア人男性、20110271試験に参加しており、心筋虚血が発現した（報告事象名：虚血性心疾患）。不安定狭心症及び常染色体劣性家族性高コレステロール血症の既往あり。併用薬としてアセチルサリチル酸／グリシン酸塩／炭酸マグネシウム、クロピドグレル、三硝酸グリセリン、アムロジピン、ビソプロロール、インダパミド、アジルサルタン、アゼルニジピン、グリチロン、ノイファーゲン、ランソプラゾール、テプレノン、アルギン酸ナトリウム、メコバラミン、トコフェロール、エチゾラム、ラメルテオン、ジクロフェナク、カルボシステイン及びリドカインを使用。

家族性高コレステロール血症の前治療及び現治療としてアトルバスタチン、エゼチミブ及びプロブコールを使用。

[redacted]年11月12日、20110271試験にてevolocumabの投与を開始した。

約5カ月後の 翌年* 4月15日、効果の欠如によりevolocumabの投与を中止した。狭心症の治療として三硝酸グリセリンの投与を開始。 翌年* 4月18日、疲労及び背部圧迫感の愁訴あり。冠動脈血管造影を実施した結果、左前下行枝狭窄（50%～70%）を認めた。治療薬としてクロピドグレル及び二硝酸イソソルビドを使用。

翌年* 6月18日、心筋虚血のため入院となり、LADにステント留置による経皮的冠インターベンションを施行した。治療薬として二硝酸イソソルビド、エチゾラム、ヘパリン、イオパミドール、リドカイン及びジクアホソルを使用。

心筋虚血の転帰は 翌年* 6月21日に回復と報告されている。同日に退院。

心筋虚血発現前のevolocumabの最終投与は 翌年* 4月15日であった。被験者は試験を継続したが、[redacted]年[redacted]月[redacted]日のデータカットオフ時点でevolocumab投与を再開していなかった。

治験担当医師は、心筋虚血の事象が evolocumab と関連する合理的な可能性があると判断している。

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study: Study 20110233, Evolocumab SC QM 420 mg Current study: Evolocumab SC QM 420 mg
Report: Chest pain

Subject [redacted] was a 32-year-old white man participating in Study 20110271 who developed chest pain). The subject's medical history included homozygous familial hypercholesterolemia, dyspepsia, and porphyria. Concomitant medications included acetylsalicylic acid and esomeprazole. Previous and ongoing treatment for familial hypercholesterolemia included atorvastatin and ezetimibe.

The subject received evolocumab in the parent study (Study 20110233) from 02 August same year* to 25 September same year*. He received the first dose of evolocumab in Study 20110271 on 23 October [redacted].

Approximately 9 months later, on 27 July one year after*, the subject felt central chest tightness. The tightness persisted intermittently; he was seen by cardiologist on 29 July one year after* and hospitalized on the same day. An electrocardiogram (ECG) revealed normal results. During an effort ECG, the subject ran for 10 minutes and 15 seconds; he wanted to stop because of fatigue and dizziness but he had no chest pain or chest tightness. The post-effort ECG revealed atrial ectopy with significant ischemia. His cardiac enzymes were normal. Echocardiography revealed no left ventricular wall motion abnormality and normal ejection fraction of 56% and dimensions of 58 mm in diastole and 41 mm in systole; septal thickness was normal at 7 cm; left atrium was normal at 38 mm; peak gradient across the aortic valve was 13 mmHg with a mean of 6 mmHg; ascending aorta measured 38 mm; mitral inflow velocities were normal; there was mild aortic regurgitation. Laboratory test results showed white blood cell (WBC) count 7.7 x 10^9/mL, D-dimer < 1 µg/L, C-reactive protein < 1 mg/L, high-sensitive (HS) troponin T < 5 ng/mL, and total cholesterol 8.8 mmol/L.

Despite the negative findings, coronary angiography was performed via right femoral artery. Peak gradient across the aortic valve was 30 mmHg. Angiography revealed a totally occluded right coronary artery. There was excellent retrograde filling from both the circumflex system and the left anterior descending (LAD) system, filling the right coronary artery retrograde. Left main

*新薬承認情報提供時に置き換え

coronary artery was normal and there were no significant stenoses noted in the left system, although there was evidence of insignificant atherosclerosis in the mid LAD. The septal perforators provided excellent collaterals to the right coronary artery and numerous collaterals. The right coronary artery after prolonged injection revealed late filling of only the proximal part of the right coronary artery but not distally. Left ventricular angiography revealed no wall abnormalities and normal left ventricular ejection fraction. The subject essentially had been asymptomatic despite this one episode.

The event of chest pain was reported to have resolved on 29 July one year after* and the subject was discharged from the hospital on 30 July one year after* on atorvastatin, ezetimibe, and acetylsalicylic acid. The subject's last dose of evolocumab prior to the event was on 02 July one year after*. Evolocumab was continued. As of the data cutoff date of [redacted], home dosing was continuing with the last in-clinic dose documented on 11 March two years after*.

The investigator reported that there was no a reasonable possibility that the event of chest pain was related to evolocumab.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study: Study 20110233, Evolocumab SC QM 420 mg Current Study: Evolocumab SC QM 420 mg
Report: Aortic stenosis, Coronary artery disease

Subject [redacted] was a 43-year-old white woman participating in Study 20110271 who had serious adverse events of coronary artery disease (reported term: worsening of coronary artery disease) and aortic stenosis (reported term: severe calcified aortic stenosis). The subject's medical history included homozygous familial hypercholesterolemia, coronary artery bypass graft, aortic stenosis since twenty-five years ago*, angina pectoris, and stent placement. Concomitant medications included paracetamol, acetylsalicylic acid, magnesium chloride, bisoprolol, and clopidogrel. Previous and ongoing treatment for familial hypercholesterolemia included atorvastatin and ezetimibe.

The subject received evolocumab in the parent study (Study 20110233) from 18 February same year* to 15 April same year*.

The subject received the first dose of evolocumab in Study 20110271 on 13 May [redacted]. Approximately 1 month later, on 06 June same year*, the subject was seen by a cardiologist and noted to have progression of her underlying aortic stenosis that was considered severe. Echocardiography was carried out and suggested calcified aortic stenosis. Angiography via transesophageal echocardiography confirmed severe calcified aortic stenosis requiring transcatheter aortic valve implant (TAVI).

Approximately 2 months after receiving the first dose of evolocumab in Study 20110271, on 08 July same year*, the subject was hospitalized due to her 25-year history of severe aortic stenosis. Computerized tomography scan of the heart and chest revealed an extremely calcified aorta. The femoral arteries were also very diseased. On the same day, the subject underwent a transapical TAVI. Treatment medications included esomeprazole and a combination of paracetamol, codeine, and meprobamate. The event of aortic stenosis was reported to have resolved on 08 July same year* and the subject was discharged from the hospital on 09 July same year*.

The subject was seen by a cardiologist on 19 July same year*. Blood pressure was 120/70 mmHg, pulses were bounding and normal and the pulse rate was 60/min. There was a short aortic

*新薬承認情報提供時に置き換え

ejection murmur across the TAVI aortic valve with a soft but definite early diastolic murmur. A resting electrocardiogram showed no significant strain pattern and no arrhythmia. Echocardiogram confirmed marked concentric left ventricular hypertrophy, related to the longstanding valvular heart disease; the TAVI aortic valve was well seated with a peak gradient of 12 mm across the valve; the peri-valvular leak was present with mild to moderate aortic regurgitation. The conclusion was that the subject had undergone successful TAVI aortic valve replacement via the transapical route; it was anticipated that there would be mild residual aortic regurgitation and this was the case; the degree of regurgitation was mild and in the cardiologist's opinion, it would not cause hemodynamic problems in the future. On 05 August same year*, the subject was seen for her study visit, and had recovered well from the TAVI aortic valve replacement.

The subject's last dose of evolocumab prior to the event of aortic stenosis was on 13 May same year*. Evolocumab was continued.

Worsening of coronary artery disease was recorded as a serious adverse event, with start date 01 February one year after* and presenting symptoms of worsening angina, tiredness, and dizziness. The subject was hospitalized. Echocardiogram showed left ventricular ejection fraction of 65% and prosthetic aortic valve peak gradient of 22 mmHg with trivial regurgitation. Post-effort EKG showed no ischemic changes; however on 11 April one year after*, coronary arteriography confirmed worsening coronary artery disease, and a coronary stent was placed. Worsening coronary artery disease was reported as resolved on 11 April one year after*. The subject's last dose of evolocumab prior to the event of worsening of coronary artery disease was on 20 January one year after*. Evolocumab was continued.

As of the data cutoff date of [redacted], home dosing was continuing with the last in-clinic dose documented on 14 April one year after*.

The investigator reported that there was not a reasonable possibility that the events of aortic stenosis and worsening of coronary artery disease were related to evolocumab.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatment: Parent study: Study 20110233, Evolocumab SC QM 420 mg Current study: Evolocumab SC QM 420 mg
Report: Angina pectoris

Subject [redacted] was a 46-year-old white man participating in Study 20110271 who developed angina pectoris (reported term: ischemic chest pain). The subject's medical history included homozygous familial hypercholesterolemia, angina pectoris, myocardial infarction, and coronary artery bypass graft. Concomitant medications included acetyl salicylic acid and omeprazole. Previous and ongoing treatment for familial hypercholesterolemia included atorvastatin and ezetimibe.

The subject received evolocumab in the parent study (Study 20110233) from 19 February same year* to 18 April same year*. He received the first dose of evolocumab in Study 20110271 on 16 May [redacted]. Approximately 5 months later, on 12 October same year*, the subject experienced chest pain and was hospitalized on the same day. The subject was admitted with central chest pain at rest, radiating to left arm with palpitation. On examination, the subject had epigastric tenderness, chest was clear, central nervous system was intact and blood pressure was 166/102 mmHg. Full blood count (FBC) was done, which showed white blood cell (WBC) count of 3.21 x 10^9/L, hemoglobin of 12.9 g/dL, and platelet count of 195 x 10^9/L. Potassium was 3.1 mmol/L, sodium 141 mmol/L, chloride 111 mmol/L, bicarbonate 18 mmol/L, urea 2.6 mmol/L, and creatinine 61 µmol/L. Troponin was 19 ng/mL. Repeat laboratory test showed troponin < 10 ng/mL. Serial electrocardiograms did not reveal any signs of ischemia. Echocardiography showed preserved systolic function, ejection fraction of 70%, and mild aortic stenosis (AS). The subject was given glyceryl trinitrate infusion, and symptoms improved. The event of angina pectoris was reported as resolved on 16 October same year*, and the subject was discharged from the hospital on the same day. Additional treatments included perindopril, glyceryl trinitrate, and clopidogrel.

On 25 November same year*, a cardiolite scan demonstrated mild to moderate exercise-induced ischemia in the mid and basal anterolateral and inferolaterol segment with good left ventricular systolic function. Physical examination at rest revealed blood pressure 164/100 mmHg, pulse 79 bpm, and ejection fraction (EF) 63%. Physical examination at stress revealed blood pressure 178/84 mmHg, pulse 165 bpm, and EF 56%.

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The subject's last dose of evolocumab prior to the event and in the study was on 01 October same year*. Evolocumab was withheld due to the physician's decision. As of the data cutoff date of [redacted], the subject continued in the study, with no documentation of further study drug administration.

The investigator reported that there was not a reasonable possibility that the event of angina pectoris was related to evolocumab.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Parent study: Study 20110233, Evolocumab SC QM 420 mg Current study: Evolocumab SC QM 420 mg
Report: Coronary artery occlusion

Subject [redacted] was a 14-year-old white man participating in Study 20110271 who developed coronary artery occlusion (reported term: occlusive coronary artery disease). The subject's medical history included homozygous familial hypercholesterolemia, chest discomfort, coronary ostial stenosis, xanthoma, arcus lipoides, headache, rash, tonsillitis, tumor excision, tendon disorder, tonsillectomy, and xanthelasma. Concomitant medications included acetylsalicylic acid and clopidogrel. Previous and ongoing treatments for familial hypercholesterolemia included atorvastatin and ezetimibe.

The subject received evolocumab in the parent study (Study 20110233) from 21 February same year* to 18 April same year*. He received the first dose of evolocumab in Study 20110271 on 16 May [redacted].

The subject had worsening angina since 15 July same year*; his stress electrocardiogram (ECG) was positive. On 18 July one year ago*, a resting ECG revealed sinus rhythm with a PR interval of 140 ms and QRS duration of 60 ms. Deep inverted T-waves in the inferior leads were noted. On effort ECG, sore calves and infero-lateral ST segment depression were noted. Severe burning pain was present. Post-effort ECG revealed accentuation of those infero-lateral changes with significant ST depression in the inferior leads as well as V4-V6. Echocardiography revealed left ventricular hypertrophy, particularly papillary muscle hypertrophy and the septum. Supravalvar aortic stenosis (AS) with a minimal luminal diameter above the valve and mild mitral regurgitation were observed. Significant ostial bilateral coronary artery stenosis was diagnosed on the same day.

On 22 July same year*, the subject complained of episodes of chest pain while dancing; on effort ECG, he showed again raised ST segments in aVR and inferior lateral significant ST segment depression. Left ventricular (LV) function remained good. On 26 July one year ago*, coronary angiography showed tight ostial stenosis on the right coronary artery. The left main had a tight ostial to mid shaft left main stenosis. Supravalvar narrowing and significant ostial bilateral coronary artery stenoses were noted, which were successfully stented.

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On 16 August same year*, coronary angiography showed apparent restenosis in the ostium of the right coronary artery in the stent. The left main coronary revealed a tight ostial stenosis in the area of the previous stenting, with very small circumflex system. The peripheral caliber of the right coronary artery and the left anterior descending (LAD) and diagonal systems were excellent. Both the right internal mammary and the left internal mammary were patent and appeared to be good vessels. LV angiography revealed an ejection fraction (EF) of 68.5%.

The subject was hospitalized and underwent bilateral mammary artery coronary grafting on 02 September same year*. On the same day, intraoperative transesophageal echo (TEE) study showed significant supravalvar component to the disease. The gradient was 37 mmHg and there was a very prominent shadow from the stent prefunding into the aorta. An aortic root patch enlargement was done. The patch was implanted and the left internal mammary artery (LIMA) was anastomosed to the LAD and right internal mammary artery (RIMA) was anastomosed to the right coronary artery. The subject underwent a resection of the stent in his aortic root. He was recovering well post operation and was discharged from the hospital on 09 September same year*. According to the last available report on 31 January one year after*, the event was ongoing.

The subject's last dose of evolocumab prior to the event was on 05 August same year*. Evolocumab was continued. As of the data cutoff date of [redacted], home dosing was continuing with the last in-clinic dose documented on 23 January one year after*.

The investigator reported that there was not a reasonable possibility that the event of coronary artery occlusion was related to evolocumab.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Parent study: Study 20110233, Placebo SC QM Current study: Evolocumab SC QM 420 mg
Report: Non-cardiac chest pain

Subject [redacted] was a 14-year-old white woman participating in the Study 20110271 who developed non-cardiac chest pain. The subject's medical history included homozygous familial hypercholesterolemia, abdominal pain, atypical non-ischemic chest pain, hand fracture, talipes, talipes correction, tendon disorder, and xanthoma. Concomitant medications included hyoscine and cyclizine. Previous and ongoing treatment for homozygous familial hypercholesterolemia included atorvastatin and ezetimibe.

The subject received the first dose of placebo in the parent study (Study 20110233) on 21 February same year* and completed the study on 16 May same year*. She received the first dose of evolocumab in Study 20110271 on 16 May [redacted].

Approximately 4 months and 2 weeks later, on 02 October same year*, the subject developed chest pain and was hospitalized on the same day. The subject complained of central chest pain which persisted for more than 30 minutes. Upon admission to the hospital, laboratory tests revealed red blood cell (RBC) count 5.23 x 10^{12}/L, white blood cell (WBC) count 7.3 x 10^{9}/L, hemoglobin 14.8 g/dL, hematocrit 0.45 frac of 1, platelet count 273 x 10^{9}/L, carbon dioxide 22.4 mEq/L, cholesterol of 13.3 mg/dL, low density lipoprotein cholesterol of 11.4 mg/dL, high density lipoprotein cholesterol 1.40 mg/dL, triglycerides 0.40 mg/dL, and D-dimer of 3.20 µg/mL. Radiography of the chest was performed due to shortness of breath and chest pain and it revealed no focal pathologies. Electrocardiogram (ECG) showed no acute ischemic changes; QRS interval was 84 ms, QT/QTcB 410/427 ms, PR 138 ms, PR/PP 920/920 ms, P/QRS/T 45/70/50 degrees, QTD/QTcBD of 26/27 ms. Cardiac enzymes were not elevated. The subject was kept under observation overnight. On 03 October same year*, computerized tomography of the chest revealed no evidence of pulmonary embolism or other acute pathology. On 04 October same year*, ultrasound of the abdomen was performed due to pain in the left hypochondrium and showed no abnormalities. On 07 October same year*, laboratory test results revealed a lymphocyte count of 0.5 x 10^{9}/L; additional blood cell count values were within normal range. During hospitalization, a heart sound navigation and ranging system (SONAR) revealed aortic stenosis with significant gradient. Treatment included tramadol, paracetamol, lornoxicam, ketorolac tromethamine, isosorbide mononitrate, acetylsalicylic acid, and

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flurbiprofen. The subject was started on bisoprolol. The investigator stated that there was no obvious cause for the chest pain. The event of non-cardiac chest pain was reported as resolved on 08 October same year* and the subject was discharged from the hospital on the same day. No co-suspect medications were reported.

The subject's last dose of evolocumab prior to the event of non-cardiac chest pain was on 06 September same year*. Evolocumab was continued. As of the data cutoff date of [redacted], home dosing was continuing with the last in-clinic dose documented on 23 January one year after*.

The investigator reported that there was no reasonable possibility that the event of non-cardiac chest pain was related to evolocumab.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Parent study: Study 20110233, Evolocumab SC QM 420 mg Current study: Evolocumab SC QM 420 mg
Report: Aortic valve disease

Subject [redacted] was a 46-year-old white man participating in Study 20110271 who developed aortic valve disease (reported term: worsening of aortic valve disease). The subject's medical history included familial hypercholesterolemia, angina pectoris, xanthoma, vascular graft, hypertension, aortic valve disease, aortic valve replacement, cardiac murmur, intermittent heartburn, bilateral corneal arcus, arcus lipoides, headache, dyspepsia, and vasectomy. Concomitant medications included acetylsalicylic acid, hydrochlorothiazide, omeprazole, lisinopril, ibuprofen, and labetalol. Previous and ongoing treatment for familial hypercholesterolemia included colesevelam, rosuvastatin, and ezetimibe.

The subject received evolocumab in the parent study (Study 20110233) from 07 April same year* to 02 June same year*. He received the first dose of evolocumab in Study 20110271 on 30 June [redacted]. Approximately 4 months later, on 01 November same year*, the subject was found to have valve regurgitation. Approximately 1 year and 2.5 months after this, on 23 January two years after*, the subject developed worsening of aortic valve disease and was hospitalized. During hospitalization, the subject underwent a pre-planned aortic valve leak repair. Treatment included warfarin. The event of worsening aortic valve disease was reported as resolved on 26 January two years after* and the subject was discharged from the hospital on the same day.

The subject's last dose of evolocumab prior to the event was on 09 November one year after*. Evolocumab was continued. As of the data cutoff date of [redacted], home dosing was continuing with the last in-clinic dose documented on 15 February two years after*.

The investigator reported that there was no reasonable possibility that the event of aortic valve disease was related to evolocumab.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatment: Evolocumab SC Q2W 420 mg
Report: Angina pectoris

Subject [redacted] was a 76-year-old white woman participating in Study 20110271 who developed angina pectoris (reported term: worsening angina).

The subject's medical history included coronary artery disease, arterial occlusive disease, myocardial ischemia, angina pectoris, transient ischemic attack, familial hypercholesterolemia, coronary artery bypass, apheresis, and allergy to statin. Prior angiography (date unknown) demonstrated an occluded left internal mammary artery bypass graft to left anterior descending artery (LAD); however, saphenous vein grafts to the circumflex distribution and the diagonal branches were patent, and the latter supplied the LAD with vigorous retrograde flow. Concomitant medications included acetylsalicylic acid and omega-3 fatty acids. No prior or ongoing treatments for familial hypercholesterolemia.

Prior to involvement in Study 20110271, the subject reported fatigue and sleepiness, but no chest discomfort or dyspnea, and underwent an exercise stress test during which she had heaviness in her chest towards peak exercise, but no specific EKG findings. On 14 March same year*, the screening EKG showed inferior and anterior ischemia, prompting another exercise stress test which was done on 19 March same year*. During this test, 1 mm of ST elevation occurred during exercise to 9.2 METs, but heart rate and blood pressure response to exercise were reported as normal. Post-exercise, the subject developed chest tightness and nausea, but no significant ST segment changes were noted on post exercise ECG. Adequate pulse and blood pressure response to exercise was observed. On 21 March same year*, she reported jaw pain.

The subject received the first dose of evolocumab in Study 20110271 on 27 March [redacted].

Based on prior findings, the subject underwent exercise stress echocardiogram on 28 March same year*. The echocardiogram showed significant exercise-induced regional wall motion abnormalities involving the distal septum, apex, and lateral wall with normal left ventricular systolic function at rest. The resting ECG was abnormal and the subject had no chest pain. The exercise echocardiogram was therefore interpreted as positive for anteroapical ischemia.

*新薬承認情報提供時に置き換え

On 02 April same year*, the subject underwent uncomplicated diagnostic coronary angiography. Native vessel findings included mild to moderate left main coronary artery stenosis; 70% proximal left anterior descending (LAD) stenosis; severe mid-LAD stenosis; and a non-dominant right coronary artery with moderate disease. The saphenous vein graft to first marginal branch showed mild irregularities, but good flow. The saphenous vein graft to first and second diagonal vessels was almost completely occluded in the mid segment. There was a suggestion of significant obstruction prior to the anastomosis with the first diagonal, with little filling beyond and no opacification of the second diagonal or LAD. The left internal mammary artery graft to LAD was chronically occluded. Left ventricular function was normal. Following the procedure, the subject was hospitalized for observation to ensure stability prior to scheduled stenting of the vein graft. Evolocumab was temporarily withheld due to the event.

On 04 April same year*, the subject underwent placement of a single drug eluting stent to the saphenous vein graft to diagonal. The cardiologist suggested the subject may have had a small cerebral thromboembolic event associated with the angioplasty procedure, but there were no corroborative neurological signs. Treatment medications included ticagrelor and clopidogrel. The subject was advised to continue dual antiplatelet therapy for a minimum of 1 year.

The outcome of the event angina pectoris was reported as resolved on 08 April same year*. The subject was discharged from the hospital on the same day.

The subject's last dose of evolocumab prior to the event of angina pectoris was on 27 March same year*. On 24 April same year*, evolocumab was restarted and as of the data cutoff date of [redacted], the subject was continuing dosing in the study.

The investigator reported that there was not a reasonable possibility that the event of angina pectoris was related to evolocumab.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatment: Evolocumab SC QM 420 mg
Report: Arteriovenous fistula thrombosis

Subject [redacted] was a 27-year-old white man participating in Study 20110271 who developed arteriovenous (AV) fistula thrombosis (reported term: thrombosis of left AV fistula). The subject's medical history included supravalvular aortic stenosis, familial hypercholesterolemia (Type IIa hyperlipidemia), AV fistula creation (right arm eleven years ago*; left arm ten years ago*), and vascular graft surgery. Concomitant medications included acetylsalicylic acid and ferrous fumarate. Previous and ongoing treatment for familial hypercholesterolemia included atorvastatin and ezetimibe.

The subject received the first dose of evolocumab in Study 20110271 on 05 Dec [redacted]. Approximately 4 months later, on 14 April one year after*, the subject developed thrombosis of his left AV fistula. The subject noticed discoloration of skin and loss of blood flow over the fistula. The subject was hospitalized on 15 April one year after* for thrombectomy and thrombolysis. Treatment medications included alteplase.

The outcome of the event of arteriovenous fistula thrombosis was reported as resolved on 15 April one year after*. The subject was discharged from the hospital on the same day.

The subject's last dose of evolocumab prior to the event of arteriovenous fistula thrombosis was on 12 April one year after*. Evolocumab was continued. As of the data cutoff date of [redacted], the subject was continuing dosing in the study.

The investigator reported that there was not a reasonable possibility that the event of arteriovenous fistula thrombosis was related to evolocumab.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatment: Evolocumab SC QM 420 mg
Report: Uterine prolapse

Subject [redacted] was a 67-year-old white woman participating in Study 20110271 who experienced uterine prolapse (reported term: worsening of the uterine prolapse). The subject's medical history included homozygous familial hypercholesterolemia, menopause, myalgia, and xanthoma. No concomitant medications were reported. Previous and ongoing treatment for familial hypercholesterolemia included atorvastatin and ezetimibe.

The subject developed non-serious uterine prolapse of moderate severity on 01 September same year*. She received the first dose of evolocumab in Study 20110271 on 04 September [redacted]. Approximately 1 month and 2 weeks after receiving the first dose of evolocumab, on 15 November same year*, uterine prolapse worsened to severe and was reported as a serious event. On 11 December same year*, the subject was hospitalized due to the worsening uterine prolapse. The following day, 12 December same year*, hysterectomy was performed. Treatment included enoxaparine. The event of uterine prolapse was reported as resolved on 12 December same year* and the subject was discharged from the hospital on 15 December same year*.

The subject's last dose of evolocumab prior to the event was on 30 October same year*. Evolocumab was continued. As of the data cutoff date of [redacted], home dosing was continuing with the last in-clinic dose documented on 19 March one year after*.

The investigator reported that there was no reasonable possibility that the event of uterine prolapse was related to evolocumab.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatment: Evolocumab SC Q2W 420 mg
Report: Hematuria

Subject [redacted] was a 22-year-old white man participating in Study 20110271 who experienced hematuria (reported term: hematuria after low-density lipoprotein [LDL]-apheresis and evolocumab administration). The subject's medical history included homozygous familial hypercholesterolemia and allergic transfusion reactions (allergic reaction related to LDL-apheresis procedure); he had no previous history of hematuria. Previous and ongoing treatment for homozygous familial hypercholesterolemia included colestyramine, ezetimibe, and rosuvastatin.

The subject received the first dose of evolocumab in Study 20110271 on 22 January [redacted]. Approximately 10 months later, on 26 November same year*, the subject was hospitalized to undergo LDL-apheresis, which was performed on the same day. Evolocumab was administered 5 minutes after completing the LDL-apheresis. Immediately after evolocumab administration, the subject observed hematuria; this led to prolongation of hospitalization. The subject also had an event reported as "feeling of vomiting probably allergic reaction from LDL-apheresis", which resolved on the same day.

The subject experienced 2 nonserious episodes reported as "allergic reaction during LDL-apheresis" on 27 December one year ago* and 08 January same year*. These were treated with methylprednisolone and omeprazole. These reactions were not associated with vomiting or hematuria.

Laboratory tests performed on 26 November same year* showed the following results: hematocrit of 31.9% to 34.2%, hemoglobin of 10.5 to 11.4 g/dL, red blood cell (RBC) count of 4.09 to 4.45 x 10^6/µL, white blood cell (WBC) count of 5.4 to 11.7 x 10^3/µL, polymorphonuclear count of 60.5% to 80.9%, eosinophils not detected, lymphocyte count of 1.3 to 1.5 x 10^3/µL (10.7% to 28.7%), basophil count of 0.1% to 0.4%, monocyte count of 0.6 to 1.0 x 10^3/µL (7.8% to 10.4%), neutrophil count of 3.2 to 9.5 x 10^3/µL, alkaline phosphatase of 67 mIU/mL, creatinine of 1.0 mg/dL, and urea of 28 mg/dL. The sample was reported as hemolyzed. Urinalysis revealed a red, clear sample with specific gravity of 1.010 and pH of 8.0, positive for albumin (7300 mg/dL), glucose (100 mg/dL), ketones (15 mg/dL), hemoglobin (+++), urobilinogen

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(4.0 mg/dL). Microscopic analysis revealed a WBC count of 1 to 2/high-power field (hpf), and an RBC count of 6 to 8/hpf; deformities in piles.

Laboratory tests performed on 27 November same year* showed following results: creatinine of 1.1 mg/dL, lactate dehydrogenase (LDH) of 2055 mIU/mL, lymphocyte count of 0.5 x 10^3/µL (6%), WBC count of 7.9 x 10^3/µL, RBC count of 4.35 x 10^6/µL, monocyte percentage of 0.5%, neutrophil count of 7.4 x 10^3/µL, hematocrit of 33.5%, potassium of 5 µmol/L, sodium of 136 µmol/L, urea of 36 mg/dL, and polymorphonuclear percentage of 60.5%.

Laboratory tests performed on 28 November same year* showed following results: WBC count of 9.3 x 10^3/µL, RBC count of 3.73 x 10^6/µL, basophil percentage of 0.3%, eosinophils not detected, lymphocyte count of 2 x 10^3/µL (22%), monocyte count of 0.9 x 10^3/µL (9.3%), neutrophil count of 6.3 x 10^3/µL, alkaline phosphatase of 76 mIU/mL, creatinine of 0.9 mg/dL, LDH of 1266 mIU/mL, urea of 35 mg/dL, and hematocrit of 28.8%.

The event of hematuria was reported as resolved on 28 November same year*, and the subject was discharged from the hospital on the same day.

The subject's last dose of evolocumab prior to the event was on 26 November same year*. Evolocumab was discontinued as subject and his physician decided to start a new therapy with lomitapide.

As of the data cutoff date of [redacted], the subject's last dose of evolocumab was on 17 December same year* and the subject completed the study on the same day. The investigator reported that there was no reasonable possibility that the event of hematuria was related to evolocumab or LDL-apheresis.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatment: Evolocumab SC Q4W 420 mg
Report: Colitis

Subject [redacted] was a 34-year-old white man participating in Study 20110271 who developed colitis (reported term: pancolitis). The subject's medical history included prior smoking (1 to 1.5 packs per day for 14 years), chronic ischemic heart disease, aortic stenosis, acute myocardial infarction, congestive heart failure, pulmonary edema, anemia, familial hypercholesterolemia (Type IIa hyperlipidemia), increased lipoprotein A, vitamin D deficiency, myalgia, chronic tendinitis, erectile dysfunction, aortic valve replacement, vascular graft surgery, cardiac catheterization, and family history of hypercholesterolemia and heart disease (father). Concomitant medications included acetylsalicylic acid, citrate/acetylsalicylic acid/caffeine, warfarin, enoxaparin, ferrous gluconate, tadalafil, and vitamin D. Previous and ongoing treatment for familial hypercholesterolemia included atorvastatin and ezetimibe.

The subject received the first dose of evolocumab in Study 20110271 on 20 April [redacted].

Approximately 2.5 months later, on 29 June same year*, the subject underwent evaluation for gastrointestinal symptoms. A breath test was positive for helicobacter pylori. The subject was treated with lansoprazole, amoxicillin and clarithromycin. He was also advised to take an anti-diarrheal diet. A colonoscopy was scheduled, and a clear diet was prescribed until that date. Laboratory tests showed white blood cell (WBC) count 1.6 × 10^9/L, hemoglobin 13.30 g/dL, hematocrit 39.70%, platelet count 227 × 10^9/Land negative hepatitis B surface antigen, hepatitis C virus antibody and Giardia.

On 01 July same year*, the subject reported abdominal pain and watery diarrhea mixed with blood about 6 times per day. On 04 July same year*, treatment with atorvastatin was discontinued. On 09 July same year*, stool culture was negative for microbial growth and positive for occult blood. Clostridium difficile toxin test was negative and stool direct microscopy showed positive leukocytes. On 22 July same year*, he was hospitalized with a diagnosis of colitis and treatment included metronidazole and prednisone. Stool culture was negative without isolation of intestinal pathogen or parasite. On 27 July same year*, the subject underwent colonoscopy and terminal ileoscopy which showed inflammatory pancolitis, but a biopsy of the ileum showed no

*新薬承認情報提供時に置き換え

inflammation or flattening. On 13 August same year*, colitis was reported as resolved and the subject was discharged from the hospital

The subject's last dose of evolocumab prior to the event of colitis was 13 July same year*. Evolocumab was continued. As of the data cutoff date of [redacted], the subject was continuing dosing in the study.

The investigator reported that there was not a reasonable possibility that the event of colitis was related to evolocumab.

*新薬承認情報提供時に置き換え

Subject No: [redacted]
Treatments: Current Study: Evolocumab SC Q2W 420 mg
Report: Carotid artery occlusion

Subject [redacted] was a 38-year-old white woman participating in Study 20110271 who developed carotid artery occlusion (reported term: carotid obstruction). The subject's medical history included angina, coronary artery disease, carotid artery disease, homozygous familial hypercholesterolemia, right internal carotid revascularization, and percutaneous coronary intervention. Concomitant medications included acetylsalicylic acid, clopidogrel, ranitidine, ferrous sulfate, and folic acid. Previous and ongoing treatment for familial hypercholesterolemia included ezetimibe and rosuvastatin.

The subject received the first dose of evolocumab in Study 20110271 on 18 February [redacted].

Approximately 3 months later on 15 May same year*, the subject was diagnosed with left internal carotid obstruction. Carotid artery ultrasound showed left internal carotid stenosis of 75%. On 21 May same year*, she was hospitalized for further testing. On 27 May same year*, magnetic resonance angiography confirmed left internal carotid stenosis. Pharmacologic stress testing was also done and showed no evidence of ischemia. On 03 June same year*, a repeat carotid artery ultrasound again showed stenosis of 60 to 70% with patency of previous revascularization. On 06 June same year*, the subject was discharged; the event of carotid artery occlusion was continuing. On 24 June same year*, the subject was hospitalized again to perform left internal carotid revascularization, which took place the next day. On 28 June same year*, the subject was discharged from the hospital.

Carotid artery occlusion was reported as resolved on 07 July same year*.

The subject's last dose of evolocumab prior to the event was 12 May same year*. Evolocumab was continued after the initial onset of the event on 15 May same year*, but was temporarily withheld prior to the revascularization on 25 June same year*. Dosing with evolocumab was reinitiated (date not reported). As of the data cutoff date of [redacted], the subject was continuing dosing in the study.

*新薬承認情報提供時に置き換え

The investigator reported that there was not a reasonable possibility that the event of carotid artery occlusion was related to evolocumab.

Subject No: [redacted]
Treatment: Evolocumab SC Q2W 420 mg
Report: Myocardial ischemia

Subject [redacted] was a 61-year-old Asian man participating in Study 20110271 who developed myocardial ischemia (reported term: ischemic cardiac disease). The subject's medical history included unstable angina and autosomal recessive familial hypercholesterolemia. Concomitant medications included acetylsalicylic acid/aluminum glycinate/magnesium carbonate, clopidogrel, glyceryl trinitrate, amlodipine, bisoprolol, indapamide, azilsartan, azelnidipine, glycyron, neuphagen, lansoprazole, teprenone, sodium alginate, mecobalamin, tocopheryl, etizolam, ramelteon, diclofenac, carbocisteine, and lidocaine.

Previous and ongoing treatment for familial hypercholesterolemia included atorvastatin, ezetimibe and probucol.

The subject received the first dose of evolocumab in Study 20110271 on 12 November [redacted].

Approximately 5 months later, on 15 April one year after*, the evolocumab was discontinued due to lack of efficacy. The subject initiated glyceryl trinitrate for angina. On 18 April one year after*, the subject reported fatigue and back pressure. He underwent coronary angiography which showed left anterior descending artery stenosis of 50 to 75%. Treatment medications included clopidogrel and isosorbide dinitrate.

On 18 June one year after*, the subject was hospitalized for myocardial ischemia and underwent percutaneous coronary intervention with placement of an LAD stent. Treatment medications included isosorbide dinitrate, etizolam, heparin, iopamidol, lidocaine, and diquafosol.

The outcome of the event of myocardial ischemia was reported as resolved on 21 June one year after*. The subject was discharged from the hospital on the same day.

The subject's last dose of evolocumab prior to the event of myocardial ischemia was 15 April one year after*. The subject continues on study, but as of the data cutoff of [redacted], evolocumab had not been restarted.

*新薬承認情報提供時に置き換え

The investigator reported that there was a reasonable possibility that the event of myocardial ischemia was related to evolocumab.