表 2.7.6.18-8　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（FAS）（続き）

器官別大分類 基本語	エゼチミブ プラセボ Q2W ＋エゼチミブ QD (N = 51) n (%)	エゼチミブ プラセボ QM ＋エゼチミブ QD (N = 51) n (%)	エゼチミブ 全体 (N = 102) n (%)	EvoMab 140 mg Q2W ＋プラセボ QD (N = 103) n (%)	EvoMab 420 mg QM＋ プラセボ QD (N = 102) n (%)	EvoMab 全体 (N = 205) n (%)
呼吸器、胸郭および縦隔障害（続き）						
鼻閉	0 (0.0)	1 (2.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
咽頭の炎症	0 (0.0)	1 (2.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
副鼻腔うっ血	1 (2.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
皮膚および皮下組織障害	5 (9.8)	9 (17.6)	14 (13.7)	5 (4.9)	8 (7.8)	13 (6.3)
多汗症	0 (0.0)	1 (2.0)	1 (1.0)	2 (1.9)	1 (1.0)	3 (1.5)
斑状皮疹	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.0)	2 (1.0)
皮膚嚢腫	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.5)
皮膚炎	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.5)
湿疹	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.5)
毛髪成長異常	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.5)
発疹	1 (2.0)	2 (3.9)	3 (2.9)	1 (1.0)	0 (0.0)	1 (0.5)
紅斑性皮疹	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.5)

N =解析対象集団で無作為割付けし治験薬を投与した被験者数、EvoMab = evolocumab (AMG 145) 、Q2W = 2 週 1 回 (皮下) 、QM = 4 週 1 回 (皮下)、QD = 1 日 1 回 (経口、錠剤)
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表 2.7.6.18-8　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（FAS）（続き）

器官別大分類 基本語	エゼチミブ プラセボ Q2W ＋エゼチミブ QD (N = 51) n (%)	エゼチミブ プラセボ QM ＋エゼチミブ QD (N = 51) n (%)	エゼチミブ 全体 (N = 102) n (%)	EvoMab 140 mg Q2W ＋プラセボ QD (N = 103) n (%)	EvoMab 420 mg QM＋ プラセボ QD (N = 102) n (%)	EvoMab 全体 (N = 205) n (%)
皮膚および皮下組織障害（続き）						
そう痒性皮疹	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.5)
脂漏	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.5)
蕁麻疹	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.5)
脱毛症	1 (2.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
皮膚乾燥	1 (2.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
紅斑	1 (2.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
爪床出血	0 (0.0)	1 (2.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
寝汗	0 (0.0)	1 (2.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
光線過敏性反応	0 (0.0)	1 (2.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
そう痒症	1 (2.0)	3 (5.9)	4 (3.9)	0 (0.0)	0 (0.0)	0 (0.0)
全身性そう痒症	0 (0.0)	2 (3.9)	2 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
外科および内科処置	0 (0.0)	1 (2.0)	1 (1.0)	2 (1.9)	1 (1.0)	3 (1.5)
骨移植	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.5)

N =解析対象集団で無作為割付けし治験薬を投与した被験者数、EvoMab = evolocumab (AMG 145) 、Q2W = 2 週 1 回 (皮下) 、QM = 4 週 1 回 (皮下)、QD = 1 日 1 回 (経口、錠剤)
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表 2.7.6.18-8　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（FAS）（続き）

器官別大分類 基本語	エゼチミブ			EvoMab		
	プラセボ Q2W ＋エゼチミブ QD (N = 51) n (%)	プラセボ QM ＋エゼチミブ QD (N = 51) n (%)	全体 (N = 102) n (%)	140 mg Q2W ＋プラセボ QD (N = 103) n (%)	420 mg QM＋ プラセボ QD (N = 102) n (%)	全体 (N = 205) n (%)
外科および内科処置（続き）						
軟骨移植	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.5)
類表皮嚢胞切除術	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.5)
骨切り術	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.5)
皮膚新生物切除	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.5)
脊髄除圧	0 (0.0)	1 (2.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
血管障害	1 (2.0)	3 (5.9)	4 (3.9)	4 (3.9)	6 (5.9)	10 (4.9)
高血圧	1 (2.0)	1 (2.0)	2 (2.0)	2 (1.9)	2 (2.0)	4 (2.0)
潮紅	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	2 (2.0)	3 (1.5)
ほてり	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.0)	2 (1.0)
末梢冷感	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.5)
血腫	0 (0.0)	1 (2.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
低血圧	0 (0.0)	1 (2.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)

N =解析対象集団で無作為割付けし治験薬を投与した被験者数、EvoMab = evolocumab (AMG 145) 、Q2W = 2 週 1 回 (皮下) 、QM = 4 週 1 回 (皮下)、QD = 1 日 1 回 (経口、錠剤)
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2.6.1.3　主な有害事象

evolocumab 群又はエゼチミブ群の 5%以上に認められた有害事象（evolocumab、エゼチミブ全体の発現率）は、頭痛（7.8%、8.8%）、筋肉痛（7.8%、17.6%）、四肢痛（6.8%、1.0%）、筋痙縮（6.3%、3.9%）、疲労（4.4%、9.8%）、悪心（4.4%、6.9%）及び下痢（2.4%、6.9%）であった。

2.6.1.4　医療機器と関連のある有害事象

9 例（2.9%）（evolocumab Q2W 群 2 例［1.9%］、evolocumab QM 群 4 例［3.9%］、エゼチミブ QM 群 3 例［5.9%］）に、医療機器と関連のある有害事象が 1 件以上認められた。医療機器と関連のある有害事象を表 2.7.6.18-9 に示す。医療機器と関連のある有害事象のほとんどは注射部位反応であり、そのうち 2 例以上に認められた有害事象は注射部位紅斑（3 例）及び注射部位内出血（2 例）であった。医療機器と関連のある有害事象はすべて軽度（CTCAE グレード 1）であり、治験薬の投与中止に至ったものはなかった。

表 2.7.6.18-9　治験中に発現した医療機器と関連のある基本語別の有害事象（FAS）

基本語	エゼチミブ			EvoMab		
	プラセボ Q2W ＋エゼチミブ QD (N = 51) n (%)	プラセボ QM ＋エゼチミブ QD (N = 51) n (%)	全体 (N = 102) n (%)	140 mg Q2W ＋プラセボ QD (N = 103) n (%)	420 mg QM ＋プラセボ QD (N = 102) n (%)	全体 (N = 205) n (%)
有害事象発現例	0 (0.0)	3 (5.9)	3 (2.9)	2 (1.9)	4 (3.9)	6 (2.9)
挫傷	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.5)
注射部位内出血	0 (0.0)	1 (2.0)	1 (1.0)	0 (0.0)	1 (1.0)	1 (0.5)
注射部位紅斑	0 (0.0)	2 (3.9)	2 (2.0)	0 (0.0)	1 (1.0)	1 (0.5)
注射部位疼痛	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.5)
注射部位腫脹	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.5)
四肢不快感	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.5)
四肢痛	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.5)
紅斑性皮疹	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.5)

N =解析対象集団で無作為割付けし治験薬を投与した被験者数、EvoMab = evolocumab (AMG 145) 、Q2W = 2 週 1 回 (皮下) 、QM = 4 週 1 回 (皮下)、QD = 1 日 1 回 (経口、錠剤)
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2.6.1.5　有害事象による投与中止

治験薬（SC 及び／又は PO）の投与中止に至った有害事象は 30 例に認められ、evolocumab 群 17 例（8.3%）、エゼチミブ群 13 例（12.7%）であった。投与中止に至った有害事象で最も多く認められたのは筋肉痛であり、evolocumab 群 4 例（2.0%）、エゼチミブ群 4 例（3.9%）に認められた。治験担当医師により治験薬と因果関係があると判断され、投与中止に至った有害事象が evolocumab 群の 4 例 7 件に認められた。evolocumab 群の 1 例は、重篤な有害事象（遠隔転移を伴う神経内分泌癌）により治験薬の投与を中止した。

2.6.1.6　死に至った有害事象

本試験において死亡は認められなかった。

2.6.1.7　重篤な有害事象

重篤な有害事象が evolocumab 群 6 例（2.9%）、エゼチミブ群 4 例（3.9%）に認められ、治験担当医師により治験薬投与と因果関係があると判断された重篤な有害事象（肝酵素上昇、脂肪腫及び背部痛）は、evolocumab Q2W 群の 3 例に認められた。evolocumab QM 群又はエゼチミブ群では、治験担当医師により投与と因果関係があると判断された重篤な有害事象はなかった。

2.6.2　臨床検査値の評価と心電図

臨床検査パラメータ、心電図又はバイタルサインにおいて、evolocumab が臨床的に重要な影響を示す兆候は認められなかった。

CK 上昇の発現率は投与群間で同様であった。基準値上限（ULN）の 5 倍を超えるが ULN の 10 倍未満の CK 上昇が 4 例（evolocumab 群 2 例［1.0%］及びエゼチミブ群 2 例［2.0%］）に認められた。この 4 例中 3 例は CK 上昇を伴う激しい労作があり、もう 1 例は CK 上昇の既往があった。エゼチミブ群の 1 例（1.0%）に ULN の 10 倍超の CK 上昇が認められた。CK 上昇により治験薬の投与を中止した被験者はいなかった。2 例（evolocumab 群 1 例及びエゼチミブ群 1 例）に、CK 上昇と同時に筋肉痛の有害事象が認められた。

ベースライン後の来院時に、アラニン・アミノトランスフェラーゼ（ALT）又はアスパラギン酸アミノトランスフェラーゼ（AST）が ULN の 3 倍を超えるか、あるいは総ビリルビンが ULN の 2 倍を超える肝機能検査（LFT）異常が認められた被験者はいなかった。

2.6.3　抗 evolocumab 抗体産生の状況

evolocumab 群全体の 204 例の被験者について、試験中に抗 evolocumab 抗体検査を実施し、ベースライン時 194 例及びベースライン後 201 例のいずれにおいても、抗 evolocumab 抗体が陽性となった被験者はいなかった。

3. 結論

本試験では、2種類以上のスタチンの投与を試みた結果、ミオパチー、すなわち筋肉痛（CK上昇を伴わない筋肉痛、筋肉痛又は筋力低下）、筋炎（CK値の上昇を伴う筋肉症状）、あるいは横紋筋融解症（著しいCK上昇を伴う筋肉症状）のため、いずれの用量も忍容できなかったか、あるいは治験実施計画書（7項参照）に規定されたスタチンの1週間の最大総投与量を超えるスタチンの増量を忍容できなかった高コレステロール血症被験者を対象としてevolocumabの評価を行った。本試験のデータから以下の結論が示された。

- evolocumabはLDL-Cの低下及びほかの対象とする脂質パラメータの改善において、エゼチミブより優れていた。
- evolocumabのQ2W投与とQM投与は臨床的に同等であり、エゼチミブと比較して有意にLDL-Cを低下させた。
- evolocumabのQ2W投与とQM投与は、エゼチミブと比較して、ApoB、総コレステロール／HDL-C比、総コレステロール、non-HDL-C、ApoB/ApoA1比及びLp（a）等のほかの脂質パラメータも改善させた。
- evolocumabを医療環境下で投与した場合と医療環境下以外（自宅）で投与した場合では、LDL-Cの低下は同様であった。
- evolocumab の投与により、エゼチミブと比較して血清中非結合型 PCSK9 濃度が著しく低下し、適切な目標範囲と一致した。
- 血清中非結合型evolocumab濃度はQM投与群がQ2W投与群より高く、AI/penでの投与頻度（Q2W又はQM）と一致する蓄積を示した。
- 治験中に発現した有害事象は、有害事象の発現率及び重症度、治験薬の投与中止に至った有害事象の発現率、並びに重篤な有害事象の発現率を含めて、エゼチミブと同様であった。
- 治験中に発現した有害事象の発現率とevolocumabの用量又は投与頻度（Q2W又はQM）との間に関連は認められなかった。
- 治験薬投与と因果関係のある臨床的に重要な臨床検査値異常を示す兆候は認められず、抗evolocumab抗体産生の所見も認められなかった。また、events of interestを評価した結果、evolocumabの全体的な安全性の評価は変わらなかった。
- AI/penを用いたevolocumabのQ2W又はQMでの投与は、医療環境下以外（自宅）での自己投与を含む使用目的及び使用条件において、安全かつ有効であった。

本試験の結果から、スタチンの忍容性が不良な患者においてevolocumabのベネフィットリスクプロファイルは良好であることが示された。

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2.7.6.18-10に要約する。

表 2.7.6.18-10　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		肝酵素上昇
2	[redacted]		X		膀胱移行上皮癌第３期
3	[redacted]		X		鼠径ヘルニア
4	[redacted]		X	X	遠隔転移を伴う神経内分泌癌、関節周囲炎
5	[redacted]		X		脂肪腫
6	[redacted]		X	X	消化管運動障害、脱毛症
7	[redacted]		X		脊髄除圧
8	[redacted]		X		軟骨移植、骨切り術
9	[redacted]		X		背部痛
10	[redacted]		X		腎感染
11	[redacted]			X	変色便、筋肉痛
12	[redacted]			X	咳嗽
13	[redacted]			X	薬物過敏症、薬物過敏症
14	[redacted]			X	腹痛、倦怠感
15	[redacted]			X	筋肉痛
16	[redacted]			X	腹痛、頭痛、筋肉痛、上腹部痛
17	[redacted]			X	尾骨痛、変形性関節症、背部痛
18	[redacted]			X	筋肉痛
19	[redacted]			X	眼刺激、背部痛、関節痛、関節痛、錯感覚、筋痙縮、睡眠の質低下
20	[redacted]			X	筋骨格痛
21	[redacted]			X	光線過敏性反応
22	[redacted]			X	そう痒性皮疹

MedDRA = ICH 国際医薬用語集

表 2.7.6.18-10　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（続き）

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	
23	[redacted]			X	筋力低下、悪心
24	[redacted]			X	胸部不快感、疲労、全身性そう痒症、筋肉痛
25	[redacted]			X	そう痒症
26	[redacted]			X	腹痛、悪心、腹痛、悪心、四肢痛
27	[redacted]			X	腹部膨満、体液貯留
28	[redacted]			X	呼吸困難
29	[redacted]			X	頭痛、筋肉痛
30	[redacted]			X	腹痛
31	[redacted]			X	発疹
32	[redacted]			X	四肢痛
33	[redacted]			X	灼熱感
34	[redacted]			X	筋痙縮
35	[redacted]			X	筋肉痛
36	[redacted]			X	不眠症
37	[redacted]			X	筋骨格痛、悪心
38	[redacted]			X	筋肉痛

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。

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Study Drug : AMG 145 Study Drug Administered : Yes

Case Number	Study ID	Patient ID	Center ID	Related Case	Death Case	Death Date	Dose	Patient Route of Administration	Frequency	Last Dose
[redacted]	20110116.2	[redacted]	[redacted]	Yes	No	---	140 mg, q2wk	Subcutaneous	q2wk	---

SAE Reported Term	SAE Preferred Term (SAE Lower Level Term)	Onset Date (Time to Onset)
ELEVATED LIVER ENZYME LEVELS	Hepatic enzyme increased (Elevated liver enzyme levels)	13-MAY-same year* ( )

Case Narrative : This 55 year old Caucasian male was participating in a double-blind, randomized, multicenter study to evaluate safety and efficacy of AMG 145, compared with ezetimibe, in hypercholesterolemic subjects unable to tolerate an effective dose of a HMG-CoA reductase inhibitor and developed elevated liver enzyme levels.

The subjects medical history included hypercholesterolemia, dyslipidemia, hypertension, former cigarette use, renal calculus, soft plaque in coronary artery, surgical repair of inguinal hernia, gastroesophageal reflux disorder, impaired glucose tolerance, erectile dysfunction, minor foot dysesthesia, vitamin D deficiency, gout and metabolic syndrome. The investigator reported that the subject did not have risk factors which had contributed to the development or worsening of the event.

Previous treatment for the condition under study included atorvastatin, pravastatin and simvastatin with associated muscle and non-muscle related statin intolerance and fluvastatin with associated muscle related statin intolerance. Previous an ongoing treatment for the condition under study included rosuvastatin. Concomitant medication included Zyloprim (allopurinol), Micardis (telmisartan), Somac (pantoprazole sodium sesquihydrate), Diabex XR (metformin hydrochloride), Zanidip (lercanidipine hydrochloride), Osteovit D (colecalciferol), fish oil, coenzyme Q10 (ubidecarenone) and influenza vaccine.

The subject received the first dose of blinded investigational product on 22/Apr/[redacted]. Approximately three weeks later, on 13/May/same year*, the subject underwent tests at a local laboratory which showed elevated liver enzymes >5X upper limit of normal (ULN). Laboratory results revealed aspartate aminotransferase (AST) of 147 U/L, alanine aminotransferase (ALT) of 248 U/L, gamma-glutamyltransferase of 407, blood bilirubin of 41 umol/L and an international normalized ratio (INR) within the normal range.

The event elevated liver enzyme levels was considered medically important. The subjects gastroenterologist felt that the time course implicated an antibiotic sensitivity as the subject had taken recent courses due to upper respiratory tract infection. The antibiotic was ceased and the resolution of transaminase elevation commenced from this time point. Blood tests were performed approximately every 72 hours and reviewed until resolution of the event.

On 17/May/same year*, laboratory tests revealed AST of 46 U/L, ALT of 111 U/L and total bilirubin of 23 umol/L. On 20/May/same year*, laboratory tests showed a marked decrease in values which included AST of 23 U/L, ALT of 54 U/L and total bilirubin of 20 umol/L. . Treatment information was not provided.

On 27/May/same year*, the subject was reviewed in the clinic and the levels of ALT, AST and bilirubin were considered normal (AST 12 U/L, ALT 17 U/L and total

bilirubin 10 umol/L). On physical examination, no hepatomegaly or signs of chronic liver disease were noted. The event was reported as resolved on 27/May/same year*.

The subjects last dose of subcutaneous blinded investigational product prior to the event was on 07/May/same year*. The subcutaneous blinded investigational product was temporarily withheld. Oral blinded investigational product was continued. On 03/Jun/same year*, further laboratory results were all within normal range. On this date, the subject was advised to administer the week 6 injection at home.

The investigator reported that there was a reasonable possibility that the event was related to subcutaneous and oral blinded investigational products. The investigator reported that there was no reasonable possibility that the event was related to the device.

ADDITIONAL INFORMATION RECEIVED ON 13/JUN/same year*: The subject had taken oral Avelox (moxifloxacin) from 01/May/same year* to 13/May/same year* for the treatment of an unspecified upper respiratory infection just before the onset of the serious adverse event of elevated liver enzymes and had also taken oral Augmentin (amoxicillin sodium, clavulanate potassium) from 14/May/same year* to 16/May/same year*. After elevated liver enzymes and the total bilirubin had an increase of 2-fold, Hy's law was suspected and the treating physician discontinued the investigational product per protocol. The subject was referred to a hepatologist for complete workup. Investigational product was restarted when all laboratory results were within normal range and the subject was cleared by the hepatologist. Results of the hepatitis evaluation would be provided by the investigator. Reportedly, liver enzymes remained within normal limits on 03/Jun/same year* and were still within normal limits on 17/Jun/same year* prior to the subject receiving the week 8 dose of investigational product. The subject received no treatment for the event other than discontinuation of Avelox and Augmentin.

The investigator considered Avelox and Augmentin as co-suspect medications.

ADDITIONAL INFORMATION RECEIVED ON 18/JUN/same year*: On 03/Jun/same year*, laboratory tests revealed an ALT of 14 U/L and total bilirubin of 22 umol/L. On 17/Jun/same year*, laboratory tests revealed an ALT of 16 U/L, AST of 12 U/L and total bilirubin of 13 umol/L. Tests for hepatitis C antibody and hepatitis B antigen were negative. Hepatitis A antibody was positive; however on 20/Jun/same year*, hepatitis A IgM antibody was negative, which indicated no recent infection. The investigator confirmed that blinded investigational product was restarted on 03/Jun/same year*.

ADDITIONAL INFORMATION RECEIVED ON 05/JUL/same year*: Subject began Avamys (fluticasone furoate - nasal spray) and Symbicort (budesonide, formoterol fumarate - inhaler) at the time of the event. The investigator reported that week six of blinded investigational product was administered at home on 03/Jun/same year*. On 17/Jun/same year*, the subjects liver function tests were within normal limits "prior to patient receiving their week 8 dose of IP".

ADDITIONAL INFORMATION RECEIVED ON 17/JUL/same year*: The subjects medical history also included a routine colonoscopy in five years ago*. It was confirmed that the subject received the first dose of blinded investigational product on 22/Apr/same year*. Additional details regarding treatment with Avamys and Augmentin were provided. Reportedly, Avamys and Symbicort were prescribed by subjects general practitioner after cessation of antibiotics for upper respiratory tract infection; Panafcort (prednisone) was subsequently added on 17/May/same year*. The subjects last dose of blinded subcutaneous investigational product prior to the event was confirmed as 07/May/same year*. It was also confirmed that blinded oral investigational product was never withheld; however, blinded subcutaneous investigational product was temporarily withheld and subsequently restarted on 17/Jun/same year* after local laboratory confirmed that liver enzymes were within normal limits. Additional laboratory tests obtained on that same day included alkaline phosphatase (ALP) of 60 U/L and gamma-glutamyltransferase (GGT)of 58 U/L. Subsequent laboratory tests obtained on 01/Jul/same year* disclosed ALT of 19 U/L, AST of 18 U/L, ALP of 42 U/L, GGT of

35 U/L and bilirubin total of 8 umol/L. Reportedly, laboratory tests were also collected on 15/Jul/same year*; however, results were not available at the time of this report.

ADDITIONAL INFORMATION RECEIVED ON 24/JUL/same year*: Laboratory tests performed on 15/Jul/same year*: revealed ALT of 27 U/L, and AST of 22U/L.

Study Drug : Study Drug Administered : Yes

Case Number	Study ID	Patient ID	Center ID	Related Case	Death Case	Death Date	Dose	Patient Route of Administration	Frequency	Last Dose
[redacted]	20110116.2	[redacted]	[redacted]	No	No	---	1 ml, q2wk	Subcutaneous	q2wk	---

SAE Reported Term	SAE Preferred Term (SAE Lower Level Term)	Onset Date (Time to Onset)
BLADDER CANCER STAGE III - TANSITIONAL CELL	Bladder transitional cell carcinoma stage III (Bladder transitional cell carcinoma stage III)	19-JUN-same year* ( )

Case Narrative : Initial Receipt Date = 10-JUL-same year*

This 62 year old Caucasian male was participating in a clinical trial, a double-blind, randomized, multicenter study to evaluate the safety and efficacy of AMG 145, compared with ezetimibe, in hypercholesterolemic subjects unable to tolerate an effective dose of an HMG-CoA reductase inhibitor, and developed bladder cancer grade 3-transitional cell.

The subjects medical history included dyslipidemia, current cigarette use, muscle related statin intolerance (atorvastatin and rosuvastatin), non-muscle related statin intolerance (rosuvastatin), varicose veins, fatty liver, elevated creatinine kinase, hyperlipidemia, basal cell carcinoma back, basal cell carcinoma left hand and left temple, and pre-diabetic (HbA1c between 6.0% and 6.4%). Previous treatment for the condition under study included atorvastatin and rosuvastatin. Previous and current treatment for the condition under study included omega 3 fish oil. Concomitant medications included Blackmores multivitamins and minerals (minerals NOS, vitamins NOS), trimethoprim, Minipress (prazosin hydrochloride), and metformin.

The subject received the first dose of blinded investigational product AMG 145 vs placebo vs ezetimibe on 03/Apr/[redacted]. The investigator reported that on the same date, a urinalysis revealed hematuria with +++ blood. The subject was contacted and a multiple chemical sensitivity test was requested. This was performed on 17/Apr/same year*, and showed an Escherichia coli urinary tract infection. The subject was then referred to his general practitioner for follow-up and treatment of hematuria and infection. The general practitioner treated the infection with Alprim (trimethoprim), diagnosed the subject with ongoing benign prostatic hypertrophy, and referred him to a urologist.

After seeing the urologist on 31/May/same year*, a Cystoscopy was planned. On the same date, a computerized scan of the bladder and renal tracts showed a possible bladder lesion. Approximately two months and two weeks after the first dose of blinded investigational product was administered, on 19/Jun/same year*,

the Cystoscopy was performed and the lesion/tumor was biopsied and resected. The lesion was found to be a grade 3 bladder tumor, a combination of carcinoma in situ as well as C3t1 bladder cancer, also described as a high grade urothelial carcinoma with invasion into the lamina proporia. The subject was scheduled for dose follow-up, re-biopsy, and Cystoscopy on 23/Jul/same year*.

The event bladder cancer grade 3-transitional cell was reported as resolved on 19/Jun/same year*. The subjects last dose of blinded investigational product prior to the event was on 12/Jun/same year*. Blinded investigational product was continued. The investigator reported that the subjects end of study date was 10/Jul/same year*.

The investigator reported that there was not a reasonable possibility that the event bladder cancer grade 3 -transitional cell was related to the blinded investigational product.

ADDITIONAL INFORMATION RECEIVED ON 15/AUG/same year*: Additional medical history included dyslipidemia diagnosed in eleven years ago*. On 19/Jun/same year*, a cystoscopy was done; bladder tumor was identified and resected. Histology result indicated bladder cancer grade 3, transitional cell. The subject returned for repeat cystoscopy on 23/Jul/same year* to check for residual disease, which revealed a small firm prostate, healing resection and biopsy sites and some small red areas. Histology results indicated polypoid cystitis of left bladder wall tumor site and anterior bladder wall, mild chronic cystitis of left bladder wall and a histologically normal bladder dome and right bladder wall. Cystoscopy and biopsies showed no further evidence of tumor. Urology plan was for subject to commence intravesical bacillus Calmette-Gurin (BCG) therapy.

ADDITIONAL INFORMATION RECEIVED ON 09/OCT/same year*: The event was updated from bladder cancer grade 3 -transitional cell to bladder cancer stage III- transitional cell. The investigator reported that subject completed a course of intravesical BCG (81 mg per dose) once every week for 6 weeks. No further treatment required.

The investigator reported that there was not a reasonable possibility that the event bladder cancer stage III- transitional cell was related to the blinded investigational product.

Study Drug : Study Drug Administered : Yes

Case Number	Study ID	Patient ID	Center ID	Related Case	Death Case	Death Date	Dose	Patient Route of Administration	Frequency	Last Dose
[redacted]	20110116.2	[redacted]	[redacted]	No	No	---	3 ml, q4wk	Subcutaneous	q4wk	---

SAE Reported Term	SAE Preferred Term (SAE Lower Level Term)	Onset Date (Time to Onset)
HERNIA INGUINALIS	Inguinal hernia (Hernia inguinal)	07-JUN-same year* ( )

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Case Narrative : Initial Receipt Date = 20/SEP/same year*

This 70 year old Caucasian female was participating in a double-blind, randomized, multicenter study to evaluate safety and efficacy of AMG 145, compared with ezetimibe, in hypercholesterolemic subjects unable to tolerate an effective dose of a HMG-COA reductase inhibitor, and developed hernia inguinalis.

The subjects medical history included dyslipidaemia, gonarthrosis, fatty liver, chronic gastritis, prolactinoma, drug intolerance due to CSE inhibitors (muscle related statin intolerance), osteoporosis, menopause, adnexal tumor, right bundle block, itching skin, lymphedema left leg, diabetic polyneuropathy, hypercholesterinemia, tiredness, dry mouth, type 2 diabetes mellitus, and hypertension (subject receiving treatment for hypertension). Previous treatment for the condition under study included fluvastatin and rosuvastatin. Concomitant medications included Blopress (candesartan cilexetil), HCT (hydrochlorothiazide), Metohexal (metoprolol tartrate), calcium, Dekristol (colecalciferol), and Voltaren (voltaren).

The subject received the first dose of the blinded investigational product on 30/Apr/[redacted]. Approximately one month and one week later, on 06/Jun/same year*, the subject was admitted to the hospital. The next day, on 07/Jun/same year*, the subject was diagnosed with hernia inguinalis. Treatment for the event included a short in hospital intervention for hernia inguinalis right. The investigator reported there were no postoperative complications and that the subject received outpatient care. The outcome of the event was reported as resolved on 07/Jun/same year* and the subject was discharged from the hospital on the same day.

The investigator reported that there was not a reasonable possibility that the event hernia inguinalis was related to the blinded investigational product or to the auto injector.

ADDITIONAL INFORMATION RECEIVED ON 09/OCT/same year*: Additional medical history included kidney insufficiency. The investigator stated that due to the groin pain, a hernia inguinal was diagnosed; therefore it was considered as pre-existing condition. The investigator reported that the subject was admitted to the hospital on 06/Sep/same year* instead of 06/Jun/same year* as previously reported. Laboratory tests results were not available. The event hernia inguinalis was reported as resolved on 07/Sep/same year* and the subject was discharged from the hospital on the same day instead of 07/Jun/same year* as previously reported.

ADDITIONAL INFORMATION RECEIVED ON 22/OCT/same year*: During visit, on 21/Jun/same year*, the subject reported a history of right groin pain since 07/Jun/same year*. No injury had occurred. Due to the subjects ongoing pain she visited a specialist, on 11/Jul/same year*, where the hernia was seen. On 06/Sep/same year*, the subject underwent surgery to remove the right inguinal hernia. The investigator confirmed that the inguinal hernia was not worsening, and that it was the same diagnosis for which groin pain was the symptom. The subjects last dose of blinded investigational product prior to the event was on 30/Apr/same year*. The blinded investigational product was continued.

Study Drug : AMG 145 Study Drug Administered : Yes

Case Number	Study ID	Patient ID	Center ID	Related Case	Death Case	Death Date	Dose	Patient Route of Administration	Frequency	Last Dose
[redacted]	20110116.2	[redacted]	[redacted]	No	No		1 ml, q2wk	Subcutaneous	q2wk	17-MAY-same year*

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SAE Reported Term	SAE Preferred Term (SAE Lower Level Term)	Onset Date (Time to Onset)
NEUROENDOCRINE CARCINOMA METASTATIC	Neuroendocrine carcinoma metastatic (Neuroendocrine carcinoma metastatic)	28-MAY-same year* (11 days)

Case Narrative : Initial Receipt Date = 16-JUL-same year*

This 69 year old Caucasian male was participating in a clinical trial, a double-blind, randomized, multicenter study to evaluate safety and efficacy of AMG 145, compared with ezetimibe, in hypercholesterolemic subjects unable to tolerate an effective dose of a HMG-CoA reductase inhibitor and developed muscle pain.

The subjects medical history included hypercholesterolemia, angina pectoris due to atherosclerotic coronary disease, NYHA class I congestive heart failure, normal systolic function with a left ventricular ejection fraction of 50%, myocardial infarction, hypertension, former cigarette use, percutaneous coronary intervention, chronic rhinitis, chronic obstructive pulmonary disease, presbycusis, frozen shoulder both sides, "cutaan T cell lymfoom" (cutaneous T-cell lymphoma) and erection problems. Previous treatment for the condition under study included atorvastatin, simvastatin and pravastatin with history of muscle related statin intolerance. Concomitant medications included Vitamin D NOS, carvedilol, lisinopril, furosemide, apixaban, Esomeprazol (esomeprazole), Ventolin (salbutamol), salmeterol, Fluticason (fluticasone propionate) and mometasone.

The subject received the first dose of blinded investigational product vs ezetimibe 03/May/[redacted]. Approximately twenty-eight days later, on 31/May/same year*, the subject developed disabling muscle pain. On 04/Jul/same year*, x-ray disclosed no abnormalities. Subsequently, on 08/Jul/same year*, the subject was admitted to the hospital due to worsening of muscle pain in the lower back. Repeated x-ray performed on that same day showed no abnormalities. Magnetic resonance imaging, performed on 10/Jul/same year*, disclosed possible collapsed vertebra L2. No further information was provided. The event muscle pain was reported as not resolved and the subject remained hospitalized at the time of this report. The subjects last dose of blinded investigational product prior to the event was on 17/May/same year*. Blinded investigational product was discontinued.

The investigator reported that there was a reasonable possibility that the event muscle pain was related to blinded investigational product. The investigator reported that there was not a reasonable possibility that the event muscle pain was related to the device.

ADDITIONAL INFORMATION RECEIVED ON 23/JUL/same year*: The causal relationship between the blinded investigational product and the reported event muscle pain was updated to unrelated, rather than related as previously reported.

ADDITIONAL INFORMATION RECEIVED ON 26/AUG/same year*: Additional medical history included hernia diafragmatica. The investigator reported that treatment for a possible collapsed vertebra L2 included radiotherapy 1x8 Gy on L2 and 5x4 Gy on brain. Treatment for the event included paracetamol and Metamizol (metamizole magnesium).

The investigators rationale for updating the causality between the blinded investigational product and the reported event muscle pain to not related, was the subjects metastasized tumor was unlikely to have developed in the short time that the subject had been participating in the trial, in retrospect some of the subjects complaints were present before the administration of the blinded investigational product and could be related to the current condition.

ADDITIONAL INFORMATION RECEIVED ON 17/SEP/same year*: The event term muscle pain was updated to collapsed vertebra. The investigator confirmed that the muscle pain from a collapsed vertebra was not the result of radiation therapy directed at a tumor located in the L2 region.

The investigator reported that there was not a reasonable possibility that the event collapsed vertebra was related to the blinded investigational product or to device.

ADDITIONAL INFORMATION RECEIVED ON 24/SEP/same year*: X ray of thorax showed suspicion metastasis, and computerized tomogram of thorax showed multiple metastases in lung, liver, and brain. On 10/Jul/same year*, magnetic resonance imaging was performed and did not show abnormalities. The subject received radiation therapy from 31/Jul/same year* to 06/Aug/same year*. No chemotherapy was started. The event collapsed vertebra was reported as not resolved and the subject remained hospitalized at the time of this report.

ADDITIONAL INFORMATION RECEIVED ON 30/SEP/same year*: The event term collapsed vertebra was update to neuroendocrine carcinoma metastatic. Reportedly on 27/Aug/same year* the subject experienced worsening of back pain after radiation along with clinical deterioration. Therefore radiation sessions were stopped and palliative care was started. A liver biopsy was performed and showed high-grade neuroendocrine carcinoma. However the primary origin remained unknown. The event was ongoing and the subject remained hospitalized.

The investigator reported that there was not a reasonable possibility that the event neuroendocrine carcinoma metastatic was related to the blinded investigational product or to device.

ADDITIONAL INFORMATION RECEIVED ON 22/OCT/same year*: The onset date for the event was updated to 28/May/same year* not 31/May/same year* as previously reported. The subject was discharged from the hospital on 22/Jul/same year*. The outcome of the event was reported as unknown not ongoing as previously reported. However an end date on 06/Oct/same year* was reported. The investigator reported that the subject died after the 30 days follow up period on 06/Oct/same year*. The cause of death was unknown and was not related to the event.

ADDITIONAL INFORMATION RECEIVED ON 25/OCT/same year*: The event was reported as not resolved at the end of study. The subject died on 06/Oct/same year*. The investigator confirmed that the origin of the tumor was unknown and the cause of death was unknown.

ADDITIONAL INFORMATION RECEIVED ON 28/NOV/same year*: The outcome of the event was reported as resolved on 06/Oct/same year*.

Study Drug : AMG 145 Study Drug Administered : Yes

Case Number	Study ID	Patient ID	Center ID	Related Case	Death Case	Death Date	Dose	Patient Route of Administration	Frequency	Last Dose
[redacted]	20110116.2	[redacted]	[redacted]	Yes	No	---	140 mg, q2wk	Subcutaneous	q2wk	11-JUL-same year*

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SAE Reported Term	SAE Preferred Term (SAE Lower Level Term)	Onset Date (Time to Onset)
LIPOMA	Lipoma (Lipoma)	18-JUL-same year* (7 days)

Case Narrative : INITIAL INFORMATION RECEIPT ON = 09/AUG/same year*

This 69 year old Caucasian female was participating in a double-blind, randomized, multicenter study to evaluate safety and efficacy of AMG 145, compared with ezetimibe, in hypercholesterolemic subjects unable to tolerate an effective dose of a HMG-CoA reductase inhibitor and experienced swelling right upper leg, MRI malignancy suspected.

The subjects medical history included hypercholesterolemia, moderate dysfunction left ventricular systolic ejection fraction of 30-39%, myocardial infarction, tonsillectomy, irritable bowel syndrome, helicobacter pylori eradication therapy, Barret esophagus and ulnaire benign tumor, left wrist. Previous treatment for the condition under study included atorvastatin, fluvastatin and rosuvastatin. Concomitant medications included paracetamol, fluvastatin, metoprolol, acenocoumarol and omeprazole.

The subject received the first dose of blinded investigational product on 02/May/[redacted]. Approximately two and a half months later, on 18/Jul/same year*, the subject experienced swelling right upper leg. Magnetic resonance imaging was performed, malignancy was suspected. The event was ongoing at the time of the report. The subject received the last dose of blinded investigational product prior to the event on 11/Jul/same year*. Blinded investigational product was continued.

The investigator reported that there was no reasonable possibility that the event swelling right upper leg, MRI malignancy suspected was related to blinded investigational product.

ADDITIONAL INFORMATION RECEIVED ON 16/AUG/same year*: The investigator updated the event term from "swelling right upper leg, MRI malignancy suspected" to "tumor left upper leg". Reportedly, the subject had not experienced previous swelling. On 08/Aug/same year*, nuclear magnetic resonance imaging (MRI) showed intramuscular mass of 24x11x6 cm anterior in left upper leg with area of incomplete fat suppression consistent with (low grade) liposarcoma; differential diagnosis (Dd) was (variant) lipoma. The investigator reported that further investigation and treatment would be determined.

The investigator reported that there was a reasonable possibility that the event tumor left upper leg was related to blinded investigational product. The investigator reported that there was not a reasonable possibility that the event tumor left upper leg was related to the device.

ADDITIONAL INFORMATION RECEIVED ON 30/SEP/same year*: Previous and ongoing treatment for the condition under study included fluvastatin. The event was reported as not resolved at the time of this report. The investigator reported that the subject would undergo surgery as treatment for the event and was on a waiting list at the time of this report.

ADDITIONAL INFORMATION RECEIVED ON 03/OCT/same year*: The subjects additional medical history included history of muscle related statin intolerance due to atorvastatin, fluvastatin and rosuvastatin administration.

ADDITIONAL INFORMATION RECEIVED ON 15/Oct/same year*: The event term was updated from tumor left upper leg to lipoma. The subject noticed leg

swelling on 18/Jul/same year*. No other symptoms were observed. On 06/Oct/same year*, the subject was hospitalized. Measurements of the mass were confirmed to be 24x11x6 cm. Mass biopsy was pending. Unspecified surgical intervention was performed for the event. The event lipoma resolved, and the subject was discharged, on 12/Oct/same year*. The investigator confirmed that the subjects last dose of blinded investigational product prior to the event was on 11/Jul/same year*.

The investigator reported that there was a reasonable possibility that the event lipoma was related to blinded investigational product. The investigator reported that there was no reasonable possibility that the event lipoma was related to the device.

ADDITIONAL INFORMATION RECEIVED ON 06/NOV/same year*: Reportedly at the beginning of the study the subject did not present with swelling on left leg even though she injected blinded investigational product in both legs during the study. Specific intervention performed as treatment for the event on 07/Oct/same year* was confirmed as a resection of the tumor with a narrow margin under general anesthesia. Mass biopsy (tumor tissue) pathology report showed mature adipose tissue without cytonuclear atypia, lipoma completely removed. The investigator confirmed that the last scheduled dose of investigational product was on 11/Jul/same year*.

ADDITIONAL INFORMATION RECEIVED ON 28/NOV/same year*: Additional medical history included difficulty to lay on her back since fifty years ago*. Supplementary concomitant medications included cortisone.

Study Drug : Study Drug Administered : Yes

Case Number	Study ID	Patient ID	Center ID	Related Case	Death Case	Death Date	Dose	Patient Route of Administration	Frequency	Last Dose
[redacted]	20110116.2	[redacted]	[redacted]	No	No	---	1 ml, q2wk	Subcutaneous	q2wk	---

SAE Reported Term	SAE Preferred Term (SAE Lower Level Term)	Onset Date (Time to Onset)
INTESTINAL MOTILITY DISORDER PROBABLY CAUSED BY TRAMADOL	Gastrointestinal motility disorder (Gastrointestinal motility disorder)	15-SEP-same year* ( )

Case Narrative : Initial Receipt Date = 30-SEP-same year*

This 70 year old Caucasian female subject was participating in a double-blind, randomized, multicenter study to evaluate safety and efficacy of AMG 145, compared with ezetimibe, in hypercholesterolemic subjects unable to tolerate an effective dose of a HMG-CoA reductase inhibitor and experienced abdominal distension.

The subjects medical history included dyslipidemia, hypertension, ulcerous colitis, lumbar discopathy, nodal osteoarthritis, osteoporosis, migraine and lumbar pain. Previous treatment for the condition under study included atorvastatin. Concomitant medications included tramadol, amitriptyline hydrochloride, alendronate sodium, colecalciferol, losartan, omeprazol, betamethasone and metamizole.

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The subject received the first dose of blinded investigational product on 20/Jun/[redacted]. Approximately three months later, on 25/Sep/same year*, the subject went to the emergency room with a history of abdominal discomfort for some previous days and was admitted to the hospital. The subject was diagnosed with abdominal distension. Laboratory tests disclosed leukocytes of 4800xul, hemoglobin of 12.7 g/dl and platelets of 191000xul. Abdominal x-ray was normal. Treatment for the event was not provided. The event abdominal distension was reported as not resolved and the subject remained hospitalized at the time of this report. The investigator reported that the subject had no risk factors for the event. The subjects last dose of blinded investigational product prior to the event was on 04/Sep/same year*. Blinded investigational product was continued.

The investigator reported that there was not a reasonable possibility that the event abdominal distension was related to the blinded investigational product or to the device.

ADDITIONAL INFORMATION RECEIVED ON 09/Oct/same year*: Event term abdominal distension was updated to intestinal motility disorder probably caused by tramadol. The subjects medical history included hypercholesterolemia. From previous treatment with atorvastatin, the subject was found to have muscle related statin intolerance. Reportedly, the subject had not had any changes in medications, lifestyle or procedures prior to the event. A colonoscopy revealed normal results, and a computerized tomography revealed probable mild pancreatitis. The event intestinal motility disorder probably caused by tramadol resolved on 08/Oct/same year*, and the subject was discharged from the hospital with the diagnosis of intestinal motility disorder probably caused by tramadol.

The investigator reported that there was not a reasonable possibility that the event intestinal motility disorder probably caused by tramadol was related to the blinded investigational product or to device.

ADDITIONAL INFORMATION RECEIVED ON 10/Oct/same year*: The subject experienced abdominal discomfort since 15/Sep/same year*. The investigator confirmed that tramadol was considered a co-suspect medication and was discontinued on 25/Sep/same year*.

ADDITIONAL INFORMATION RECEIVED ON 14/OCT/same year*: The onset date of the event was updated to 15/Sep/same year* instead of 25/Sep/same year* as previously reported. The investigator stated that probable mild pancreatitis, indicated in computerized tomography results, was not considered as the final diagnosis. Additionally, the investigator reported that the pharmacological etiology was not totally confirmed.

Study Drug : Study Drug Administered : Yes

Case Number	Study ID	Patient ID	Center ID	Related Case	Death Case	Death Date	Dose	Patient Route of Administration	Frequency	Last Dose
[redacted]	20110116.2	[redacted]	[redacted]	No	No	---	3 ml, q4wk	Subcutaneous	q4wk	---

SAE Reported Term	SAE Preferred Term (SAE Lower Level Term)	Onset Date (Time to Onset)
L-4, L-5 DECOMPRESSION	Spinal decompression (Lumbar nerve decompression)	06-MAR-same year* ( )

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Case Narrative : This 60 year old Caucasian female subject was in a screening phase for a double-blind, randomized, multicenter study to evaluate safety and efficacy of AMG 145, compared with ezetimibe, in hypercholesterolemic subjects unable to tolerate an effective dose of a HMG-CoA reductase inhibitor and developed L-4, L-5 decompression.

The subjects medical history included hypercholesterolemia, type 2 diabetes mellitus, hypertension, insomnia, back pain, anxiety, right rotator cuff repair, carpal tunnel surgery, appendectomy, umbilical hernia, umbilical hernia repair, statin associated myalgia, neuropathy peripheral, sensitivity to fenofibrate, sensitivity to Zestril, sleep apnea syndrome, kidney stone, tubal ligation and allergy to penicillin. Previous treatment for the condition under study included atorvastatin and simvastatin. Concomitant medications included multivitamin (ascorbic acid, calcium pantothenate, ergocalciferol, nicotinamide, pyridoxine hydrochloride, retinol, riboflavin, thiamine hydrochloride), aspirin (acetylsalicylic acid), metformin, Byetta (exenatide), Ambien (zolpidem tartrate), citalopram hydrobromide, Neurontin (gabapentin), Diovan (valsartan), Amaryl (glimepiride) and lovastatin.

The subject received the first dose of blinded investigational product on 20/Feb/[redacted]. Approximately two weeks later, on 06/Mar/same year*, the subject developed L-4, L-5 decompression. On 07/Mar/same year* the event was reported as resolved and the subject was discharged from the hospital. The subjects last dose of blinded investigational product prior to the event was on 20/Feb/same year*. Blinded investigational product was continued.

The investigator reported that there was not a reasonable possibility that the event L-4, L-5 decompression was related to investigational product.

ADDITIONAL INFORMATION RECEIVED ON 24/JUN/same year*: Further medical history included statin intolerance, post-menopausal status, insomnia and torn right rotator cuff. Previous treatment for the condition under study included rosuvastatin. Concomitant medication details were updated. The investigator reported degenerative disc disease as a predisposing factor that contributed to the event L-4, L-5 decompression. Treatment medications for the event included oxycodone, Acetaminophen (paracetamol), diazepam, Ancef (cefazolin sodium) and Vicodin (hydrocodone bitartrate, paracetamol).

Study Drug : Study Drug Administered : Yes

Case Number	Study ID	Patient ID	Center ID	Related Case	Death Case	Death Date	Dose	Patient Route of Administration	Frequency	Last Dose
[redacted]	20110116.2	[redacted]	[redacted]	No	No	---	UNK UNK, q4wk	Subcutaneous	q4wk	---

SAE Reported Term	SAE Preferred Term (SAE Lower Level Term)	Onset Date (Time to Onset)
CARTILAGE ALLOGRAFT	Cartilage graft (Cartilage allograft)	16-APR-same year* ( )
OSTEOTOMY	Osteotomy (Osteotomy)	16-APR-same year* ( )

Case Narrative : This 66 year old white male subject was participating in a double-blind, randomized, multicenter study to evaluate safety and efficacy of AMG 145, compared with ezetimibe, in hypercholesterolemic subjects unable to tolerate an effective dose of a HMG-CoA reductase inhibitor and underwent osteotomy and cartilage allograft.

The subjects medical history included dyslipidemia. Previous treatment for the condition under study and concomitant medications were not provided at the time of this report.

The subject received the first dose of blinded investigational product on an unspecified date. On 16/Apr/same year*, the subject underwent osteotomy and cartilage allograft. The subject was hospitalized on an unspecified date. No further information was provided at the time of this report. The events osteotomy and cartilage allograft were reported to have resolved on 17/Apr/same year*. The subjects last dose of blinded investigational product prior to the event and the action taken was not provided.

The investigator reported that there was a no reasonable possibility that the events osteotomy and cartilage allograft were related to blinded investigational product or the device.

ADDITIONAL INFORMATION RECEIVED ON 30/APR/same year*: Concomitant medications reported included Lexapro (escitalopram oxalate), Multivitamin (ascorbic acid, calcium pantothenate, ergocalciferol, nicotinamide, pyridoxine hydrochloride, retinol, riboflavin, thiamine hydrochloride), Aspirin (acetylsalicylic acid), CoQ10 (ubidecarenone), Saw Palmetto (serenoa repens), and Krinoil.

The investigator confirmed that the subject received the test placebo dose during screening period. On 11/Apr/[redacted], the subject received the first dose of blinded investigational product. On 16/Apr/same year*, the subject was hospitalized to undergo osteotomy and cartilage allograft. No further information was available at the time of reporting. The subject was discharged from the hospital on 17/Apr/same year*. The last dose of blinded investigational product was on 11/Apr/same year*. No concomitant medications were considered as co-suspect.

ADDITIONAL INFORMATION RECEIVED ON 04/JUN/same year*: The subjects medical history included atrial fibrillation/flutter, statin intolerance, sciatica pain, seasonal allergy, lumbar disc disease, torn meniscus of left and right knee, torn right bicep, torn right supraspinatus, basal cell on left eyelid removed, anxiety, cardiac ablation, left hernia repair, right knee arthroscopy, edema of the feet, left inguinal hernia, constipation, colonoscopy, benign prostatic hypertrophy, shingles and mild hypothyroidism. Previous treatment for the condition under study included atorvastatin and rosuvastatin. Concomitant medication details were updated.

Study Drug : AMG 145 Study Drug Administered : Yes

Case Number	Study ID	Patient ID	Center ID	Related Case	Death Case	Death Date	Dose	Patient Route of Administration	Frequency	Last Dose
[redacted]	20110116.2	[redacted]	[redacted]	Yes	No	---	---	Subcutaneous	q2wk	---

SAE Reported Term	SAE Preferred Term (SAE Lower Level Term)	Onset Date (Time to Onset)
ACUTE BACK PAIN	Back pain (Acute back pain)	24-MAY-same year* ( )

Case Narrative : This 70 year old Caucasian male was participating in a clinical trial, a double-blind, randomized, multicenter study to evaluate safety and

efficacy of AMG 145, compared with ezetimibe, in hypercholesterolemic subjects unable to tolerate an effective dose of a HMG-CoA reductase inhibitor and developed acute back pain.

The subjects medical history included hypercholesterolemia, former atrial fluter/fibrillation, former cigarette use, percutaneous coronary intervention, peripheral arterial disease, history of muscle related statin intolerance (Atorvastatin, Rosuvastatin, Simvastatin), pulmonary embolism, coronary artery disease, hyperlipidemia, pelvic joint pain and hand joint pain, malignant bladder lining, lumbago, pain in limb, lumbar disc displacement, lumbosacral neuritis, shortness of breath, benign prostatic hypertrophy without urinary obstruction, spinal stenosis lumbar, chronic anticoagulation, degenerative arthritis of thumb, generalized osteoarthritis of hand, inguinal hernia, right flank pain, hematuria, nephrolithiasis, chronic bronchitis, right rotator cuff repair, obstructive sleep apnea, left shoulder arthroscopy, right total hip replacement, right knee pain, arthritis of knee; right knee arthroscopic partial meniscectomy, medial meniscus right knee, cardioversion, seborrheic keratosis on right infraorbital skin, cutaneous tag, morbid obesity, insomnia, general osteoarthritis, femoral deep/superficial vein phlebitis swelling of limb and enthesopathy of hip.

No previous treatment for the condition under study was provided at the time of this report. Concomitant medications included Vitamin D2 (ergocalciferol), acetaminophen, magnesium oxide, sotalol, warfarin and Aspirin (acetylsalicylic acid).

The subject received the first dose of blinded investigational product AMG 145 vs placebo vs ezetimibe on 05/Apr/[redacted]. Approximately seven weeks later, on 24/May/same year*, the subject developed right sided lower back pain without history of trauma or heavy lifting.

On 28/May/same year*, the subject saw his primary care physician who prescribed Flexeril (cyclobenzaprine hydrochloride) and Percocet (oxycodone hydrochloride/oxycodone terephthalate/paracetamol) with some pain improvement.

On 31/May/same year*, the subject developed acute worsening of pain reporting muscle tightness. The following day, on 01/Jun/same year*, the subject presented to the hospital with worsening right sided back pain of 1 week duration and the subject was hospitalized on that same day. According to physicians notes, the subject presented likely lumbar muscle sprain. On an unknown date during hospitalization, the subjects pain improved and he continued with Flexeril. No further information was provided. On 03/Jun/same year*, oxycodone plus acetaminophen (oxycodone hycdrochloride/paracetamol) was started. On that same day, the event acute back pain was reported to have resolved and the subject was discharged from hospital. No further information was provided.

The subjects last dose of blinded investigational product prior to the event was on 18/Apr/same year*. Blinded investigational product was continued.

The investigator reported that there was a reasonable possibility that the event acute back pain was related with the blinded investigational product. The investigator reported that there was no a reasonable possibility that the event acute back pain was related with the device.

ADDITIONAL INFORMATION RECEIVED ON 13/JUN/same year*: The subjects medical history included primary hypercoagulable state.

ADDITIONAL INFORMATION RECEIVED ON 20/JUN/same year*: Additional medical history included coronary artery disease with bare metal stent to left circumflex artery and drug-eluting stent to right coronary artery; obstructive sleep apnea on continuous positive airway pressure therapy and direct-current cardioversion.