クロスオーバー群及び CD25 陰性群）では，早期に中止した被験者が多く認められた。4 サイクル以下で投与を中止した被験者は，E7272 既投与の群（再発・再投与群及び 8 サイクル SD 群）では約 25%であったのに対し，E7272 未投与の群では約 45～60%であった。

2.7.6.6.6 薬物動態の結果

血清中 E7272 濃度について評価可能な 48 例（先行試験で E7272 投与を受けていない被験者のみ）を対象として，E7272 の薬物動態を評価した。

E7272 18 μg/kg/日の投与を受けた被験者における平均血清中 E7272 濃度推移を図 2.7.6.6-1 に示した。

血清中 E7272 濃度は静脈内投与開始後 30 分でピークに達し，その後の 4 時間で緩やかに低下した（静脈内投与時間は約 30 分間）。

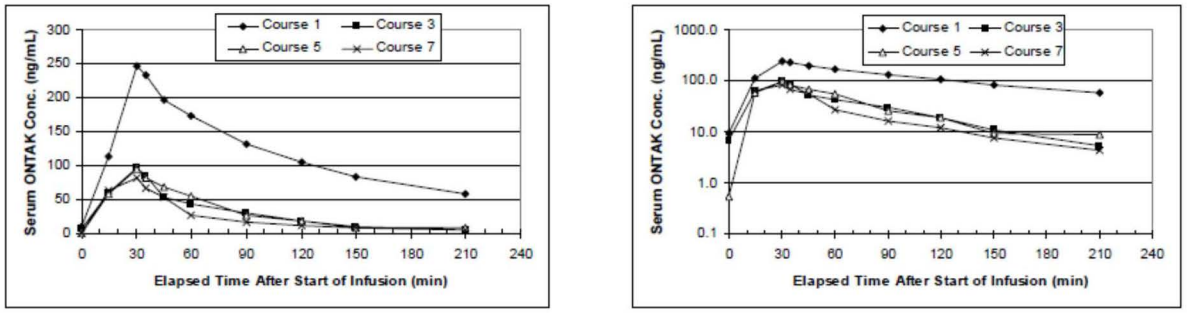


図 2.7.6.6-1　Cycle 1，3，5 及び 7 において E7272 を 18 μg/kg/日で投与したときの平均血清中 E7272 濃度推移（外国 L4389-14 試験）

ONTAK = E7272
左図：線形目盛，右図：対数目盛

（添付資料 5.3.5.4.3 の Figure 4 を引用）

E7272 18 μg/kg/日を投与したときの E7272 の薬物動態パラメータを表 2.7.6.6-3 に示した。

E7272 の暴露量パラメータ（C_{max} 及び $AUC_{(0\text{-}inf)}$）は，Cycle 1 において，その後の投与期間よりも高かった。Cycle 1 と比較して Cycle 3 の平均 C_{max} は 60%減少し，以降はその付近で安定した。Cycle 1 と Cycle 3 の間で平均 $AUC_{(0\text{-}inf)}$は約 80%減少し，全身クリアランスは 5 倍に増加した。また，$t_{1/2}$ も約 50%短縮したが，t_{max} については顕著な変化はみられなかった。

C_{max}，$AUC_{(0\text{-}inf)}$及び $t_{1/2}$ の減少はベースライン（Cycle 1）と Cycle 3 の間で認められたが，この期間は抗 DD 抗体価の約 4 倍の上昇（1.2 から 4.9 に上昇，抗体濃度は約 625 倍以上の上昇）が認められている期間と一致していた。Cycle 5 及び 7 の E7272 濃度は Cycle 3 と同程度であったことから，Cycle 3 以降の血清中 E7272 濃度及び薬物動態にはほとんど変化がないことが示唆された。

表 2.7.6.6-3　Cycle 1，3，5 及び 7 において E7272 を 18 μg/kg/日で投与したときの薬物動態パラメータ（外国 L4389-14 試験）

薬物動態パラメータ	統計量	Cycle 1 (N=42)	Cycle 3 (N=21)	Cycle 5 (N=18)	Cycle 7 (N=10)
C_{max} (ng/mL)	平均値	271	108	111	93
	標準偏差	±126	±51	±66	±47
t_{max} (min)	平均値	37	34	38	32
	標準偏差	±13	±17	±20	±11
$AUC_{(0\text{-inf})}$ (ng•min/mL)	平均値	33,253	6,925	6,480 [a]	4,818 [b]
	標準偏差	±16,931	±4,254	±3,700	±2,371
$t_{1/2}$ (min)	平均値	84	40	43 [a]	31 [b]
	標準偏差	±32	±21	±26	±16
CL (mL/min/kg)	平均値	0.7	3.6	3.8 [a]	4.9 [b]
	標準偏差	±0.4	±2.1	±2.1	±3.0
V_{ss} (mL/kg)	平均値	77	189	235 [a]	186 [b]
	標準偏差	±28	±124	±182	±154

$AUC_{(0\text{-inf})}$ = area under the curve of serum concentration vs. time, from 0 to infinity, CL = rate of clearance of drug from the blood, C_{max} = maximum serum concentration measured, t_{max} = time from the start of administration to attain the maximum serum concentration, $t_{1/2}$ = the time required for the plasma level of drug to fall to half of a measured level,
V_{ss} = steady state volume of distribution.
a: n=16
b: n=9

（添付資料 5.3.5.4.3 の Table 12 を引用）

抗 DD 抗体濃度及び t_{max} を除く E7272 の薬物動態パラメータで認められた変化から，薬物動態パラメータの変化と抗体産生との相関が示唆された。抗 DD 抗体の産生によって E7272 の血中クリアランスが上昇すると考えられたが，Cycle 1 及び 3 における E7272 のクリアランスと抗 DD 抗体価に対する線形回帰分析を行った結果，抗体産生と薬物クリアランスとの明確な関連性は示されなかった。

2.7.6.6.7 有効性の結果

2.7.6.6.7.1 主要評価項目：奏効率

最良効果の内訳を表 2.7.6.6-4 に示した。

奏効率（最良効果が CR，CCR 又は PR の被験者の割合）は，プラセボクロスオーバー群 59.3%，再発・再投与群 40.0%，CD25 陰性群 30.6%であり，プラセボクロスオーバー群で最も高かった。8 サイクル SD 群では，奏効例は認められなかった。いずれの患者群でも，奏効例で最も多く認められた効果は PR であった。

表 2.7.6.6-4　最良効果（ITT 集団）（外国 L4389-14 試験）

項目	プラセボクロスオーバー群 (N=27)	再発・再投与群 (N=20)	8 サイクル SD 群 (N=9)	CD25 陰性群 (N=36)
奏効例（完全奏効［CR］，臨床的完全奏効［CCR］及び部分奏効［PR］），n (%)	16 (59.3)	8 (40.0)	0 (0.0)	11 (30.6)
正確な 95%信頼区間	(38.8, 77.6)	(19.1, 63.9)	-	(16.3, 48.1)
CR 及び CCR，n (%)	6 (22.2)	2 (10.0)	-	3 (8.3)
PR，n (%)	10 (37.0)	6 (30.0)	-	8 (22.2)
安定（SD），n (%)	6 (22.2)	5 (25.0)	6 (66.7)	16 (44.4)
進行（PD），n (%)	4 (14.8)	7 (35.0)	3 (33.3)	9 (25.0)
評価不能[a]，n (%)	1 (3.7)	-	-	-

a: データ不足のため評価不能。
最良効果は，2006 年 8 月 7 日の Data Endpoint Review Committee による最終評価及び治験実施計画書の規定に基づき分類した。最良効果の定義は，観察期間中かつ進行が認められる前に確認された最も良い効果とした。
（添付資料 5.3.5.4.3 の Table 14，Table 21，Table 28 及び Table 32 を引用）

2.7.6.6.7.2 副次評価項目

2.7.6.6.7.2.1 無増悪生存期間（PFS）

Kaplan-Meier 法により推定した PFS の中央値は，プラセボクロスオーバー群 870 日，再発・再投与群 205 日，8 サイクル SD 群 183 日，CD25 陰性群 487 日超（最終データ時点，中央値未達）であった。

2.7.6.6.7.2.2 治療成功期間

Kaplan-Meier 法により推定した治療成功期間の中央値は，プラセボクロスオーバー群 102 日，再発・再投与群 189 日，8 サイクル SD 群 183 日，CD25 陰性群 68.5 日であった。

2.7.6.6.7.3 その他の評価項目

2.7.6.6.7.3.1 奏効までの期間（TTR）

Kaplan-Meier 法により推定した TTR の中央値は，プラセボクロスオーバー群 45 日，再発・再投与群 102 日，CD25 陰性群 204 日超（最終データ時点，中央値未達）であった。8 サイクル SD 群では奏効は認められなかった。

2.7.6.6.7.3.2 奏効持続期間（DOR）

Kaplan-Meier 法により推定した DOR の中央値は，プラセボクロスオーバー群 820 日，再発・再投与群 274 日，CD25 陰性群 340 日であった。8 サイクル SD 群では奏効は認められなかった。

2.7.6.6.7.3.3 疾患の徴候・症状の改善（患者及び医師報告による評価）

(1)患者による全般的な皮膚状態の評価

治療期及び追跡調査期間中に臨床的に意義のある改善が認められた被験者の割合は，プラセボクロスオーバー群 44.4%，再発・再投与群 45.0%，8 サイクル SD 群 0.0%，CD25 陰性群 33.3%であった。

(2)患者によるそう痒感の評価

治療期及び追跡調査期間中に臨床的に意義のある改善が認められた被験者の割合は，プラセボクロスオーバー群 33.3%，再発・再投与群 25.0%，8 サイクル SD 群 33.3%，CD25 陰性群 27.8%であった。

(3)医師による紅皮症の重症度の評価

治療期及び追跡調査期間中に臨床的に意義のある改善が認められた被験者の割合は，プラセボクロスオーバー群 29.6%，再発・再投与群 15.0%，8 サイクル SD 群 0.0%，CD25 陰性群 13.9%であった。

(4)医師による全般的な CTCL の重症度の評価

治療期及び追跡調査期間中に臨床的に意義のある改善が認められた被験者の割合は，プラセボクロスオーバー群 29.6%，再発・再投与群 20.0%，8 サイクル SD 群 11.1%，CD25 陰性群 27.8%であった。

2.7.6.6.8 安全性の結果

本治験における有害事象の概要を表 2.7.6.6-5 に示した。

全体で有害事象及び副作用の発現率はそれぞれ 96.7%（89/92 例）及び 91.3%（84/92 例）であり，4 つの患者群で同程度であった。

重症度が高度の有害事象，重篤な有害事象，重篤な副作用，及び治験中止に至った有害事象の発現率は，それぞれ 30.4%（28/92 例），41.3%（38/92 例），34.8%（32/92 例），26.1%（24/92 例）であり，E7272 既投与の群（再発・再投与群及び 8 サイクル SD 群）よりも E7272 未治療の群（プラセボクロスオーバー群及び CD25 陰性群）で高かった。

表 2.7.6.6-5　有害事象の概要（ITT 集団）（外国 L4389-14 試験）

項目	プラセボクロスオーバー群 (N=27) n (%)	再発・再投与群 (N=20) n (%)	CD25 陰性群 (N=36) n (%)	8 サイクル SD 群 (N=9) n (%)	合計 (N=92) n (%)
有害事象	25 (92.6)	20 (100.0)	35 (97.2)	9 (100.0)	89 (96.7)
副作用 [a]	24 (88.9)	17 (85.0)	35 (97.2)	8 (88.9)	84 (91.3)
高度の有害事象	8 (29.6)	3 (15.0)	15 (41.7)	2 (22.2)	28 (30.4)
重篤な有害事象	11 (40.7)	4 (20.0)	23 (63.9)	0 (0.0)	38 (41.3)
重篤な副作用	11 (40.7)	1 (5.0)	20 (55.6)	0 (0.0)	32 (34.8)
治験中止に至った有害事象	8 (29.6)	3 (15.0)	12 (33.3)	1 (11.1)	24 (26.1)

SD = stable disease.

a: 副作用は，治験薬との因果関係が「関連あり」「おそらく関連あり」「関連あるかもしれない」と判定された有害事象とした。

（添付資料 5.3.5.4.3 の Table 43 及び Table 46 を引用）

2.7.6.6.8.1 主な有害事象及び副作用

主な有害事象（全体で 10%以上に発現）を表 2.7.6.6-6 に示し，主な副作用（全体で 10%以上に発現）を表 2.7.6.6-7 に示した。

全体で発現率が 20%以上であった有害事象は，悪心（53.3%），発熱（44.6%），疲労（41.3%），悪寒（39.1%），嘔吐（31.5%），末梢性浮腫（27.2%），頭痛（25.0%），下痢（23.9%），咳嗽，そう痒症（各 20.7%）であった。

主な有害事象は，E7272 未投与の群（プラセボクロスオーバー群及び CD25 陰性群）と E7272 既投与の群（再発・再投与群及び 8 サイクル SD 群）で概ね同様であり，悪心，発熱，疲労，悪寒，嘔吐はいずれも E7272 の投与で予測される有害事象であった。有害事象の大部分は，軽度又は中等度であった。

悪心，発熱，嘔吐，発疹，食欲不振，毛細血管漏出症候群は，E7272 未投与の群と比較して，E7272 既投与の群の発現率が明らかに低く，重症度も低かった。

全体で発現率が 20%以上であった副作用は，悪心（51.1%），疲労（38.0%），発熱（37.0%），悪寒（34.8%），嘔吐（27.2%），末梢性浮腫（22.8%）であった。

表 2.7.6.6-6　全体で発現率 10%以上の有害事象（ITT 集団）（外国 L4389-14 試験）

MedDRA 器官別大分類 基本語	プラセボクロスオーバー群 (N=27) n (%)	再発・再投与群 (N=20) n (%)	CD25 陰性群 (N=36) n (%)	8 サイクル SD 群 (N=9) n (%)	合計 (N=92) n (%)
有害事象	25 (92.6)	20 (100.0)	35 (97.2)	9 (100.0)	89 (96.7)
感染症および寄生虫症	15 (55.6)	15 (75.0)	14 (38.9)	4 (44.4)	48 (52.2)
上気道感染	4 (14.8)	7 (35.0)	1 (2.8)	1 (11.1)	13 (14.1)
代謝および栄養障害	11 (40.7)	6 (30.0)	16 (44.4)	1 (11.1)	34 (37.0)
食欲不振	5 (18.5)	0 (0.0)	6 (16.7)	0 (0.0)	11 (12.0)
神経系障害	11 (40.7)	8 (40.0)	14 (38.9)	4 (44.4)	37 (40.2)
頭痛	7 (25.9)	5 (25.0)	8 (22.2)	3 (33.3)	23 (25.0)
浮動性めまい	5 (18.5)	1 (5.0)	7 (19.4)	1 (11.1)	14 (15.2)
呼吸器，胸郭および縦隔障害	14 (51.9)	9 (45.0)	18 (50.0)	4 (44.4)	45 (48.9)
咳嗽	7 (25.9)	4 (20.0)	7 (19.4)	1 (11.1)	19 (20.7)
呼吸困難	7 (25.9)	2 (10.0)	5 (13.9)	1 (11.1)	15 (16.3)
毛細血管漏出症候群	3 (11.1)	0 (0.0)	7 (19.4)	0 (0.0)	10 (10.9)
胃腸障害	22 (81.5)	11 (55.0)	23 (63.9)	3 (33.3)	59 (64.1)
悪心	22 (81.5)	8 (40.0)	18 (50.0)	1 (11.1)	49 (53.3)
嘔吐	14 (51.9)	1 (5.0)	13 (36.1)	1 (11.1)	29 (31.5)
下痢	8 (29.6)	4 (20.0)	8 (22.2)	2 (22.2)	22 (23.9)
便秘	5 (18.5)	2 (10.0)	4 (11.1)	0 (0.0)	11 (12.0)
皮膚および皮下組織障害	19 (70.4)	9 (45.0)	25 (69.4)	3 (33.3)	56 (60.9)
そう痒症	9 (33.3)	2 (10.0)	8 (22.2)	0 (0.0)	19 (20.7)
発疹	5 (18.5)	0 (0.0)	8 (22.2)	0 (0.0)	13 (14.1)
筋骨格系および結合組織障害	13 (48.1)	9 (45.0)	9 (25.0)	5 (55.6)	36 (39.1)
関節痛	10 (37.0)	1 (5.0)	1 (2.8)	2 (22.2)	14 (15.2)
筋痛	4 (14.8)	1 (5.0)	4 (11.1)	1 (11.1)	10 (10.9)
全身障害および投与局所様態	24 (88.9)	11 (55.0)	34 (94.4)	7 (77.8)	76 (82.6)
発熱	15 (55.6)	3 (15.0)	20 (55.6)	3 (33.3)	41 (44.6)
疲労	13 (48.1)	6 (30.0)	14 (38.9)	5 (55.6)	38 (41.3)
悪寒	14 (51.9)	6 (30.0)	13 (36.1)	3 (33.3)	36 (39.1)
末梢性浮腫	10 (37.0)	2 (10.0)	10 (27.8)	3 (33.3)	25 (27.2)
浮腫	6 (22.2)	2 (10.0)	6 (16.7)	1 (11.1)	15 (16.3)
無力症	4 (14.8)	2 (10.0)	4 (11.1)	1 (11.1)	11 (12.0)

SD = stable disease.
MedDRA (medical dictionary for regulatory activities) Version 6.1
被験者は各基本語につき 1 回のみカウントし，各器官別大分類でも 1 回までのカウントとした。
（添付資料 5.3.5.4.3 の Table 46 を引用）

表 2.7.6.6-7　全体で発現率 10%以上の副作用（ITT 集団）（外国 L4389-14 試験）

MedDRA 器官別大分類 基本語	プラセボクロスオーバー群 (N=27) n (%)	再発・再投与群 (N=20) n (%)	CD25 陰性群 (N=36) n (%)	8 サイクル SD 群 (N=9) n (%)	合計 (N=92) n (%)
副作用	24 (88.9)	17 (85.0)	35 (97.2)	8 (88.9)	84 (91.3)
代謝および栄養障害	10 (37.0)	3 (15.0)	14 (38.9)	1 (11.1)	28 (30.4)
食欲不振	4 (14.8)	0 (0.0)	6 (16.7)	0 (0.0)	10 (10.9)
神経系障害	10 (37.0)	7 (35.0)	10 (27.8)	2 (22.2)	29 (31.5)
浮動性めまい	5 (18.5)	1 (5.0)	5 (13.9)	1 (11.1)	12 (13.0)
頭痛	5 (18.5)	3 (15.0)	3 (8.3)	1 (11.1)	12 (13.0)
呼吸器，胸郭および縦隔障害	12 (44.4)	3 (15.0)	13 (36.1)	2 (22.2)	30 (32.6)
毛細血管漏出症候群	3 (11.1)	0 (0.0)	7 (19.4)	0 (0.0)	10 (10.9)
呼吸困難	6 (22.2)	1 (5.0)	3 (8.3)	1 (11.1)	11 (12.0)
胃腸障害	21 (77.8)	9 (45.0)	21 (58.3)	2 (22.2)	53 (57.6)
悪心	21 (77.8)	7 (35.0)	18 (50.0)	1 (11.1)	47 (51.1)
嘔吐	13 (48.1)	0 (0.0)	11 (30.6)	1 (11.1)	25 (27.2)
皮膚および皮下組織障害	17 (63.0)	4 (20.0)	22 (61.1)	2 (22.2)	45 (48.9)
そう痒症	7 (25.9)	1 (5.0)	6 (16.7)	0 (0.0)	14 (15.2)
発疹	3 (11.1)	0 (0.0)	7 (19.4)	0 (0.0)	10 (10.9)
筋骨格系および結合組織障害	13 (48.1)	7 (35.0)	8 (22.2)	5 (55.6)	33 (35.9)
関節痛	8 (29.6)	1 (5.0)	0 (0.0)	2 (22.2)	11 (12.0)
筋痛	4 (14.8)	1 (5.0)	4 (11.1)	1 (11.1)	10 (10.9)
全身障害および投与局所様態	24 (88.9)	9 (45.0)	34 (94.4)	6 (66.7)	73 (79.3)
無力症	4 (14.8)	1 (5.0)	4 (11.1)	1 (11.1)	10 (10.9)
疲労	12 (44.4)	5 (25.0)	13 (36.1)	5 (55.6)	35 (38.0)
浮腫	5 (18.5)	1 (5.0)	6 (16.7)	1 (11.1)	13 (14.1)
末梢性浮腫	8 (29.6)	0 (0.0)	10 (27.8)	3 (33.3)	21 (22.8)
発熱	11 (40.7)	2 (10.0)	18 (50.0)	3 (33.3)	34 (37.0)
悪寒	12 (44.4)	4 (20.0)	13 (36.1)	3 (33.3)	32 (34.8)

SD = stable disease.
MedDRA (medical dictionary for regulatory activities) Version 6.1
被験者は各基本語につき 1 回のみカウントし，各器官別大分類でも 1 回までのカウントとした。副作用は，治験薬との因果関係が「関連あり」「おそらく関連あり」「関連あるかもしれない」と判定された有害事象とした。
（添付資料 5.3.5.4.3 の Table 47 を引用）

2.7.6.6.8.2 死亡及び重篤な有害事象

本治験では，治験期間中（最終投与から 30 日後まで）に死亡した被験者はいなかった。

重篤な有害事象は全体で 41.3%（38/92 例）に認められた。患者群別の発現率は，CD25 陰性群が 63.9%（23/36 例）で最も高く，次いでプラセボクロスオーバー群 40.7%（11/27 例），再発・再投与群 20.0%（4/20 例）であった。8 サイクル SD 群では，重篤な有害事象は認められなかった。全体で 4 例以上に報告された重篤な有害事象は，発熱（9 例），悪心（8 例），毛細血管漏出症候群（6 例），嘔吐（5 例），呼吸困難，浮腫，末梢性浮腫（各 4 例）であった。

重篤な副作用は全体で 34.8%（32/92 例）に認められた。患者群別の発現率は，CD25 陰性群 55.6%（20/36 例），プラセボクロスオーバー群 40.7%（11/27 例），再発・再投与群 5.0%（1/20 例）であった。全体で 4 例以上に報告された重篤な副作用は，悪心（8 例），発熱，毛細血管漏出症候群（各 6 例），嘔吐（5 例），浮腫，末梢性浮腫（各 4 例）であった。

2.7.6.6.8.3 治験中止に至った有害事象

治験中止に至った有害事象は，全体で 26.1%（24/92 例）に認められた。患者群別の発現率は，CD25 陰性群 33.3%（12/36 例），プラセボクロスオーバー群 29.6%（8/27 例），再発・再投与群 15.0%（3/20 例），8 サイクル SD 群 11.1%（1/9 例）であった。全体で 2 例以上に報告された治験中止に至った有害事象は，毛細血管漏出症候群（5 例），そう痒症（3 例），過敏症，低アルブミン血症（各 2 例）であり，これらは全て治験薬の副作用と判断された。

2.7.6.6.8.4 投与変更に至った副作用

治験薬の減量，休薬又は投与中止に至った副作用が全体で 41.3%（38/92 例）に認められた（減量に至った副作用 4.3%［4/92 例］，休薬に至った副作用 16.3%［15/92 例］，投与中止に至った副作用 29.3%［27/92 例］）。全体で 2 例以上に報告された投与中止に至った副作用は，毛細血管漏出症候群（5 例），低血圧，呼吸困難，悪心（各 3 例），過敏症，頻脈，紅斑性皮疹，疲労，末梢性浮腫，尿量減少（各 2 例）であった。全体で 2 例以上に報告された休薬に至った副作用は，低アルブミン血症，悪心，肝炎，背部痛，胸部不快感，血圧低下（各 2 例）であった。減量に至った副作用で 2 例以上に報告されたものはなかった。

2.7.6.6.8.5 臨床検査値

治験期間中，各臨床検査パラメータの中央値に明確な変化は認められず，大部分は Cycle 8 まで通して基準範囲内であった。いくつかのパラメータでは中央値が基準範囲外となる測定値もあったが，これらは概ね最初の 4 サイクルで認められた。

大部分の臨床検査異常値は Cycle 1 で認められ，以降の試験期間で基準範囲内に回復した。

主な Grade 3～4 の臨床検査異常値は，概ね Cycle 1～3 で認められた。Grade 3 の異常値が認められた臨床検査パラメータは，リンパ球絶対数，好中球絶対数（プラセボクロスオーバー群のみ），白血球数（CD25 陰性群のみ），ナトリウム，アルブミン，カルシウム，アラニンアミノトランスフェラーゼ及びアスパラギン酸アミノトランスフェラーゼ（プラセボクロスオーバー群及び CD25 陰性群のみ）であった。Grade 4 の異常値が認められた臨床検査パラメータは好中球絶対数のみで，Cycle 8 で CD25 陰性群の 1 例に認められた。

E7272 未投与の群（プラセボクロスオーバー群及び CD25 陰性群）では早期のサイクルで Grade 2～3 のトランスアミナーゼ増加が認められたが，Cycle 4 までに回復した。

2.7.6.6.8.6 バイタルサイン

治験期間中のバイタルサイン（収縮期及び拡張期血圧，脈拍数，呼吸数及び体温）を評価した結果，臨床的に意義のある変化は認められなかった。

2.7.6.6.9 結論

- 有効性の主要評価項目及び副次評価項目について，本治験の 4 つの患者群のうち，プラセボクロスオーバー群，再発・再投与群及び CD25 陰性群では良好な結果が得られ，本治験で認められた奏効率は，CTCL 患者を対象とした先行試験で認められていたものと同程度であった。8 サイクル SD 群では奏効は認められなかったが，多くの患者で疾患の安定が持続した。
- 本治験で確認された E7272 の安全性プロファイルは，先行試験と同様であった。E7272 未投与患者では Cycle 2 以降に有害事象，副作用，重篤な有害事象の発現率が低下した。また，E7272 既投与患者では，投与期間を通じて有害事象，副作用，重篤な有害事象の発現率が E7272 未投与患者よりも低かった。

2.7.6.7 付録

付録 2.7.6-1 MedDRA SOC/PT 別の全有害事象発現率（国内 101 試験）
付録 2.7.6-2 MedDRA SOC/PT 別の Grade 3 以上の有害事象発現率（国内 101 試験）
付録 2.7.6-3 死亡又は重篤な有害事象の被験者ごとの叙述（国内 101 試験）
付録 2.7.6-4 MedDRA SOC/PT 別の全有害事象発現率（国内 205 試験）
付録 2.7.6-5 MedDRA SOC/PT 別の Grade 3 以上の有害事象発現率（国内 205 試験）
付録 2.7.6-6 死亡又は重篤な有害事象の被験者ごとの叙述（国内 205 試験）
付録 2.7.6-7 外国 302 試験（第 3 相パート）重篤な有害事象一覧（CIOMS 情報；2019 年 4 月 26 日カットオフ）

付録 2.7.6-1　MedDRA SOC/PT 別の全有害事象発現率（国内101試験）（安全性解析対象集団）

MedDRA Version 18.0 器官別大分類 基本語	6 μg/kg/day (N=3) n (%)	9 μg/kg/day (N=7) n (%)	12 μg/kg/day (N=3) n (%)	合計 (N=13) n (%)
有害事象	3 (100.0)	7 (100.0)	3 (100.0)	13 (100.0)
General disorders and administration site conditions	3 (100.0)	7 (100.0)	3 (100.0)	13 (100.0)
Fatigue	3 (100.0)	5 (71.4)	3 (100.0)	11 (84.6)
Pyrexia	0	4 (57.1)	2 (66.7)	6 (46.2)
Oedema peripheral	2 (66.7)	2 (28.6)	1 (33.3)	5 (38.5)
Malaise	0	4 (57.1)	0	4 (30.8)
Face oedema	0	2 (28.6)	0	2 (15.4)
Generalised oedema	0	1 (14.3)	1 (33.3)	2 (15.4)
Infusion site extravasation	0	1 (14.3)	1 (33.3)	2 (15.4)
Injection site swelling	0	0	1 (33.3)	1 (7.7)
Peripheral swelling	0	1 (14.3)	0	1 (7.7)
Investigations	3 (100.0)	7 (100.0)	3 (100.0)	13 (100.0)
Alanine aminotransferase increased	3 (100.0)	6 (85.7)	3 (100.0)	12 (92.3)
Aspartate aminotransferase increased	2 (66.7)	6 (85.7)	3 (100.0)	11 (84.6)
Lymphocyte count decreased	3 (100.0)	4 (57.1)	3 (100.0)	10 (76.9)
Platelet count decreased	2 (66.7)	4 (57.1)	2 (66.7)	8 (61.5)
Lipase increased	2 (66.7)	1 (14.3)	2 (66.7)	5 (38.5)
Blood alkaline phosphatase increased	1 (33.3)	2 (28.6)	1 (33.3)	4 (30.8)
Neutrophil count decreased	1 (33.3)	1 (14.3)	2 (66.7)	4 (30.8)
Weight increased	1 (33.3)	1 (14.3)	2 (66.7)	4 (30.8)
Amylase increased	1 (33.3)	1 (14.3)	1 (33.3)	3 (23.1)
Blood cholesterol increased	1 (33.3)	2 (28.6)	0	3 (23.1)
White blood cell count decreased	1 (33.3)	1 (14.3)	1 (33.3)	3 (23.1)
Blood albumin decreased	0	2 (28.6)	0	2 (15.4)
Blood creatinine increased	1 (33.3)	0	1 (33.3)	2 (15.4)
Blood bilirubin increased	1 (33.3)	0	0	1 (7.7)
Blood cholinesterase decreased	0	1 (14.3)	0	1 (7.7)
Blood creatine phosphokinase increased	1 (33.3)	0	0	1 (7.7)
Blood fibrinogen decreased	0	0	1 (33.3)	1 (7.7)
Blood fibrinogen increased	0	1 (14.3)	0	1 (7.7)

付録 2.7.6-1　MedDRA SOC/PT 別の全有害事象発現率（国内101試験）（安全性解析対象集団）

MedDRA Version 18.0 器官別大分類 基本語	6 μg/kg/day (N=3) n (%)	9 μg/kg/day (N=7) n (%)	12 μg/kg/day (N=3) n (%)	合計 (N=13) n (%)
Cytomegalovirus test positive	0	1 (14.3)	0	1 (7.7)
Electrocardiogram QT prolonged	0	1 (14.3)	0	1 (7.7)
Gamma-glutamyltransferase increased	0	1 (14.3)	0	1 (7.7)
Weight decreased	0	1 (14.3)	0	1 (7.7)
Metabolism and nutrition disorders	3 (100.0)	7 (100.0)	3 (100.0)	13 (100.0)
Decreased appetite	3 (100.0)	5 (71.4)	3 (100.0)	11 (84.6)
Hypoalbuminaemia	3 (100.0)	5 (71.4)	2 (66.7)	10 (76.9)
Hypertriglyceridaemia	3 (100.0)	4 (57.1)	0	7 (53.8)
Hypokalaemia	1 (33.3)	0	3 (100.0)	4 (30.8)
Hyperglycaemia	0	2 (28.6)	1 (33.3)	3 (23.1)
Hyponatraemia	0	1 (14.3)	2 (66.7)	3 (23.1)
Hypophosphataemia	1 (33.3)	0	2 (66.7)	3 (23.1)
Hyperkalaemia	2 (66.7)	0	0	2 (15.4)
Hypocalcaemia	0	1 (14.3)	0	1 (7.7)
Hypoglycaemia	0	0	1 (33.3)	1 (7.7)
Blood and lymphatic system disorders	3 (100.0)	5 (71.4)	2 (66.7)	10 (76.9)
Leukocytosis	3 (100.0)	3 (42.9)	1 (33.3)	7 (53.8)
Anaemia	2 (66.7)	1 (14.3)	2 (66.7)	5 (38.5)
Febrile neutropenia	0	1 (14.3)	0	1 (7.7)
Lymphadenitis	0	1 (14.3)	0	1 (7.7)
Gastrointestinal disorders	2 (66.7)	5 (71.4)	3 (100.0)	10 (76.9)
Nausea	2 (66.7)	4 (57.1)	3 (100.0)	9 (69.2)
Constipation	2 (66.7)	3 (42.9)	2 (66.7)	7 (53.8)
Diarrhoea	0	0	3 (100.0)	3 (23.1)
Vomiting	1 (33.3)	2 (28.6)	0	3 (23.1)
Abdominal distension	1 (33.3)	0	0	1 (7.7)
Abdominal pain upper	1 (33.3)	0	0	1 (7.7)
Dyspepsia	1 (33.3)	0	0	1 (7.7)
Stomatitis	1 (33.3)	0	0	1 (7.7)
Upper gastrointestinal haemorrhage	0	0	1 (33.3)	1 (7.7)

付録 2.7.6-1　MedDRA SOC/PT 別の全有害事象発現率（国内101試験）（安全性解析対象集団）

MedDRA Version 18.0 器官別大分類 基本語	6 µg/kg/day (N=3) n (%)	9 µg/kg/day (N=7) n (%)	12 µg/kg/day (N=3) n (%)	合計 (N=13) n (%)
Skin and subcutaneous tissue disorders	2 (66.7)	2 (28.6)	3 (100.0)	7 (53.8)
Rash	1 (33.3)	1 (14.3)	2 (66.7)	4 (30.8)
Toxic skin eruption	0	0	2 (66.7)	2 (15.4)
Drug eruption	1 (33.3)	0	0	1 (7.7)
Erythema	0	1 (14.3)	0	1 (7.7)
Palmar erythema	1 (33.3)	0	0	1 (7.7)
Pruritus	1 (33.3)	0	0	1 (7.7)
Purpura	0	0	1 (33.3)	1 (7.7)
Infections and infestations	3 (100.0)	2 (28.6)	1 (33.3)	6 (46.2)
Pneumonia	1 (33.3)	1 (14.3)	0	2 (15.4)
Bacterial infection	0	0	1 (33.3)	1 (7.7)
Cellulitis	0	0	1 (33.3)	1 (7.7)
Conjunctivitis	1 (33.3)	0	0	1 (7.7)
Cystitis	1 (33.3)	0	0	1 (7.7)
Infected skin ulcer	1 (33.3)	0	0	1 (7.7)
Nasopharyngitis	1 (33.3)	0	0	1 (7.7)
Oral herpes	0	1 (14.3)	0	1 (7.7)
Otitis externa	1 (33.3)	0	0	1 (7.7)
Respiratory, thoracic and mediastinal disorders	1 (33.3)	3 (42.9)	1 (33.3)	5 (38.5)
Hypoxia	0	2 (28.6)	1 (33.3)	3 (23.1)
Epistaxis	0	1 (14.3)	0	1 (7.7)
Oropharyngeal pain	0	1 (14.3)	0	1 (7.7)
Pleural effusion	0	1 (14.3)	0	1 (7.7)
Respiratory failure	0	0	1 (33.3)	1 (7.7)
Throat irritation	1 (33.3)	0	0	1 (7.7)
Renal and urinary disorders	0	2 (28.6)	2 (66.7)	4 (30.8)
Proteinuria	0	2 (28.6)	1 (33.3)	3 (23.1)
Haematuria	0	0	1 (33.3)	1 (7.7)
Renal impairment	0	1 (14.3)	0	1 (7.7)
Vascular disorders	0	2 (28.6)	2 (66.7)	4 (30.8)
Hypotension	0	0	2 (66.7)	2 (15.4)

付録 2.7.6-1　MedDRA SOC/PT 別の全有害事象発現率（国内101試験）（安全性解析対象集団）

MedDRA Version 18.0 器官別大分類 基本語	6 μg/kg/day (N=3) n (%)	9 μg/kg/day (N=7) n (%)	12 μg/kg/day (N=3) n (%)	合計 (N=13) n (%)
Capillary leak syndrome	0	1 (14.3)	0	1 (7.7)
Hypertension	0	1 (14.3)	0	1 (7.7)
Eye disorders	0	3 (42.9)	0	3 (23.1)
Conjunctival oedema	0	1 (14.3)	0	1 (7.7)
Eyelid oedema	0	1 (14.3)	0	1 (7.7)
Vision blurred	0	1 (14.3)	0	1 (7.7)
Visual impairment	0	1 (14.3)	0	1 (7.7)
Immune system disorders	1 (33.3)	1 (14.3)	1 (33.3)	3 (23.1)
Hypersensitivity	1 (33.3)	1 (14.3)	1 (33.3)	3 (23.1)
Psychiatric disorders	0	3 (42.9)	0	3 (23.1)
Insomnia	0	2 (28.6)	0	2 (15.4)
Delirium	0	1 (14.3)	0	1 (7.7)
Cardiac disorders	1 (33.3)	0	1 (33.3)	2 (15.4)
Atrial fibrillation	1 (33.3)	0	0	1 (7.7)
Sinus tachycardia	0	0	1 (33.3)	1 (7.7)
Congenital, familial and genetic disorders	1 (33.3)	0	1 (33.3)	2 (15.4)
Antithrombin III deficiency	0	0	1 (33.3)	1 (7.7)
Colour blindness	1 (33.3)	0	0	1 (7.7)
Musculoskeletal and connective tissue disorders	0	2 (28.6)	0	2 (15.4)
Back pain	0	1 (14.3)	0	1 (7.7)
Myalgia	0	1 (14.3)	0	1 (7.7)
Nervous system disorders	0	2 (28.6)	0	2 (15.4)
Central nervous system lesion	0	1 (14.3)	0	1 (7.7)
Somnolence	0	1 (14.3)	0	1 (7.7)
Hepatobiliary disorders	0	0	1 (33.3)	1 (7.7)
Hepatic failure	0	0	1 (33.3)	1 (7.7)

6 及び12 μg/kg/日群の実際の投与量は，それぞれ6.84 及び13.68 μg/kg/日であった。

（添付資料5.3.3.2.1のTable 14.3.1.2.3.1を引用）

付録 2.7.6-2　MedDRA SOC/PT別のGrade 3以上の有害事象発現率（国内101試験）（安全性解析対象集団）

MedDRA Version 18.0 器官別大分類 基本語 CTCAE Grade	6 µg/kg/day (N=3) n (%)	9 µg/kg/day (N=7) n (%)	12 µg/kg/day (N=3) n (%)	合計 (N=13) n (%)
Any system / Any term	3 (100.0)	6 (85.7)	3 (100.0)	12 (92.3)
3	3 (100.0)	3 (42.9)	0	6 (46.2)
4	0	3 (42.9)	2 (66.7)	5 (38.5)
5	0	0	1 (33.3)	1 (7.7)
Blood and lymphatic system disorders	0	1 (14.3)	2 (66.7)	3 (23.1)
3	0	1 (14.3)	2 (66.7)	3 (23.1)
4	0	0	0	0
5	0	0	0	0
Anaemia				
Any Grade (grade 3 - 5)	0	0	2 (66.7)	2 (15.4)
3	0	0	2 (66.7)	2 (15.4)
4	0	0	0	0
5	0	0	0	0
Febrile neutropenia				
Any Grade (grade 3 - 5)	0	1 (14.3)	0	1 (7.7)
3	0	1 (14.3)	0	1 (7.7)
4	0	0	0	0
5	0	0	0	0
Gastrointestinal disorders	0	0	1 (33.3)	1 (7.7)
3	0	0	1 (33.3)	1 (7.7)
4	0	0	0	0
5	0	0	0	0
Diarrhoea				
Any Grade (grade 3 - 5)	0	0	1 (33.3)	1 (7.7)
3	0	0	1 (33.3)	1 (7.7)
4	0	0	0	0
5	0	0	0	0

付録 2.7.6-2　MedDRA SOC/PT別のGrade 3以上の有害事象発現率（国内101試験）（安全性解析対象集団）

MedDRA Version 18.0 器官別大分類 基本語 CTCAE Grade	6 μg/kg/day (N=3) n (%)	9 μg/kg/day (N=7) n (%)	12 μg/kg/day (N=3) n (%)	合計 (N=13) n (%)
General disorders and administration site conditions	0	1 (14.3)	1 (33.3)	2 (15.4)
3	0	1 (14.3)	0	1 (7.7)
4	0	0	1 (33.3)	1 (7.7)
5	0	0	0	0
Fatigue				
Any Grade (grade 3 - 5)	0	1 (14.3)	1 (33.3)	2 (15.4)
3	0	1 (14.3)	1 (33.3)	2 (15.4)
4	0	0	0	0
5	0	0	0	0
Pyrexia				
Any Grade (grade 3 - 5)	0	0	1 (33.3)	1 (7.7)
3	0	0	0	0
4	0	0	1 (33.3)	1 (7.7)
5	0	0	0	0
Hepatobiliary disorders	0	0	1 (33.3)	1 (7.7)
3	0	0	0	0
4	0	0	0	0
5	0	0	1 (33.3)	1 (7.7)
Hepatic failure				
Any Grade (grade 3 - 5)	0	0	1 (33.3)	1 (7.7)
3	0	0	0	0
4	0	0	0	0
5	0	0	1 (33.3)	1 (7.7)
Investigations	3 (100.0)	6 (85.7)	3 (100.0)	12 (92.3)
3	3 (100.0)	4 (57.1)	0	7 (53.8)
4	0	2 (28.6)	3 (100.0)	5 (38.5)
5	0	0	0	0

付録 2.7.6-2　MedDRA SOC/PT別のGrade 3以上の有害事象発現率（国内101試験）（安全性解析対象集団）

MedDRA Version 18.0 器官別大分類 基本語 CTCAE Grade	6 µg/kg/day (N=3) n (%)	9 µg/kg/day (N=7) n (%)	12 µg/kg/day (N=3) n (%)	合計 (N=13) n (%)
Alanine aminotransferase increased				
Any Grade (grade 3 - 5)	1 (33.3)	6 (85.7)	2 (66.7)	9 (69.2)
3	1 (33.3)	6 (85.7)	2 (66.7)	9 (69.2)
4	0	0	0	0
5	0	0	0	0
Aspartate aminotransferase increased				
Any Grade (grade 3 - 5)	0	4 (57.1)	2 (66.7)	6 (46.2)
3	0	4 (57.1)	2 (66.7)	6 (46.2)
4	0	0	0	0
5	0	0	0	0
Gamma-glutamyltransferase increased				
Any Grade (grade 3 - 5)	0	1 (14.3)	0	1 (7.7)
3	0	1 (14.3)	0	1 (7.7)
4	0	0	0	0
5	0	0	0	0
Lipase increased				
Any Grade (grade 3 - 5)	0	1 (14.3)	1 (33.3)	2 (15.4)
3	0	1 (14.3)	1 (33.3)	2 (15.4)
4	0	0	0	0
5	0	0	0	0
Lymphocyte count decreased				
Any Grade (grade 3 - 5)	3 (100.0)	2 (28.6)	3 (100.0)	8 (61.5)
3	3 (100.0)	1 (14.3)	1 (33.3)	5 (38.5)
4	0	1 (14.3)	2 (66.7)	3 (23.1)
5	0	0	0	0

付録 2.7.6-2　MedDRA SOC/PT別のGrade 3以上の有害事象発現率（国内101試験）（安全性解析対象集団）

MedDRA Version 18.0 器官別大分類 基本語 CTCAE Grade	6 μg/kg/day (N=3) n (%)	9 μg/kg/day (N=7) n (%)	12 μg/kg/day (N=3) n (%)	合計 (N=13) n (%)
Neutrophil count decreased				
Any Grade (grade 3 - 5)	0	1 (14.3)	2 (66.7)	3 (23.1)
3	0	0	2 (66.7)	2 (15.4)
4	0	1 (14.3)	0	1 (7.7)
5	0	0	0	0
Platelet count decreased				
Any Grade (grade 3 - 5)	0	1 (14.3)	1 (33.3)	2 (15.4)
3	0	1 (14.3)	0	1 (7.7)
4	0	0	1 (33.3)	1 (7.7)
5	0	0	0	0
Weight increased				
Any Grade (grade 3 - 5)	0	0	1 (33.3)	1 (7.7)
3	0	0	1 (33.3)	1 (7.7)
4	0	0	0	0
5	0	0	0	0
White blood cell count decreased				
Any Grade (grade 3 - 5)	0	1 (14.3)	0	1 (7.7)
3	0	0	0	0
4	0	1 (14.3)	0	1 (7.7)
5	0	0	0	0
Metabolism and nutrition disorders	0	3 (42.9)	3 (100.0)	6 (46.2)
3	0	2 (28.6)	2 (66.7)	4 (30.8)
4	0	1 (14.3)	1 (33.3)	2 (15.4)
5	0	0	0	0
Decreased appetite				
Any Grade (grade 3 - 5)	0	1 (14.3)	1 (33.3)	2 (15.4)
3	0	1 (14.3)	1 (33.3)	2 (15.4)
4	0	0	0	0
5	0	0	0	0

付録 2.7.6-2　MedDRA SOC/PT別のGrade 3以上の有害事象発現率（国内101試験）（安全性解析対象集団）

MedDRA Version 18.0 器官別大分類 基本語 CTCAE Grade	6 µg/kg/day (N=3) n (%)	9 µg/kg/day (N=7) n (%)	12 µg/kg/day (N=3) n (%)	合計 (N=13) n (%)
Hyperglycaemia				
Any Grade (grade 3 - 5)	0	1 (14.3)	0	1 (7.7)
3	0	1 (14.3)	0	1 (7.7)
4	0	0	0	0
5	0	0	0	0
Hypertriglyceridaemia				
Any Grade (grade 3 - 5)	0	2 (28.6)	0	2 (15.4)
3	0	1 (14.3)	0	1 (7.7)
4	0	1 (14.3)	0	1 (7.7)
5	0	0	0	0
Hypoalbuminaemia				
Any Grade (grade 3 - 5)	0	0	2 (66.7)	2 (15.4)
3	0	0	2 (66.7)	2 (15.4)
4	0	0	0	0
5	0	0	0	0
Hypokalaemia				
Any Grade (grade 3 - 5)	0	0	2 (66.7)	2 (15.4)
3	0	0	2 (66.7)	2 (15.4)
4	0	0	0	0
5	0	0	0	0
Hyponatraemia				
Any Grade (grade 3 - 5)	0	0	2 (66.7)	2 (15.4)
3	0	0	1 (33.3)	1 (7.7)
4	0	0	1 (33.3)	1 (7.7)
5	0	0	0	0

付録 2.7.6-2　MedDRA SOC/PT別のGrade 3以上の有害事象発現率（国内101試験）（安全性解析対象集団）

MedDRA Version 18.0 器官別大分類 基本語 CTCAE Grade	6 µg/kg/day (N=3) n (%)	9 µg/kg/day (N=7) n (%)	12 µg/kg/day (N=3) n (%)	合計 (N=13) n (%)
Hypophosphataemia				
Any Grade (grade 3 - 5)	0	0	1 (33.3)	1 (7.7)
3	0	0	1 (33.3)	1 (7.7)
4	0	0	0	0
5	0	0	0	0
Psychiatric disorders	0	1 (14.3)	0	1 (7.7)
3	0	1 (14.3)	0	1 (7.7)
4	0	0	0	0
5	0	0	0	0
Delirium				
Any Grade (grade 3 - 5)	0	1 (14.3)	0	1 (7.7)
3	0	1 (14.3)	0	1 (7.7)
4	0	0	0	0
5	0	0	0	0
Respiratory, thoracic and mediastinal disorders	0	1 (14.3)	1 (33.3)	2 (15.4)
3	0	1 (14.3)	0	1 (7.7)
4	0	0	0	0
5	0	0	1 (33.3)	1 (7.7)
Hypoxia				
Any Grade (grade 3 - 5)	0	1 (14.3)	1 (33.3)	2 (15.4)
3	0	1 (14.3)	0	1 (7.7)
4	0	0	1 (33.3)	1 (7.7)
5	0	0	0	0
Respiratory failure				
Any Grade (grade 3 - 5)	0	0	1 (33.3)	1 (7.7)
3	0	0	0	0
4	0	0	0	0
5	0	0	1 (33.3)	1 (7.7)

付録 2.7.6-2　MedDRA SOC/PT別のGrade 3以上の有害事象発現率（国内101試験）（安全性解析対象集団）

MedDRA Version 18.0 器官別大分類 基本語 CTCAE Grade	6 µg/kg/day (N=3) n (%)	9 µg/kg/day (N=7) n (%)	12 µg/kg/day (N=3) n (%)	合計 (N=13) n (%)
Skin and subcutaneous tissue disorders	0	0	1 (33.3)	1 (7.7)
3	0	0	1 (33.3)	1 (7.7)
4	0	0	0	0
5	0	0	0	0
Rash				
Any Grade (grade 3 - 5)	0	0	1 (33.3)	1 (7.7)
3	0	0	1 (33.3)	1 (7.7)
4	0	0	0	0
5	0	0	0	0
Vascular disorders	0	1 (14.3)	1 (33.3)	2 (15.4)
3	0	1 (14.3)	0	1 (7.7)
4	0	0	1 (33.3)	1 (7.7)
5	0	0	0	0
Capillary leak syndrome				
Any Grade (grade 3 - 5)	0	1 (14.3)	0	1 (7.7)
3	0	1 (14.3)	0	1 (7.7)
4	0	0	0	0
5	0	0	0	0
Hypotension				
Any Grade (grade 3 - 5)	0	0	1 (33.3)	1 (7.7)
3	0	0	0	0
4	0	0	1 (33.3)	1 (7.7)
5	0	0	0	0

CTCAE v4.0を用いて有害事象のグレードを決定した。
6 及び12 µg/kg/日群の実際の投与量は，それぞれ6.84 及び13.68 µg/kg/日であった。

（添付資料5.3.3.2.1のTable 14.3.1.2.11.1を引用）

付録 2.7.6-3 死亡又は重篤な有害事象の被験者ごとの叙述（国内 101 試験）

被験者 10011401: 死亡に至った重篤な有害事象
被験者 10021201: 死亡以外の重篤な有害事象
被験者 10011303: 死亡以外の重篤な有害事象
被験者 10041301: 死亡以外の重篤な有害事象
被験者 10041303: 死亡以外の重篤な有害事象

Study / Subject ID	E7777-J081-101 / 10011401
Age (year), Sex, Race, Dose Group	6[redacted], Male, Japanese, 12 µg/kg/day group
Current Medical Conditions (Dictionary-derived Term)	Anaemia, Constipation, Insomnia, Peripheral sensory neuropathy, Dry skin, Cough, Back pain, Abdominal pain upper
Concomitant Medications	magnesium oxide, hydrophilic, zolpidem tartrate, sodium picosulfate, paracetamol, paracetamol, chlorphenamine maleate, dexamethasone, granisetron, lansoprazole, furosemide, metoclopramide hydrochloride, sennoside a+b calcium, alprazolam, nutrients nos, sodium chloride, rabeprazole sodium, sodium chloride, metoclopramide hydrochloride, hydrocortisone sodium succinate, amino acids nos w/electrolytes nos/glucose/th, cefepime hydrochloride, olopatadine hydrochloride, alclometasone dipropionate, clobetasol propionate, furosemide, potassium chloride, salipara codeine, sucralfate, bactrim, prednisolone, ursodeoxycholic acid, albumin human, antithrombin iii, red blood cells, concentrated, enterococcus faecalis, amino acids nos w/electrolytes nos/glucose/th, loperamide, ringer-lactatis, prednisolone, lansoprazole, guaiazulene, amino acids nos w/carbohydrates nos/07403701/, morphine hydrochloride, potassium chloride, hydrocortisone sodium succinate, rocuronium bromide, methylprednisolone sodium succinate, meropenem, amphotericin b, liposome, ganciclovir, fentanyl, insulin human, norepinephrine, dexmedetomidine hydrochloride, propofol, albumin human, bactrim, propofol, carbohydrates nos w/potassium chloride/sodium, landiolol hydrochloride, chlorphenamine maleate, plasma, platelets, concentrated, thrombomodulin alfa, elemeal, carperitide, erythromycin, ciprofloxacin, linezolid, vasopressin, pip/tazo, hydrocortisone
Date of First/Last Dose of Study Drug	2011-12-12 / 2011-12-16
Treatment-emergent Non-Serious Adverse Events (Preferred Term)	Hypoalbuminaemia, Nausea, Weight increased, Aspartate aminotransferase increased, Hyponatraemia, Decreased appetite, Alanine aminotransferase increased, Lymphocyte count decreased, Platelet count decreased, Hypoalbuminaemia, Fatigue, Leukocytosis, Pyrexia, Rash, Hypokalaemia, Alanine aminotransferase increased, Aspartate aminotransferase increased, Hypoxia, Blood alkaline phosphatase increased, Antithrombin III deficiency, Anaemia, Decreased appetite, Diarrhoea, Platelet count decreased, Lymphocyte count decreased, Blood fibrinogen decreased, Purpura, Hypokalaemia, Hyperglycaemia, Pyrexia, Hyponatraemia, Upper gastrointestinal

	haemorrhage, Hypotension, Sinus tachycardia, Generalised oedema, Weight increased, Blood alkaline phosphatase increased, Haematuria
Serious Adverse Event (Preferred Term / Investigator Term)	Respiratory failure / Respiratory failure Hepatic failure / hepatic failure
AE Start Date (Study Day) / AE Stop Date (Study Day)	Respiratory failure: 2011-12-28 (17) / 2012-01-18 (38) Hepatic failure: 2012-01-04 (24) / 2012-01-18 (38)
Study Phase of AE Onset	Treatment Phase
Dose at or prior to AE Onset	Both SAEs: 12 µg/kg/day
Seriousness Criteria	Respiratory failure: Death Hepatic failure: Death
Maximum CTCAE Grade / Outcome	Respiratory failure: Grade 5 / Fatal Hepatic failure: Grade 5 / Fatal
Study Drug Action Taken/ Other Action Taken	Respiratory failure: Drug withdrawn / Treatment given, withdrawn from study Hepatic failure: Not applicable / None
Concomitant Medications Used until date of AE Onset	Respiratory failure: magnesium oxide, hydrophilic, zolpidem tartrate, sodium picosulfate, paracetamol, paracetamol, chlorphenamine maleate, dexamethasone, granisetron, lansoprazole, furosemide, metoclopramide hydrochloride, sennoside a+b calcium, alprazolam, nutrients nos, sodium chloride, rabeprazole sodium, sodium chloride, metoclopramide hydrochloride, hydrocortisone sodium succinate, amino acids nos w/electrolytes nos/glucose/th, cefepime hydrochloride, olopatadine hydrochloride, alclometasone dipropionate, clobetasol propionate, furosemide, potassium chloride, salipara codeine, sucralfate, bactrim, prednisolone, ursodeoxycholic acid, albumin human, antithrombin iii Hepatic failure (in addition to above medications): red blood cells, concentrated, enterococcus faecalis, amino acids nos w/electrolytes nos/glucose/th, loperamide, ringer-lactatis, prednisolone, lansoprazole
Relationship to Study Drug as per Investigator	Respiratory failure: Not related Hepatic failure: Not related

Investigator's Opinion:

Interstitial pneumonia (SAE) was previously reported as a diagnostic name of event however it was changed to "respiratory failure" based on the autopsy result. Possibility of drug-induced pneumonia was not deniable before the patient's death. The autopsy result was warranted to evaluate infiltration of malignant lymphoma in lung (with immunostaining method); progression of lung infiltration of malignant lymphoma presented prior to initial administration of the study drug; and hepatic infiltration of lymphoma which was not observed before death of the patient. The cause of death was believed to be severe

respiratory and hepatic failures due to infiltration of malignant lymphoma to the lung and liver; therefore, the reported events were not related to the study drug E7777.

Sponsor's Opinion:

Progression of lung infiltration of malignant lymphoma presented prior to initial administration of the study drug, and cause of death was confirmed not to be interstitial pneumonia, but respiratory failure based on the autopsy result. The events were due to progressive disease, and causality to study drug was deniable.

The events of respiratory failure and hepatic failure were not related to the study drug (E7777).

Narrative

2011-11-30: An informed consent of the clinical study of E7777 was obtained.

2011-12-07: The result of the screening test of PET/CT showed multiple infiltrative shadows in bilateral lobes. Accumulation of fluordeoxyglucose (FDG) was (~9.6) which revealed development of pneumonic lesion associated with malignant lymphoma.

2011-12-09: The patient was enrolled in the clinical study of E7777.

2011-12-19: BT 38.0°C, WBC 11900 /μL, no marked sign of infection developed.

2011-12-20: The patient had experienced mild cough before the clinical trial was started. Hypoxemia occurred in the morning; and oxygen saturation 95.9%, PCO_2 34.5, PO_2 75.2. Newly development of shadow at lobe and decrease in permeability were not observed. No interstitial shadow on CT was detected. Scattered pneumonic lesion including newly development suggested possibility of pneumonia was not ruled out. Two gram per day of Cefepime (cefepime dihydrochloride hydrate) was started.

2011-12-22: No newly development of infiltrative shadow at lobe and pleural effusion were detected. Cefepime was discontinued because risk of skin eruption and hepatic function disorder were considered.

2011-12-23: Chief complaint of the patient was difficulty of breathing. Two liters of O_2 was temporary discontinued.

2011-12-24: One liter of O_2 was restarted.

2011-12-26: BT 38.8°C and pyrexia persisted. No symptom of infection disease appeared and fever pattern slightly improved after the previous administration of Cefepime. Thus 2 g per day of Cefepime was resumed. Around this time, hypoxemia and cytopenia (WBC 8700/μL, PLAT 79000/μL) gradually appeared.

2011-12-27: O_2 was increased to 2 L because SpO_2 was 94%.

2011-12-28: Hypoxemia worsened. CT was performed and it was compared to its result performed on 2011-12-20. The result of CT performed this time showed enlargement of multiple nodule; relatively high density of ground-glass opacities ~ infiltrative shadow at bilateral lobes; enhancement of thickened bronchial walls at bilateral lower lobes; and small amount of pleural effusion at the right lobe. WBC 6200 /μL, oxygen saturation 88.5%, PCO_2 38.4, and

PO_2 52.4. The patient was given a diagnosis of interstitial pneumonia and 50 mg PSL was started. Fever pattern tended to improved. Cefepime was continued because it was possibly responded to event.
Subsequently, oxygenation of blood gradually worsened without improvement.

2012-01-02: Diarrhea occurred. CD toxin negative.

2012-01-04: In comparison to CT result obtained on 2011-12-28, while some nodule-like infiltrative shadows at bilateral lobes were smaller, new foci of disease appeared, indicating an overall worsening of the symptom. Around the nodule-like infiltrative shadows, non-ground-glass opacity was observed. Despite the ongoing PSL 50mg, respiratory state was not improved. Fever had been decreasing since 2011-12-29. WBC 6600 /μL, CRP 0.34 mg/dL

2012-01-06: Diarrhea persisted. No specific causes were found. Morphine hydrochloride injection (morphine hydrochloride hydrate) was initiated on 2012-01-06.

2012-01-07: He did not respond to steroids. Considering a potential adverse event induced by continuing PSL 1 mg/kg, gradual reduction in PSL was initiated (50 mg to 40 mg). Body temperature increased again to 38.6°C. Considering a possibility of infection, Cefepime 4 g/day was resumed. WBC 3300 /μL, CRP 1.33 mg/dL. Due to worsening of blood oxygenation, O_2 10 L was given via reservoir mask. Diarrhea was gradually improving.

2012-01-08: Oxygenation was poor. General condition worsened. He was admitted to ICU for whole-body management. Oxygen saturation 89.4%, PCO_2 31.2, PO_2 53.2. CT showed enhancement of multiple infiltrative shadows and ground-glass opacities. Traction bronchiectasis was also noted. Interstitial pneumonia was more likely to be caused by drug, rather than by infection. The underlying disease was gradually worsening. mPSL 1 g/day for 3 days was initiated. Considering a possibility of infection, MEPM+L-AMB+GCV was also initiated (2012-01-06: CMV C7-HRP 3/50000). Oxygen saturation after ICU admission 85.3%, PCO_2 31.0, PO_2 46.6. NPPV and O_2 15 L with reservoir mask were initiated; however, oxygenation further worsened afterword. SpO_2 below 80. Management with intubation and ventilator were initiated. Platelet transfusion for thrombocytopenia as well as FFP and AT-3 replacement therapy for coagulation abnormalities were ongoing.

2012-01-10: Findings in the lungs and respiratory state were slightly improving. Thrombocytopenia and coagulation abnormalities persisted. KL-6 346, SP-D 342.1, ChE 22.

2012-01-11: X-ray image showed lower permeability at the entire left lobe. PSL was reduced to 40 mg per day.

2012-01-12: Oxygenation was gradually worsening again. Enhancement of shadows was more predominant in the left lung than the right.

2012-01-14: Oxygenation was worsening further. Liver disorder worsened. MEPM was replaced with EM+CPFX.

2012-01-15: Pattern of fever ranging from 38°C to 39°C worsened further; body temperature was over 40°C.

2012-01-16: Blood pressure and conscious level started decreasing during daytime. Dose of hypertensive drug was increased. Large quantity of fluid was given and then blood pressure increased. Sepsis due to unknown cause was likely to occur; thus, treatment was changed as follows:
EM+CPFX+L-AMB+GCV+ST to
TAZ/PIPC+CPFX+LZD+ST+L-AMB+GCV.
Bronchoalveolar lavage (BAL) was performed; no findings such as sputum were found in the bronchi. Bacterial culture negative. CMV-PCR negative. PSL was reduced to 30 mg per day.

2012-01-17: Blood pressure was being controlled; however, a large quantity of fluid was still required. Because of the fluid replacement, edema progressed. Thrombocytopenia and coagulation abnormalities also worsened. Large quantity of platelets and FFP were transfused.

2012-01-18: Liver disorder worsened. Due to negative BDG result, ST was discontinued. No improvement in blood pressure was noted. Hypertensive drug was gradually increased. Subsequently, blood pressure gradually decreased and he died at 23:50.

Study / Subject ID	E7777-J081-101 / 10021201
Age (year), Sex, Race, Dose Group	7[redacted], Male, Japanese, 6 µg/kg/day group
Current Medical Conditions (Dictionary-derived Term)	Hypertension, Diabetes mellitus, Intervertebral disc protrusion, Bundle branch block right, Oedema peripheral, Hypoaesthesia, Haemorrhoids
Concomitant Medications	marzulene s, mecobalamin, tandospirone citrate, gentamicin sulfate, magnesium oxide, faropenem sodium, omeprazole, carbohydrates nos w/potassium chloride/sodium, paracetamol, dexamethasone, sodium chloride, ramosetron hydrochloride, dexchlorpheniramine maleate, loxoprofen sodium, loxoprofen sodium, povidone-iodine, glucose, ursodeoxycholic acid, allopurinol, sodium polystyrene sulfonate, sodium bicarbonate, magnesium oxide, rabeprazole sodium, u-pasta, allopurinol, solita-t1, sulperazon, misoprostol, paracetamol, guaiazulene, diphenhydramine, furosemide, cefditoren pivoxil, paracetamol, baramycin /00324701/, sodium bicarbonate, solita-t1, acetazolamide, potacol r
Date of First/Last Dose of Study Drug	2011-07-11 /2011-07-15
Treatment-emergent Non-Serious Adverse Events (Preferred Term)	Leukocytosis, Hypoalbuminaemia, Alanine aminotransferase increased, Hypertriglyceridaemia, Hyperkalaemia, Platelet count decreased, Lymphocyte count decreased, Fatigue, Decreased appetite, Rash, Colour blindness
Serious Adverse Event (Preferred Term / Investigator Term)	Infected skin ulcer/ infection of skin ulcer
AE Start Date (Study Day) / AE Stop Date (Study Day)	2011-07-19 (9) / - (-)
Study Phase of AE Onset	Treatment Phase
Dose at or prior to AE Onset	6 µg/kg/day
Seriousness Criteria	Requires inpatient hospitalization or prolongation of exiting hospitalization
Maximum CTCAE Grade / Outcome	Grade 2 / Recovering
Study Drug Action Taken/ Other Action Taken	Dose not changed / Treatment given
Concomitant Medications Used until date of AE Onset	marzulene s, mecobalamin, tandospirone citrate, gentamicin sulfate, magnesium oxide, faropenem sodium, omeprazole, carbohydrates nos w/potassium chloride/sodium, paracetamol, dexamethasone, sodium chloride, ramosetron hydrochloride, dexchlorpheniramine maleate, loxoprofen sodium, loxoprofen sodium, povidone-iodine, glucose, ursodeoxycholic acid, allopurinol, sodium polystyrene

	sulfonate, sodium bicarbonate
Relationship to Study Drug as per Investigator	Not related

Investigator's Opinion:

The patient was hospitalized for treatment as adequate management of the lesion at home was difficult, but the severity of the ulcer infection was considered to be moderate (Grade 2). The event of ulcer infection was considered not related to the study drug (E7777).

Sponsor's Opinion:

The event was not related to the study drug (E7777).

Narrative:

2011-06-27: An informed consent of the clinical study of E7777 was obtained.
Prior to enrollment the patient had a 10×3 cm ulcerated tumor mass on the back of his left knee joint and a 1.4×1.5 cm tumor mass on the back of his right knee joint.

2011-07-11 to 2011-7-15:The patient was administered E7777 at 351 μg/body/day (6 μg/kg/day).

2011-07-15: WBC 12700 /μL, Hb 11.4 g/dL, PLT 10.2×10^4 /μL, Neutro 9081 /μL, Lympho 1588 /μL, GOT 38 U/L, GPT 38 U/L, LDH 697 U/L, ALP 201 U/L, Cr 0.76 mg/dL, BUN 19 mg/dL, UA 5.2 mg/dL, Na 136 mEq/L, K 4.9 mEq/L, Cl 98 mEq/L, Ca 9.28 mg/dL, IP 2.9 mg/dL, T-Bil 0.2 mg/dL.
No change was observed at the patient's ulcer site, there was no pain or swelling growth at the disease site and no fever was observed. No visible signs of infection were observed, but the patient did have an increased white blood cell count that the investigator believed was possibly caused by dexamethasone premedication. The patient continued to be observed.

2011-07-19: WBC 16000 /μL, Hb 13.8 g/dL, PLT 5.4×10^4 /μL, Neutro 13120 /μL, Lympho 480 /μL, GOT 54 U/L, GPT 97 U/L, LDH 922 U/L, ALP 247 U/L, Cr 1.07 mg/dL, BUN 20 mg/dL, UA 6.7 mg/dL, Na 140 mEq/L, K 5.7 mEq/L, Cl 101 mEq/L, Ca 9.68 mg/dL, IP 3.3 mg/dL, T-Bil 0.6 mg/dL, CRP 15.42 mg/dL.
No fever was observed (36.5°C), but disintegration of ulcer site was enlarged and there was pain and swelling at the site. There were no visible signs of infection except for elevated C-reactive protein (CRP) and white blood cells (WBC). The patient was hospitalized the next day for treatment as adequate management of the lesion at home was difficult because of the large amount of effusion from the ulcer. Elevation of CRP and WBC was considered possibly due to ulcer infection or tumor disintegration.

2011-07-20 to 2011-07-31: Once admitted the patient was treated with Sulperazon (a combination of sulbactam and cefoperazone) 3 g/day and the lesion site with U-pasta (povidone iodine), Azunol (dimethyl isopropylazulene), Baramycin (bacitracin and fradiomycin sulfate), etc., twice daily. The patient's CRP and WBC values improved and there was still no fever, so the patient's ulcer

infection was considered to be resolving. Nevertheless, the patient's elevated lactate dehydrogenase and level of effusion did not improve, which taken together with the continued expansion of the ulcer indicated possible primary disease progression.

2011-08-01: BT 36.8°C, WBC 9400 /μL, Hb 10.4 g/dL, PLT 14.4×10^4 /μL, Neutro 17238 /μL, Lympho 658 /μL, GOT 45 U/L, GPT 54 U/L, LDH 1701 U/L, ALP 194 U/L, Cr 0.79 mg/dL, BUN 10 mg/dL, UA 6.1 mg/dL, Na 140 mEq/L, K 4.3 mEq/L, Cl 102 mEq/L, Ca 9.1 mg/dL, IP 3.5 mg/dL, T-Bil 0.6 mg/dL, CRP 4.45 mg/dL.
The patient had a CT scan which showed enlarged lymph node swelling from the left iliac artery to both sides of the inguinal region. New skin lesions were also noted and the patient was diagnosed with progressive disease and withdrawn from the study.

Study / Subject ID	E7777-J081-101 / 10011303
Age (year), Sex, Race, Dose Group	7[redacted], Male, Japanese, 9 µg/kg/day group
Current Medical Conditions (Dictionary-derived Term)	Anaemia, Colour blindness, Constipation, Diabetes mellitus, Tumour associated fever, Insomnia, Cough, Cataract
Concomitant Medications	insulin human, insulin aspart, diphenhydramine, daikenchuto, dextromethorphan hydrobromide, zolpidem, new lecicarbon, sodium picosulfate, paracetamol, bactrim, magnesium oxide, prednisolone, rabeprazole, sitagliptin phosphate monohydrate, voriconazole, sennoside a+b, paracetamol, chlorphenamine maleate, dexamethasone, granisetron, albumin human, strong neo-minophagen c, ganciclovir, alclometasone dipropionate, betamethasone butyrate propionate, pentamidine isethionate, furosemide, salbutamol sulfate, esomeprazole, filgrastim, paracetamol, chlorphenamine maleate, dexamethasone, granisetron, aciclovir, furosemide, albumin human, strong neo-minophagen c, guaiazulene, trazodone hydrochloride, filgrastim, pip/tazo, amphotericin b, liposome, potassium chloride, carbohydrates nos w/potassium chloride/sodium, furosemide, paracetamol, chlorphenamine maleate, dexamethasone, granisetron, valganciclovir hydrochloride, pentamidine isethionate, furosemide, albumin human, filgrastim, cefepime hydrochloride, immunoglobulin human normal, ringer-lactatis, chlorphenamine maleate, human red blood cells, filgrastim, paracetamol, chlorphenamine maleate, aprepitant, granisetron, albumin human, sodium chloride, metoclopramide, human red blood cells, paracetamol, dexamethasone, granisetron, chlorphenamine maleate, albumin human, cefepime hydrochloride, human red blood cells, risperidone, filgrastim, immunoglobulin human normal, fluconazole, cefepime hydrochloride, metoclopramide, amino acids nos w/electrolytes nos/glucose/th, prednisolone, haloperidol, voriconazole, chlorpromazine hydrochloride, metoclopramide, amphotericin b, liposome, omeprazole, immunoglobulin human normal, dexpanthenol, human red blood cells, human red blood cells
Date of First/Last Dose of Study Drug	2014-10-06 / 2015-03-06
Treatment-emergent Non-Serious Adverse Events (Preferred Term)	Aspartate aminotransferase increased, Alanine aminotransferase increased, Hypoalbuminaemia, Malaise, Platelet count decreased, Pyrexia, Cytomegalovirus test positive, Epistaxis, Weight increased, Blood alkaline phosphatase increased, Gamma-glutamyltransferase increased, Pyrexia, White blood cell count decreased,

	Neutrophil count decreased, Face oedema, Aspartate aminotransferase increased, Alanine aminotransferase increased, Hypoalbuminaemia, Renal impairment, Platelet count decreased, White blood cell count decreased, Neutrophil count decreased, Pneumonia, Weight increased, White blood cell count decreased, Aspartate aminotransferase increased, Vomiting, Hypoalbuminaemia, Vision blurred, Neutrophil count decreased, Pyrexia, Febrile neutropenia, Aspartate aminotransferase increased, Hypoalbuminaemia, Pyrexia, Hypersensitivity, Neutrophil count decreased, Weight increased, Aspartate aminotransferase increased, Alanine aminotransferase increased, Fatigue, Hypoalbuminaemia, White blood cell count decreased, Neutrophil count decreased, Nausea, Vomiting, Hypoalbuminaemia, Hypoxia, Weight decreased, Alanine aminotransferase increased, Aspartate aminotransferase increased, Hypoalbuminaemia, Neutrophil count decreased, Platelet count decreased, Pyrexia, Decreased appetite, Hypoxia, Pneumonia, Central nervous system lesion, Proteinuria, Hypoalbuminaemia, Hypoxia
Serious Adverse Event (Preferred Term / Investigator Term)	Delirium / Delirium
AE Start Date (Study Day) / AE Stop Date (Study Day)	2015-03-10 (156) / - (-)
Study Phase of AE Onset	Treatment Phase
Dose at or prior to AE Onset	9 μg/kg/day
Seriousness Criteria	Requires inpatient hospitalization or prolongation of exiting hospitalization
Maximum CTCAE Grade / Outcome	Grade 3/ Not recovered
Study Drug Action Taken/ Other Action Taken	Drug withdrawn / Treatment given, withdrawn from study
Concomitant Medications Used until date of AE Onset	insulin human, insulin aspart, diphenhydramine, daikenchuto, dextromethorphan hydrobromide, zolpidem, new lecicarbon, sodium picosulfate, paracetamol, bactrim, magnesium oxide, prednisolone, rabeprazole, sitagliptin phosphate monohydrate, voriconazole, sennoside a+b, paracetamol, chlorphenamine maleate, dexamethasone, granisetron, albumin human, strong neo-minophagen c, ganciclovir, alclometasone dipropionate, betamethasone butyrate propionate, pentamidine isethionate, furosemide, salbutamol sulfate, esomeprazole, filgrastim, paracetamol, chlorphenamine maleate, dexamethasone, granisetron, aciclovir, furosemide, albumin human, strong neo-minophagen c, guaiazulene, trazodone hydrochloride,

	filgrastim, pip/tazo, amphotericin b, liposome, potassium chloride, carbohydrates nos w/potassium chloride/sodium, furosemide, paracetamol, chlorphenamine maleate, dexamethasone, granisetron, valganciclovir hydrochloride, pentamidine isethionate, furosemide, albumin human, filgrastim, cefepime hydrochloride, immunoglobulin human normal, ringer-lactatis, chlorphenamine maleate, human red blood cells, filgrastim, paracetamol, chlorphenamine maleate, aprepitant, granisetron, albumin human, sodium chloride, metoclopramide, human red blood cells, paracetamol, dexamethasone, granisetron, chlorphenamine maleate, albumin human, cefepime hydrochloride, human red blood cells
Relationship to Study Drug as per Investigator	Possibly related

Investigator's Opinion:

It was delirium that developed during his treatment. The cause of the infiltrative shadow in the brain MRI was unknown, but the shadow may be the cause of the delirium. The cerebrospinal fluid (CSF) examination was performed twice, but the both results were virus-negative and fungus-negative. The possibility of lymphoma infiltration cannot be ruled out, but it is difficult to make a definitive diagnosis. The above course was observed. This does not positively suggest the causal relationship with the study drug, but the cause has not been identified and it is difficult to completely rule out the causal relationship with the study drug. Autopsy was not performed since the subject's family did not request it. The direct cause of the death is aggravation of the primary disease. The cause of the delirium can be either a reactive factor associated with prolonged hospitalization and the primary disease or a structural factor due to the infiltrative shadow in the brain. As for the infiltrative shadow, the CSF examination did not suggest infection at least on two occasions as described in the narrative. Infiltration of CSF due to tumor was also absent.

Sponsor's Opinion:

The event was not related to the study drug (E7777).

Narrative:

2014-09-17: An informed consent of the clinical study of E7777 was obtained.

2014-10-05: The subject was enrolled at the clinical Phase 1/1b study of E7777 targeted at peripheral T-cell lymphoma.

2014-10-06: The 1st cycle of E7777 9μg/kg/day for 5 consecutive days was initiated.

2015-03-02: The 5th cycle of E7777 9μg/kg/day for 5 consecutive days was initiated. During this time, the subject's hospitalization had been prolonged due to study drug treatment and infection treatment, etc.

2015-03-10: The subject experienced delirium. The subject developed various symptoms that had not been observed until yesterday: glaring eyes in the night, talkativeness, seeing a nurse's face on the wall, severe forgetfulness

(being unable to find the position of the nurse call, not knowing what he was doing), not knowing what to do with himself, etc. For a differential diagnosis, delirium due to long-term hospitalization, steroid withdrawal symptoms, meningitis, encephalitis, visual hallucination due to Vfend (voriconazole), and central nervous system infiltration of the underlying disease were considered, and detailed examinations and treatment were started.

2015-03-11: After evaluation of the subject by a specialist of psycho-oncology, oral treatment with Risperdal (risperidone) was started.

2015-03-12: Head MRI examination was performed. MRI findings: T2-weight and fluid-attenuated inversion recovery (FLAIR) MRI sequences showed high-intensity area in deep white matter in the left parietal lobe, but it is unknown if it is of clinical significance.

Date unknown: In the CSF examination, no clear infection or tumor infiltration was observed. With Risperdal treatment, the subject showed a tendency of improvement in delirium. The results of PCR analysis were CMV negative, HHV6 negative, and JCV negative. Various microbial cultures were negative. There was no increase in CSF cell count. No neck stiffness was observed.

2015-03-25: Head MRI examination was performed. MRI findings: An infiltrative shadow was observed in the cerebral cortex of the right temporal lobe. From the images, the possibilities of both infection and lymphoma infiltration were considered.

2015-03-26: The CSF examination was performed again, but there was no increase in CSF cell count. Microscopy did not show the cell count increased or appearance of abnormal cells. No virus PCR such as CMV, HHV6 or JCV was detected, and aspergillus PCR was negative. Various microbial cultures were negative.

2015-03-31: Rapid aggravation of delirium had been observed in the subject from around 2015-03-29, and he developed communication difficulty. His disease condition was explained to his family, and the subject was withdrawn from the clinical study because it was considered difficult to continue.

2015-04-01: Prednisolone injection 5 mg/day for the primary disease, Ambisome (amphotericin B) injection 126 mg/day for suspected fungal infection, and symptomatic treatment were continued. The subject did not recover from the delirium to the degree that he was able to communicate with others. Furthermore, the primary disease worsened day by day.

2015-05-02: At 05:10, the subject died of progression of the primary disease. A biopsy of the infiltrative shadow noted on the brain MRI was not performed.

Study / Subject ID	E7777-J081-101 / 10041301
Age (year), Sex, Race, Dose Group	7[redacted], Male, Japanese, 9 µg/kg/day group
Current Medical Conditions (Dictionary-derived Term)	Refractive amblyopia, Diabetes mellitus, Joint injury, Joint injury, Hyperlipidaemia
Concomitant Medications	pitavastatin calcium, diclofenac, pioglitazone hydrochloride, glimepiride, vildagliptin, febuxostat, dexamethasone, granisetron hydrochloride, paracetamol, chlorphenamine maleate, furosemide, paracetamol, sodium chloride, hydrocortisone sodium succinate, gluaceto 35, amino acids nos w/electrolytes nos/glucose/th, cefepime hydrochloride, sodium chloride, prochlorperazine, insulin lispro, insulin human, furosemide, strong neo-minophagen c, pioglitazone hydrochloride, glimepiride, vildagliptin, zolpidem tartrate, betamethasone butyrate propionate, bactrim, brotizolam, paracetamol, dexamethasone, granisetron hydrochloride, chlorphenamine maleate, hydrocortisone sodium succinate, sennoside a+b calcium, sodium chloride, levofloxacin, osmosal /00501801/, furosemide, vidarabine, valaciclovir hydrochloride, aciclovir
Date of First/Last Dose of Study Drug	2012-12-17 / 2013-01-15
Treatment-emergent Non-Serious Adverse Events (Preferred Term)	Constipation, Lymphocyte count decreased, Leukocytosis, Oedema peripheral, Blood albumin decreased, Aspartate aminotransferase increased, Alanine aminotransferase increased, Nausea, Malaise, Pyrexia, Infusion site extravasation, Blood cholinesterase decreased, Face oedema, Pleural effusion, Capillary leak syndrome, Insomnia, Proteinuria, Pyrexia, Oedema peripheral, Capillary leak syndrome, Constipation, Hypoalbuminaemia, Lymphocyte count decreased, Aspartate aminotransferase increased, Alanine aminotransferase increased, Blood cholinesterase decreased, Leukocytosis, Oral herpes, Rash
Serious Adverse Event (Preferred Term / Investigator Term)	Decreased appetite / anorexia Hypoxia / hypoxia
AE Start Date (Study Day) / AE Stop Date (Study Day)	Decreased appetite: 2012-12-22 (6) / 2013-01-15 (30) Hypoxia: 2013-01-15 (30) / 2013-01-17 (32)
Study Phase of AE Onset	Treatment Phase
Dose at or prior to AE Onset	Decreased appetite: 9 µg/kg/day Hypoxia: 6 µg/kg/day
Seriousness Criteria	Both SAEs: Requires inpatient hospitalization or prolongation of exiting hospitalization
Maximum CTCAE Grade / Outcome	Decreased appetite: Grade 3 / Recovered Hypoxia: Grade 3 / Recovered

Study Drug Action Taken/ Other Action Taken	Decreased appetite: Dose reduced / Treatment given Hypoxia: Drug interrupted / Treatment given
Concomitant Medications Used until date of AE Onset	Decreased appetite: pitavastatin calcium, diclofenac, pioglitazone hydrochloride, glimepiride, vildagliptin, febuxostat, dexamethasone, granisetron hydrochloride, paracetamol, chlorphenamine maleate, furosemide Hypoxia (in addition to above medications): paracetamol, sodium chloride, hydrocortisone sodium succinate, gluaceto 35, amino acids nos w/electrolytes nos/glucose/th, cefepime hydrochloride, sodium chloride, prochlorperazine, insulin lispro, insulin human, furosemide, strong neo-minophagen c, pioglitazone hydrochloride, glimepiride, vildagliptin, zolpidem tartrate, betamethasone butyrate propionate, bactrim, brotizolam, paracetamol, dexamethasone, granisetron hydrochloride, chlorphenamine maleate, hydrocortisone sodium succinate, sennoside a+b calcium, sodium chloride, levofloxacin
Relationship to Study Drug as per Investigator	Decreased appetite: Possibly related Hypoxia: Probably related

Investigator's Opinion:

The patient suffered anorexia and hypoxia after the study drug administration, so the relationship to the study drug cannot be excluded.

Sponsor's Opinion:

The event of decreased appetite was not related to the study drug (E7777), and hypoxia was possibly related to the study drug.

Narrative:

2012-12-17: E7777 for Cycle 1 Day 1 was administered.

2012-12-21: E7777 for Cycle 1 Day 5 was administered. The patient seemed to have inappetence.

2012-12-22: He was discharged from the investigator's hospital in the afternoon. He subsequently ate little because of inappetence.

2012-12-23: In the evening, he had a fever of over 38°C. At midnight, he visited an emergency outpatient unit. Owing to severe inappetence and malaise (not reported as SAE), he was admitted to the hospital. CT findings: absence of pneumonia and pleural effusion. CX-P findings: absence of pulmonary congestion, negative for flu. He had hepatic function disorder (Grade 3).

2012-12-24: Intravenous infusion of Maxipime (cefepime dihydrochloride hydrate) was initiated. Calonal Tab. (acetaminophen) was taken. Body temperature: 37.8°C (at 01:15), 38.4°C (at 07:01), 37.8°C (at 09:27). Physio 35 Injection (maintenance medium with glucose), sodium chloride injection, and Bfluid Injection (electrolysis and vitamin) were initiated. Body temperature: 38.9°C

(at 14:00); Solu-Cortef (hydrocortisone sodium succinate) Injection 1A was given.

2012-12-25: He still had severe inappetence (Grade 3), nausea (Grade 2) and malaise (Grade 2).

2012-12-26: He was able to eat and drink a small amount. His general condition tended to improve gradually.

2013-01-03: Hospital meal was resumed. The nausea improved.

2013-01-04: Intravenous infusion of Maxipime and drip infusion with Bfluid were discontinued.

2013-01-06: He was discharged from the hospital.

2013-01-07: Due to the hepatic function disorder (Grade 2), the study drug for Day 1 in Cycle 2 was postponed.

2013-01-15: He came to be able to eat and recovered from the inappetence. The hepatic function disorder improved so the study drug for Cycle 2 Day 1 was started to be administered. At 10:10, his BT was 37.3°C.
From 12:15 to 13:15, the study drug was administered. At 13:20, his BT was 37.2°C. At 13:45, his BT was 37.4°C.
Around 15:30, he had chills and shivering.
At 16:05, SPO_2 was 89% to 90%. He had no dyspnoea. He was followed up with heat-retention. His BT was 37.9°C.
At 16:20, SPO_2 was 89% to 91%. He had no dyspnoea. His BT was 39.7°C.
At 16:55, he was taken to the emergency outpatient department due to the hypoxia.
At 17:00, SPO_2 was 86%. He started to receive 2 L of oxygen inhalation and the amount was increased to 5 L. SPO_2 increased to 95%. Plain chest CT was performed and showed no abnormality.
At 18:45, his BT was 40.1°C. Due to the hypoxia (Grade 3), he was hospitalized. At 19:45, SPO_2 was 93%.
At 17:09, he took Calonal Tab. and CRP was 1.57.
At 20:15, BT was 39.8°C and SPO_2 was 96%.
At 20:30, the amount of oxygen inhalation was increased to 10 L/min and Solu-Cortef was intravenously administered.
At 23:45, BT went down to 37.6°C and SPO_2 was 96%. He started to take Cravit (levofloxacin hydrate) for infection prophylaxis.

2013-01-16: At 2:00, BT was 36.9°C and SPO_2 was 98%. The amount of oxygen inhalation was decreased to 3 L/min.
At 5:00, the way of oxygen inhalation was changed to nasal cannula mask 3 L/min. Administration of the study drug for Cycle 2 Day 2 was suspended.
At 17:40, BT was 36.5°C and SPO_2 was 98%. The amount of oxygen inhalation with nasal cannula mask was decreased to 1 L/min.

2013-01-17: Administration of the study drug for Cycle 2 Day 3 was suspended.
At 10:00, oxygen inhalation with nasal cannula mask was discontinued.
At 13:55, BT was 36.5°C and SPO_2 was 92%. He recovered from the hypoxia so was discharged from the hospital.

Study / Subject ID	E7777-J081-101 / 10041303
Age (year), Sex, Race, Dose Group	4[redacted], Female, Japanese, 9 µg/kg/day group
Current Medical Conditions (Dictionary-derived Term)	Goitre, Osteoporosis, Neuropathy peripheral, Rhinitis allergic, Sinusitis
Concomitant Medications	paracetamol, loxoprofen sodium, white soft paraffin, sulfadiazine, fexofenadine hydrochloride, cinal, goshajinkigan, mecobalamin, carbocisteine, tranexamic acid, eldecalcitol, clarithromycin, paracetamol, chlorphenamine maleate, dexamethasone, granisetron hydrochloride, zolpidem tartrate, sennoside a+b calcium, ursodeoxycholic acid, metoclopramide hydrochloride, flebobag ring lact, amino acids nos w/electrolytes nos/glucose/th, strong neo-minophagen c, metoclopramide hydrochloride, omeprazole, fexofenadine hydrochloride, cinal, eldecalcitol, goshajinkigan, clarithromycin, mecobalamin, carbocisteine, tranexamic acid, prochlorperazine, ursodeoxycholic acid
Date of First/Last Dose of Study Drug	2013-10-07 / 2013-10-11
Treatment-emergent Non-Serious Adverse Events (Preferred Term)	Insomnia, Leukocytosis, Lymphocyte count decreased, Myalgia, Blood albumin decreased, Hypertriglyceridaemia, Nausea, Platelet count decreased, Amylase increased, Vomiting, Eyelid oedema, Conjunctival oedema, Blood albumin decreased
Serious Adverse Event (Preferred Term / Investigator Term)	Aspartate aminotransferase increased / AST increased Alanine aminotransferase increased / ALT increased Fatigue / Fatigue
AE Start Date (Study Day) / AE Stop Date (Study Day)	Aspartate aminotransferase increased : 2013-10-11 (5) / 2013-11-11 (36) Alanine aminotransferase increased: 2013-10-11 (5) / 2013-11-11 (36) Fatigue: 2013-10-14 (8) / 2013-10-28 (22)
Study Phase of AE Onset	Treatment Phase
Dose at or prior to AE Onset	All SAEs: 9 µg/kg/day
Seriousness Criteria	All SAEs: Requires inpatient hospitalization or prolongation of exiting hospitalization
Maximum CTCAE Grade / Outcome	Aspartate aminotransferase increased: Grade 2 / Recovered Alanine aminotransferase increased: Grade 3 / Recovered Fatigue: Grade 3 / Recovered
Study Drug Action Taken/ Other Action Taken	Aspartate aminotransferase increased: Dose not changed / Treatment given Alanine aminotransferase increased: Dose not changed / Treatment given Fatigue: Dose not changed / None
Concomitant Medications	Aspartate aminotransferase increased and Alanine

Used until date of AE Onset	aminotransferase increased: paracetamol, loxoprofen sodium, white soft paraffin, sulfadiazine, fexofenadine hydrochloride, cinal, goshajinkigan, mecobalamin, carbocisteine, tranexamic acid, eldecalcitol, clarithromycin, paracetamol, chlorphenamine maleate, dexamethasone, granisetron hydrochloride, zolpidem tartrate, sennoside a+b calcium, ursodeoxycholic acid Fatigue (in addition to above medications): metoclopramide hydrochloride
Relationship to Study Drug as per Investigator	Aspartate aminotransferase increased : Probably related Alanine aminotransferase increased: Probably related Fatigue: Probably related

Investigator's Opinion:

These events developed during administration of the study drug so there were strongly suspected to be causal relationship.

Sponsor's Opinion:

The subject experienced malaise while being treated with E7777, thus the causality of the study drug could not be ruled out. Events of AST increased and ALT increased were possibly related to the study drug.

Narrative:

2013-10-07: E7777 for Day 1 in Cycle 1 was initiated.

2013-10-11: The patient was discharged from the hospital after administration of E7777 for Cycle 1 Day 5.

2013-10-14: She had malaise and queasy strongly. That made her difficult to take food and water, and she visited the emergency department. Dehydration was seen. Sodium chloride and Primperan (metoclopramide) were given, and then she went home.

2013-10-15: Visited on Cycle 1 Day 8. She had a strong malaise (PS: 2 to 3). AST and ALT increased. Therefore, she was hospitalized. She began to receive Bfluid, Lactated ringer's solution and Stronger Neo-Minophagen C (monoammonium glycyrrhizinate) intravenously.

2013-10-16: Due to queasy and vomiting, Omepral (omeprazole sodium) was initiated. The malaise persisted.

2013-10-17: She complained of difficulty in seeing so visited the department of ophthalmology. She was diagnosed with conjunctival edema of both eyelids and conjunctival edema of both eyeballs.

2013-10-19: The malaise and queasy improved, so she was discharged from the hospital.

2013-10-22: Visited on Cycle 1 Day 15. The malaise improved to Grade 1. The increased AST (Grade 2) and ALT (Grade 3) persisted. She visited the

ophthalmology, and she was considered to have recovered from the conjunctival edema of both eyelids and conjunctival edema of both eyeballs.

2013-10-28: Visited on Cycle 1 Day 22. The malaise resolved. Although the increased AST (Grade 1) and ALT (Grade 2) showed towards resolution, they persisted.

2013-11-11: AST and ALT were restored to normal. She withdrew the informed consent, and the study was discontinued.

付録 2.7.6-4　MedDRA SOC/PT 別の全有害事象発現率（国内205試験）（安全性解析対象集団）

MedDRA Version 21.1 器官別大分類 基本語	PTCL (N=17) n (%)	CTCL (N=19) n (%)	その他 (N=1) n (%)	全体 (N=37) n (%)
Subjects with any TEAEs	17 (100.0)	19 (100.0)	1 (100.0)	37 (100.0)
Blood and lymphatic system disorders	16 (94.1)	15 (78.9)	1 (100.0)	32 (86.5)
Lymphopenia	14 (82.4)	11 (57.9)	1 (100.0)	26 (70.3)
Thrombocytopenia	9 (52.9)	3 (15.8)	1 (100.0)	13 (35.1)
Anaemia	3 (17.6)	2 (10.5)	0	5 (13.5)
Leukocytosis	0	4 (21.1)	0	4 (10.8)
Leukopenia	4 (23.5)	0	0	4 (10.8)
Neutropenia	2 (11.8)	0	0	2 (5.4)
Lymphadenopathy	0	1 (5.3)	0	1 (2.7)
Lymphocytosis	1 (5.9)	0	0	1 (2.7)
Thrombocytosis	0	1 (5.3)	0	1 (2.7)
Cardiac disorders	3 (17.6)	0	0	3 (8.1)
Cardiomegaly	1 (5.9)	0	0	1 (2.7)
Sinus bradycardia	1 (5.9)	0	0	1 (2.7)
Sinus tachycardia	1 (5.9)	0	0	1 (2.7)
Supraventricular extrasystoles	1 (5.9)	0	0	1 (2.7)
Ventricular arrhythmia	1 (5.9)	0	0	1 (2.7)
Ear and labyrinth disorders	1 (5.9)	0	0	1 (2.7)
Hypoacusis	1 (5.9)	0	0	1 (2.7)
Endocrine disorders	1 (5.9)	1 (5.3)	0	2 (5.4)
Adrenal insufficiency	0	1 (5.3)	0	1 (2.7)
Hypothyroidism	1 (5.9)	0	0	1 (2.7)
Eye disorders	3 (17.6)	2 (10.5)	0	5 (13.5)
Eye pain	1 (5.9)	1 (5.3)	0	2 (5.4)
Conjunctivitis allergic	1 (5.9)	0	0	1 (2.7)

付録 2.7.6-4　MedDRA SOC/PT 別の全有害事象発現率（国内205試験）（安全性解析対象集団）

MedDRA Version 21.1 器官別大分類 基本語	PTCL (N=17) n (%)	CTCL (N=19) n (%)	その他 (N=1) n (%)	全体 (N=37) n (%)
Disorder of orbit	0	1 (5.3)	0	1 (2.7)
Dry eye	0	1 (5.3)	0	1 (2.7)
Eczema eyelids	1 (5.9)	0	0	1 (2.7)
Photopsia	0	1 (5.3)	0	1 (2.7)
Retinal exudates	0	1 (5.3)	0	1 (2.7)
Vision blurred	0	1 (5.3)	0	1 (2.7)
Gastrointestinal disorders	13 (76.5)	15 (78.9)	1 (100.0)	29 (78.4)
Constipation	4 (23.5)	10 (52.6)	0	14 (37.8)
Nausea	5 (29.4)	6 (31.6)	0	11 (29.7)
Vomiting	4 (23.5)	3 (15.8)	0	7 (18.9)
Diarrhoea	2 (11.8)	0	1 (100.0)	3 (8.1)
Stomatitis	2 (11.8)	1 (5.3)	0	3 (8.1)
Abdominal discomfort	0	1 (5.3)	0	1 (2.7)
Abdominal pain upper	0	1 (5.3)	0	1 (2.7)
Ascites	1 (5.9)	0	0	1 (2.7)
Colitis	1 (5.9)	0	0	1 (2.7)
Dyspepsia	0	1 (5.3)	0	1 (2.7)
Dysphagia	1 (5.9)	0	0	1 (2.7)
Gingival pain	1 (5.9)	0	0	1 (2.7)
Haemorrhoids	1 (5.9)	0	0	1 (2.7)
Mouth ulceration	0	1 (5.3)	0	1 (2.7)
Perianal erythema	1 (5.9)	0	0	1 (2.7)
Toothache	0	1 (5.3)	0	1 (2.7)
General disorders and administration site conditions	14 (82.4)	16 (84.2)	1 (100.0)	31 (83.8)
Pyrexia	11 (64.7)	7 (36.8)	1 (100.0)	19 (51.4)
Malaise	4 (23.5)	8 (42.1)	0	12 (32.4)
Oedema peripheral	5 (29.4)	3 (15.8)	0	8 (21.6)
Fatigue	3 (17.6)	1 (5.3)	0	4 (10.8)

付録 2.7.6-4　MedDRA SOC/PT 別の全有害事象発現率（国内205試験）（安全性解析対象集団）

MedDRA Version 21.1 器官別大分類 基本語	PTCL (N=17) n (%)	CTCL (N=19) n (%)	その他 (N=1) n (%)	全体 (N=37) n (%)
Generalised oedema	0	3 (15.8)	0	3 (8.1)
Face oedema	1 (5.9)	0	0	1 (2.7)
Facial pain	0	1 (5.3)	0	1 (2.7)
Injection site erythema	0	1 (5.3)	0	1 (2.7)
Pain	0	1 (5.3)	0	1 (2.7)
Puncture site pain	0	1 (5.3)	0	1 (2.7)
Vessel puncture site erythema	1 (5.9)	0	0	1 (2.7)
Hepatobiliary disorders	0	1 (5.3)	0	1 (2.7)
Hepatic function abnormal	0	1 (5.3)	0	1 (2.7)
Immune system disorders	1 (5.9)	1 (5.3)	0	2 (5.4)
Contrast media allergy	0	1 (5.3)	0	1 (2.7)
Drug hypersensitivity	1 (5.9)	0	0	1 (2.7)
Infections and infestations	9 (52.9)	9 (47.4)	0	18 (48.6)
Angular cheilitis	1 (5.9)	1 (5.3)	0	2 (5.4)
Lung infection	2 (11.8)	0	0	2 (5.4)
Pneumonia	1 (5.9)	1 (5.3)	0	2 (5.4)
Cellulitis	1 (5.9)	0	0	1 (2.7)
Conjunctivitis	1 (5.9)	0	0	1 (2.7)
Cytomegalovirus chorioretinitis	1 (5.9)	0	0	1 (2.7)
Cytomegalovirus infection	0	1 (5.3)	0	1 (2.7)
Enterocolitis infectious	0	1 (5.3)	0	1 (2.7)
Folliculitis	1 (5.9)	0	0	1 (2.7)
Gastroenteritis	1 (5.9)	0	0	1 (2.7)
Genital candidiasis	0	1 (5.3)	0	1 (2.7)
Gingivitis	0	1 (5.3)	0	1 (2.7)
Herpes virus infection	0	1 (5.3)	0	1 (2.7)
Herpes zoster	0	1 (5.3)	0	1 (2.7)

付録 2.7.6-4　MedDRA SOC/PT 別の全有害事象発現率（国内205試験）（安全性解析対象集団）

MedDRA Version 21.1 器官別大分類 基本語	PTCL (N=17) n (%)	CTCL (N=19) n (%)	その他 (N=1) n (%)	全体 (N=37) n (%)
Impetigo	0	1 (5.3)	0	1 (2.7)
Nasopharyngitis	1 (5.9)	0	0	1 (2.7)
Parotitis	1 (5.9)	0	0	1 (2.7)
Skin candida	0	1 (5.3)	0	1 (2.7)
Skin infection	0	1 (5.3)	0	1 (2.7)
Tinea pedis	0	1 (5.3)	0	1 (2.7)
Upper respiratory tract infection	1 (5.9)	0	0	1 (2.7)
Wound infection	0	1 (5.3)	0	1 (2.7)
Injury, poisoning and procedural complications	0	1 (5.3)	0	1 (2.7)
Wound	0	1 (5.3)	0	1 (2.7)
Investigations	16 (94.1)	17 (89.5)	1 (100.0)	34 (91.9)
Aspartate aminotransferase increased	16 (94.1)	16 (84.2)	1 (100.0)	33 (89.2)
Alanine aminotransferase increased	16 (94.1)	16 (84.2)	0	32 (86.5)
Gamma-glutamyltransferase increased	9 (52.9)	7 (36.8)	1 (100.0)	17 (45.9)
Lipase increased	6 (35.3)	4 (21.1)	0	10 (27.0)
Weight increased	4 (23.5)	3 (15.8)	0	7 (18.9)
Blood alkaline phosphatase increased	2 (11.8)	3 (15.8)	1 (100.0)	6 (16.2)
Amylase increased	3 (17.6)	2 (10.5)	0	5 (13.5)
Blood cholesterol increased	3 (17.6)	2 (10.5)	0	5 (13.5)
Blood lactate dehydrogenase increased	3 (17.6)	0	0	3 (8.1)
Blood creatine phosphokinase increased	1 (5.9)	1 (5.3)	0	2 (5.4)
C-reactive protein increased	0	1 (5.3)	1 (100.0)	2 (5.4)
Weight decreased	2 (11.8)	0	0	2 (5.4)
Blood bilirubin increased	1 (5.9)	0	0	1 (2.7)
Blood creatinine increased	1 (5.9)	0	0	1 (2.7)
Blood fibrinogen decreased	1 (5.9)	0	0	1 (2.7)
Blood urea increased	1 (5.9)	0	0	1 (2.7)
Brain natriuretic peptide increased	1 (5.9)	0	0	1 (2.7)

付録 2.7.6-4　MedDRA SOC/PT 別の全有害事象発現率（国内205試験）（安全性解析対象集団）

MedDRA Version 21.1 器官別大分類 基本語	PTCL (N=17) n (%)	CTCL (N=19) n (%)	その他 (N=1) n (%)	全体 (N=37) n (%)
Cytomegalovirus test positive	1 (5.9)	0	0	1 (2.7)
Electrocardiogram QT prolonged	1 (5.9)	0	0	1 (2.7)
N-terminal prohormone brain natriuretic peptide increased	1 (5.9)	0	0	1 (2.7)
Metabolism and nutrition disorders	14 (82.4)	15 (78.9)	1 (100.0)	30 (81.1)
Hypoalbuminaemia	12 (70.6)	14 (73.7)	0	26 (70.3)
Decreased appetite	5 (29.4)	5 (26.3)	1 (100.0)	11 (29.7)
Hypertriglyceridaemia	5 (29.4)	5 (26.3)	0	10 (27.0)
Hyperglycaemia	2 (11.8)	2 (10.5)	0	4 (10.8)
Hyponatraemia	3 (17.6)	0	1 (100.0)	4 (10.8)
Dehydration	3 (17.6)	0	0	3 (8.1)
Hypokalaemia	3 (17.6)	0	0	3 (8.1)
Hypophosphataemia	3 (17.6)	0	0	3 (8.1)
Hyperkalaemia	0	2 (10.5)	0	2 (5.4)
Hyperuricaemia	1 (5.9)	1 (5.3)	0	2 (5.4)
Dyslipidaemia	0	1 (5.3)	0	1 (2.7)
Hypocalcaemia	0	1 (5.3)	0	1 (2.7)
Tumour lysis syndrome	1 (5.9)	0	0	1 (2.7)
Musculoskeletal and connective tissue disorders	2 (11.8)	7 (36.8)	1 (100.0)	10 (27.0)
Myalgia	0	4 (21.1)	0	4 (10.8)
Back pain	0	2 (10.5)	1 (100.0)	3 (8.1)
Arthralgia	1 (5.9)	1 (5.3)	0	2 (5.4)
Rhabdomyolysis	0	2 (10.5)	0	2 (5.4)
Muscle spasms	0	1 (5.3)	0	1 (2.7)
Musculoskeletal stiffness	1 (5.9)	0	0	1 (2.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (29.4)	1 (5.3)	0	6 (16.2)
Tumour associated fever	3 (17.6)	0	0	3 (8.1)
Cancer pain	1 (5.9)	0	0	1 (2.7)

付録 2.7.6-4　MedDRA SOC/PT 別の全有害事象発現率（国内205試験）（安全性解析対象集団）

MedDRA Version 21.1 器官別大分類 基本語	PTCL (N=17) n (%)	CTCL (N=19) n (%)	その他 (N=1) n (%)	全体 (N=37) n (%)
Squamous cell carcinoma of skin	0	1 (5.3)	0	1 (2.7)
Tumour pain	1 (5.9)	0	0	1 (2.7)
Nervous system disorders	6 (35.3)	5 (26.3)	0	11 (29.7)
Dysgeusia	3 (17.6)	0	0	3 (8.1)
Headache	1 (5.9)	2 (10.5)	0	3 (8.1)
Dizziness	0	2 (10.5)	0	2 (5.4)
Peripheral sensory neuropathy	2 (11.8)	0	0	2 (5.4)
Altered state of consciousness	1 (5.9)	0	0	1 (2.7)
Post herpetic neuralgia	0	1 (5.3)	0	1 (2.7)
Psychiatric disorders	5 (29.4)	5 (26.3)	0	10 (27.0)
Insomnia	3 (17.6)	4 (21.1)	0	7 (18.9)
Delirium	1 (5.9)	1 (5.3)	0	2 (5.4)
Hallucination, auditory	1 (5.9)	0	0	1 (2.7)
Renal and urinary disorders	2 (11.8)	2 (10.5)	1 (100.0)	5 (13.5)
Proteinuria	2 (11.8)	1 (5.3)	1 (100.0)	4 (10.8)
Renal impairment	0	1 (5.3)	0	1 (2.7)
Reproductive system and breast disorders	0	1 (5.3)	0	1 (2.7)
Prostatic pain	0	1 (5.3)	0	1 (2.7)
Respiratory, thoracic and mediastinal disorders	4 (23.5)	3 (15.8)	0	7 (18.9)
Oropharyngeal pain	1 (5.9)	1 (5.3)	0	2 (5.4)
Cough	1 (5.9)	0	0	1 (2.7)
Hiccups	0	1 (5.3)	0	1 (2.7)
Laryngeal haemorrhage	1 (5.9)	0	0	1 (2.7)
Laryngeal pain	1 (5.9)	0	0	1 (2.7)
Pharyngeal inflammation	0	1 (5.3)	0	1 (2.7)

付録 2.7.6-4　MedDRA SOC/PT 別の全有害事象発現率（国内205試験）（安全性解析対象集団）

MedDRA Version 21.1 器官別大分類 基本語	PTCL (N=17) n (%)	CTCL (N=19) n (%)	その他 (N=1) n (%)	全体 (N=37) n (%)
Upper respiratory tract inflammation	1 (5.9)	0	0	1 (2.7)
Skin and subcutaneous tissue disorders	4 (23.5)	7 (36.8)	1 (100.0)	12 (32.4)
Dermatitis exfoliative generalised	1 (5.9)	1 (5.3)	0	2 (5.4)
Pruritus	0	2 (10.5)	0	2 (5.4)
Skin erosion	0	2 (10.5)	0	2 (5.4)
Dermal cyst	0	1 (5.3)	0	1 (2.7)
Dermatitis contact	0	1 (5.3)	0	1 (2.7)
Dermatosis	1 (5.9)	0	0	1 (2.7)
Drug eruption	1 (5.9)	0	0	1 (2.7)
Rash	0	0	1 (100.0)	1 (2.7)
Rash generalised	1 (5.9)	0	0	1 (2.7)
Skin fissures	0	1 (5.3)	0	1 (2.7)
Skin ulcer	0	1 (5.3)	0	1 (2.7)
Toxic skin eruption	0	1 (5.3)	0	1 (2.7)
Vascular disorders	2 (11.8)	12 (63.2)	0	14 (37.8)
Capillary leak syndrome	0	5 (26.3)	0	5 (13.5)
Hypertension	1 (5.9)	4 (21.1)	0	5 (13.5)
Hot flush	0	2 (10.5)	0	2 (5.4)
Hypotension	0	1 (5.3)	0	1 (2.7)
Vasculitis	1 (5.9)	0	0	1 (2.7)

（添付資料5.3.5.2.1のTable 14.3.1.2.2.1を引用）

付録 2.7.6-5　MedDRA SOC/PT別のGrade 3以上の有害事象発現率（国内205試験）（安全性解析対象集団）

MedDRA Version 21.1 器官別大分類 基本語 CTCAE Grade	PTCL (N=17) n (%)	CTCL (N=19) n (%)	その他 (N=1) n (%)	全体 (N=37) n (%)
Any system / Any term	17 (100.0)	17 (89.5)	1 (100.0)	35 (94.6)
3	8 (47.1)	11 (57.9)	0	19 (51.4)
4	9 (52.9)	5 (26.3)	1 (100.0)	15 (40.5)
5	0	1 (5.3)	0	1 (2.7)
Blood and lymphatic system disorders	13 (76.5)	9 (47.4)	1 (100.0)	23 (62.2)
3	5 (29.4)	4 (21.1)	0	9 (24.3)
4	8 (47.1)	5 (26.3)	1 (100.0)	14 (37.8)
5	0	0	0	0
Lymphopenia	12 (70.6)	8 (42.1)	1 (100.0)	21 (56.8)
3	5 (29.4)	4 (21.1)	1 (100.0)	10 (27.0)
4	7 (41.2)	4 (21.1)	0	11 (29.7)
5	0	0	0	0
Thrombocytopenia	3 (17.6)	2 (10.5)	1 (100.0)	6 (16.2)
3	1 (5.9)	1 (5.3)	0	2 (5.4)
4	2 (11.8)	1 (5.3)	1 (100.0)	4 (10.8)
5	0	0	0	0
Anaemia	1 (5.9)	1 (5.3)	0	2 (5.4)
3	1 (5.9)	1 (5.3)	0	2 (5.4)
4	0	0	0	0
5	0	0	0	0
Neutropenia	2 (11.8)	0	0	2 (5.4)
3	2 (11.8)	0	0	2 (5.4)
4	0	0	0	0
5	0	0	0	0

付録 2.7.6-5　MedDRA SOC/PT別のGrade 3以上の有害事象発現率（国内205試験）（安全性解析対象集団）

MedDRA Version 21.1 器官別大分類 基本語 CTCAE Grade	PTCL (N=17) n (%)	CTCL (N=19) n (%)	その他 (N=1) n (%)	全体 (N=37) n (%)
Leukopenia	1 (5.9)	0	0	1 (2.7)
3	1 (5.9)	0	0	1 (2.7)
4	0	0	0	0
5	0	0	0	0
Gastrointestinal disorders	0	1 (5.3)	0	1 (2.7)
3	0	1 (5.3)	0	1 (2.7)
4	0	0	0	0
5	0	0	0	0
Mouth ulceration	0	1 (5.3)	0	1 (2.7)
3	0	1 (5.3)	0	1 (2.7)
4	0	0	0	0
5	0	0	0	0
General disorders and administration site conditions	0	1 (5.3)	0	1 (2.7)
3	0	1 (5.3)	0	1 (2.7)
4	0	0	0	0
5	0	0	0	0
Generalised oedema	0	1 (5.3)	0	1 (2.7)
3	0	1 (5.3)	0	1 (2.7)
4	0	0	0	0
5	0	0	0	0
Pain	0	1 (5.3)	0	1 (2.7)
3	0	1 (5.3)	0	1 (2.7)
4	0	0	0	0
5	0	0	0	0

付録 2.7.6-5　MedDRA SOC/PT別のGrade 3以上の有害事象発現率（国内205試験）（安全性解析対象集団）

MedDRA Version 21.1 器官別大分類 基本語 CTCAE Grade	PTCL (N=17) n (%)	CTCL (N=19) n (%)	その他 (N=1) n (%)	全体 (N=37) n (%)
Infections and infestations	4 (23.5)	2 (10.5)	0	6 (16.2)
3	4 (23.5)	2 (10.5)	0	6 (16.2)
4	0	0	0	0
5	0	0	0	0
Pneumonia	1 (5.9)	1 (5.3)	0	2 (5.4)
3	1 (5.9)	1 (5.3)	0	2 (5.4)
4	0	0	0	0
5	0	0	0	0
Cytomegalovirus chorioretinitis	1 (5.9)	0	0	1 (2.7)
3	1 (5.9)	0	0	1 (2.7)
4	0	0	0	0
5	0	0	0	0
Herpes zoster	0	1 (5.3)	0	1 (2.7)
3	0	1 (5.3)	0	1 (2.7)
4	0	0	0	0
5	0	0	0	0
Lung infection	1 (5.9)	0	0	1 (2.7)
3	1 (5.9)	0	0	1 (2.7)
4	0	0	0	0
5	0	0	0	0
Parotitis	1 (5.9)	0	0	1 (2.7)
3	1 (5.9)	0	0	1 (2.7)
4	0	0	0	0
5	0	0	0	0

付録 2.7.6-5　MedDRA SOC/PT別のGrade 3以上の有害事象発現率（国内205試験）（安全性解析対象集団）

MedDRA Version 21.1 器官別大分類 基本語 CTCAE Grade	PTCL (N=17) n (%)	CTCL (N=19) n (%)	その他 (N=1) n (%)	全体 (N=37) n (%)
Investigations	13 (76.5)	14 (73.7)	1 (100.0)	28 (75.7)
3	11 (64.7)	13 (68.4)	1 (100.0)	25 (67.6)
4	2 (11.8)	1 (5.3)	0	3 (8.1)
5	0	0	0	0
Alanine aminotransferase increased	10 (58.8)	11 (57.9)	0	21 (56.8)
3	9 (52.9)	11 (57.9)	0	20 (54.1)
4	1 (5.9)	0	0	1 (2.7)
5	0	0	0	0
Aspartate aminotransferase increased	10 (58.8)	6 (31.6)	0	16 (43.2)
3	9 (52.9)	6 (31.6)	0	15 (40.5)
4	1 (5.9)	0	0	1 (2.7)
5	0	0	0	0
Lipase increased	4 (23.5)	3 (15.8)	0	7 (18.9)
3	3 (17.6)	2 (10.5)	0	5 (13.5)
4	1 (5.9)	1 (5.3)	0	2 (5.4)
5	0	0	0	0
Gamma-glutamyltransferase increased	3 (17.6)	2 (10.5)	1 (100.0)	6 (16.2)
3	3 (17.6)	2 (10.5)	1 (100.0)	6 (16.2)
4	0	0	0	0
5	0	0	0	0
Amylase increased	2 (11.8)	1 (5.3)	0	3 (8.1)
3	2 (11.8)	1 (5.3)	0	3 (8.1)
4	0	0	0	0
5	0	0	0	0

付録 2.7.6-5　MedDRA SOC/PT別のGrade 3以上の有害事象発現率（国内205試験）（安全性解析対象集団）

MedDRA Version 21.1 器官別大分類 基本語 CTCAE Grade	PTCL (N=17) n (%)	CTCL (N=19) n (%)	その他 (N=1) n (%)	全体 (N=37) n (%)
Metabolism and nutrition disorders	6 (35.3)	6 (31.6)	1 (100.0)	13 (35.1)
3	5 (29.4)	5 (26.3)	1 (100.0)	11 (29.7)
4	1 (5.9)	1 (5.3)	0	2 (5.4)
5	0	0	0	0
Hypertriglyceridaemia	2 (11.8)	3 (15.8)	0	5 (13.5)
3	2 (11.8)	3 (15.8)	0	5 (13.5)
4	0	0	0	0
5	0	0	0	0
Hyperglycaemia	2 (11.8)	1 (5.3)	0	3 (8.1)
3	1 (5.9)	1 (5.3)	0	2 (5.4)
4	1 (5.9)	0	0	1 (2.7)
5	0	0	0	0
Hyponatraemia	2 (11.8)	0	1 (100.0)	3 (8.1)
3	2 (11.8)	0	1 (100.0)	3 (8.1)
4	0	0	0	0
5	0	0	0	0
Decreased appetite	1 (5.9)	1 (5.3)	0	2 (5.4)
3	1 (5.9)	1 (5.3)	0	2 (5.4)
4	0	0	0	0
5	0	0	0	0
Hypoalbuminaemia	1 (5.9)	1 (5.3)	0	2 (5.4)
3	1 (5.9)	1 (5.3)	0	2 (5.4)
4	0	0	0	0
5	0	0	0	0

付録 2.7.6-5　MedDRA SOC/PT別のGrade 3以上の有害事象発現率（国内205試験）（安全性解析対象集団）

MedDRA Version 21.1 器官別大分類 基本語 CTCAE Grade	PTCL (N=17) n (%)	CTCL (N=19) n (%)	その他 (N=1) n (%)	全体 (N=37) n (%)
Hypokalaemia	2 (11.8)	0	0	2 (5.4)
3	2 (11.8)	0	0	2 (5.4)
4	0	0	0	0
5	0	0	0	0
Dyslipidaemia	0	1 (5.3)	0	1 (2.7)
3	0	1 (5.3)	0	1 (2.7)
4	0	0	0	0
5	0	0	0	0
Hyperkalaemia	0	1 (5.3)	0	1 (2.7)
3	0	0	0	0
4	0	1 (5.3)	0	1 (2.7)
5	0	0	0	0
Hypophosphataemia	1 (5.9)	0	0	1 (2.7)
3	1 (5.9)	0	0	1 (2.7)
4	0	0	0	0
5	0	0	0	0
Tumour lysis syndrome	1 (5.9)	0	0	1 (2.7)
3	1 (5.9)	0	0	1 (2.7)
4	0	0	0	0
5	0	0	0	0
Musculoskeletal and connective tissue disorders	0	1 (5.3)	0	1 (2.7)
3	0	0	0	0
4	0	0	0	0
5	0	1 (5.3)	0	1 (2.7)

付録 2.7.6-5　MedDRA SOC/PT別のGrade 3以上の有害事象発現率（国内205試験）（安全性解析対象集団）

MedDRA Version 21.1 器官別大分類 基本語 CTCAE Grade	PTCL (N=17) n (%)	CTCL (N=19) n (%)	その他 (N=1) n (%)	全体 (N=37) n (%)
Rhabdomyolysis	0	1 (5.3)	0	1 (2.7)
3	0	0	0	0
4	0	0	0	0
5	0	1 (5.3)	0	1 (2.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (5.3)	0	1 (2.7)
3	0	1 (5.3)	0	1 (2.7)
4	0	0	0	0
5	0	0	0	0
Squamous cell carcinoma of skin	0	1 (5.3)	0	1 (2.7)
3	0	1 (5.3)	0	1 (2.7)
4	0	0	0	0
5	0	0	0	0
Nervous system disorders	1 (5.9)	0	0	1 (2.7)
3	1 (5.9)	0	0	1 (2.7)
4	0	0	0	0
5	0	0	0	0
Peripheral sensory neuropathy	1 (5.9)	0	0	1 (2.7)
3	1 (5.9)	0	0	1 (2.7)
4	0	0	0	0
5	0	0	0	0
Respiratory, thoracic and mediastinal disorders	1 (5.9)	0	0	1 (2.7)
3	0	0	0	0
4	1 (5.9)	0	0	1 (2.7)
5	0	0	0	0

付録 2.7.6-5　MedDRA SOC/PT別のGrade 3以上の有害事象発現率（国内205試験）（安全性解析対象集団）

MedDRA Version 21.1 器官別大分類 基本語 CTCAE Grade	PTCL (N=17) n (%)	CTCL (N=19) n (%)	その他 (N=1) n (%)	全体 (N=37) n (%)
Laryngeal haemorrhage	1 (5.9)	0	0	1 (2.7)
3	0	0	0	0
4	1 (5.9)	0	0	1 (2.7)
5	0	0	0	0
Skin and subcutaneous tissue disorders	2 (11.8)	0	0	2 (5.4)
3	2 (11.8)	0	0	2 (5.4)
4	0	0	0	0
5	0	0	0	0
Dermatitis exfoliative generalised	1 (5.9)	0	0	1 (2.7)
3	1 (5.9)	0	0	1 (2.7)
4	0	0	0	0
5	0	0	0	0
Drug eruption	1 (5.9)	0	0	1 (2.7)
3	1 (5.9)	0	0	1 (2.7)
4	0	0	0	0
5	0	0	0	0
Vascular disorders	1 (5.9)	4 (21.1)	0	5 (13.5)
3	1 (5.9)	4 (21.1)	0	5 (13.5)
4	0	0	0	0
5	0	0	0	0
Capillary leak syndrome	0	4 (21.1)	0	4 (10.8)
3	0	4 (21.1)	0	4 (10.8)
4	0	0	0	0
5	0	0	0	0

付録 2.7.6-5　MedDRA SOC/PT別のGrade 3以上の有害事象発現率（国内205試験）（安全性解析対象集団）

MedDRA Version 21.1 器官別大分類 基本語 CTCAE Grade	PTCL (N=17) n (%)	CTCL (N=19) n (%)	その他 (N=1) n (%)	全体 (N=37) n (%)
Hypertension	1 (5.9)	0	0	1 (2.7)
3	1 (5.9)	0	0	1 (2.7)
4	0	0	0	0
5	0	0	0	0

CTCAE v4.0 を用いて有害事象のグレードを決定した。

（添付資料5.3.5.2.1のTable 14.3.1.2.6.1を引用）

付録 2.7.6-6 死亡又は重篤な有害事象の被験者ごとの叙述（国内 205 試験）

被験者番号	死亡に至った重篤な有害事象	死亡以外の重篤な有害事象
10011001		X
10011002		X
10021001		X
10021002		X
10021003		X
10031001		X
10031008		X
10041001		X
10041002		X
10061001		X
10061002		X
10071001		X
10101001		X
10131001		X
10131002		X
10141003	X	X
10191002		X

Study:	E7777-J081-205
Subject ID:	10011001
Age, race, sex:	5[redacted] years, Japanese, Male
Medical history: (MedDRA Preferred Term)	-
Current medical conditions: (MedDRA Preferred Term)	Anaemia, Constipation, Facial pain, Insomnia, Leukopenia, Pyrexia
Concomitant medications:	ACICLOVIR(1), ALBUMIN HUMAN(2), AMINO ACIDS NOS W/ELECTROLYTES NOS/GLUCOSE/TH(3), BACTRIM(4), BROTIZOLAM(5), CALCIUM(6), CEFEPIME(7), CHLORPHENAMINE(8), CHLORPHENAMINE(9), DEXAMETHASONE(10), DEXMEDETOMIDINE(11), DOPAMINE(12), FENTANYL(13), FLEBOBAG RING LACT(14), FUROSEMIDE(15), GANCICLOVIR(16), GENTAMICIN(17), GRANISETRON(18), HALOPERIDOL(19), HYDROCORTISONE(20), HYDROCORTISONE(21), HYDROCORTISONE(22), LANSOPRAZOLE(23), LANSOPRAZOLE(24), MAGNESIUM OXIDE(25), NICARDIPINE(26), NOREPINEPHRINE(27), OMEPRAZOLE(28), OSMOSAL /00501801/(29), OXYCODONE(30), PARACETAMOL(31), PARACETAMOL(32), PARACETAMOL(33), PARACETAMOL(34), PHENYLEPHRINE(35), PIP/TAZO(36), PLASMA(37), PLATELETS(38), PLATELETS(39), POTASSIUM(40), PROPOFOL(41), RED BLOOD CELLS(42), SENNOSIDE A+B(43), SODIUM CHLORIDE(44), SODIUM PICOSULFATE(45), SUGAMMADEX(46), VANCOMYCIN(47)
Date of first dose/last dose of study drug (Study Day):	09 MAY 2016 / 13 MAY 2016 (Study Day 5)
Other events: (MedDRA Preferred Term)	Weight increased, Aspartate aminotransferase increased, Alanine aminotransferase increased, Hypoalbuminaemia, Hypokalaemia, Headache, Dysphagia
Date of diagnosis:	17 DEC 2012
Disease Histology:	Peripheral T-cell lymphoma, NOS (PTCL)

Serious adverse events (Investigator term/MedDRA preferred term):	Bleeding(laryngeal) / Laryngeal haemorrhage
Dose at or prior to adverse event onset:	9 µg/kg
Start date of adverse event (Study Day)/ outcome date of adverse event (Study Day):	23 MAY 2016 (Study Day 15) / 26 MAY 2016 (Study Day 18)
TEAE?	Yes
Serious criteria:	Life threatening, Requires inpatient hospitalization or prolongation of existing hospitalization
Outcome:	RECOVERED/RESOLVED
Study drug action taken/other action taken:	DRUG WITHDRAWN / Treatment given and Withdrawn from study
Concomitant medications (used until the start date):	1, 2, 4, 5, 6, 7, 8, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20, 23, 24, 25, 27, 30, 31, 32, 33, 34, 35, 37, 38, 41, 42, 43, 45
Relationship of event:	NOT RELATED

Serious adverse events (Investigator term/MedDRA preferred term):	tumor assosiated fever / Tumour associated fever
Dose at or prior to adverse event onset:	9 µg/kg
Start date of adverse event (Study Day)/ outcome date of adverse event (Study Day):	15 MAY 2016 (Study Day 7) / -
TEAE?	Yes
Serious criteria:	Requires inpatient hospitalization or prolongation of existing hospitalization
Outcome:	RECOVERING/RESOLVING
Study drug action taken/other action taken:	DOSE NOT CHANGED / Treatment given
Concomitant medications (used until the start date):	1, 2, 4, 5, 7, 8, 10, 15, 16, 17, 18, 23, 25, 30, 31, 32, 43, 45
Relationship of event:	NOT RELATED

Narrative

A 5[redacted]-year-old male received DENILEUKIN DIFTITOX as a participant in a clinical trial Protocol # E7777-J081-205: "A Phase 2 Study of E7777 in Patients with Relapsed or Refractory Peripheral T-cell Lymphoma and Cutaneous T-cell Lymphoma."

Apr/20/2016: Informed consent was obtained.
May/09/2016: The subject initiated treatment with E7777 (denileukin diftitox) 9 µg/kg on Days 1 through 5 of each 3-week cycle.
May/13/2016: Cycle 1 Day 5: Administration in five consecutive days was completed.
May/15/2016: The subject experienced tumour associated fever requiring hospitalization. Pyrexia with body temperature of 39.2 °C (Grade 2) occurred and intravenous antibiotic injection with Denosine (ganciclovir) 330 mg, once/day was initiated.
May/17/2016: Although discharge was scheduled, given no improvement of pyrexia with body temperatures of 38.1 °C, 38.4 °C, hospitalization had to be prolonged. Given the possibly infection-induced condition, blood culture test was performed, which however resulted in negative. Chest and head computed tomography (CT) were performed, which only indicated reticular shadow in the right lung field and sinusitis. These imaging findings were showing improving tendencies.
May/18/2016: Body temperature was 38.2 °C. There were no findings suggestive of infection.
May/19/2016: Oedema-like changes were intraorally observed, dominantly on the right cheek mucosa and right tongue. The subject was seen by a dentist, but there were no findings decisively suggestive of infection. Body temperature moved in the range from 38.0 °C to 37.0 °C. A general bacteria test was performed, which resulted in negative.
May/20/2016: Body temperature moved in the range from 38.0 °C to 37.0 °C.
May/21/2016: Body temperature moved in the range from 37.0 °C to 36.0 °C.
May/23/2016: Disease progression was confirmed based on body temperature moved in the range from 38.0 °C to 36.0 °C. Around 15:00, haematemesis occurred. Given massive bleeding (laryngeal), the subject temporarily fell into a state of decreased blood pressure, depressed level of consciousness, and

haemorrhagic shock. The subject experienced bleeding (laryngeal), considered a life-threatening event by the investigator and required hospitalization. As an emergency treatment, airway management was performed. Subsequently, the subject was placed under intensive care unit (ICU) care. Bleeding (laryngeal) was confirmed to be due to the arterial rupture secondary to enlargement of the right tonsillar tumour, which was the haemorrhagic site. Compression hemostasis was performed for the haemorrhagic site, and the progress was observed. The event was assessed to be due to aggravation of the underlying disease, thus leading to the withdrawal of the subject from the study.

May/24/2016: After the subject was transferred to the ICU, the course was without massive bleeding (laryngeal). Body temperature stayed at 36.0 °C, hospitalization had to be prolonged. Blood pressure and physical condition were stable. Embolization was performed for the arteries suspected to be the haemorrhagic sources. Coils were inserted into the facial artery and lingual artery. The subject did not recover from the tumour associated fever.

May/25/2016: The gauze used for the compression hemostasis was removed, but no obvious recurrent bleeding (laryngeal) was indicated. Hemodynamics was also stable, without recurrent bleeding (laryngeal). Therefore, extubation was performed.

May/26/2016: The subject was in a stable condition without bleeding (laryngeal), thus was transferred to the general ward from the ICU. The subject recovered from the bleeding (laryngeal).

May/27/2016: Because of enlarged tumour and persistent pyrexia (body temperature 37.0 °C to 37.6 °C), Solu-Cortef (hydrocortisone sodium succinate) 100 mg/day was administered.

May/30/2016: Body temperature moved between 36.0 °C and 36.9 °C.

Jun/01/2016: Therapy with mogamulizumab 60 mg/day was initiated.

Jun/06/2016: Pyrexia of 38.0 °C occurred. Zosyn (tazobactam/piperacillin hydrate) 4.5 g/day was initiated, and Solu-Cortef 100 mg/day was discontinued.

Jun/08/2016: Mogamulizumab 60 mg/day was administered.

Jun/10/2016: Body temperature moved between 36.0 °C to 37.0 °C.

Jun/12/2016: Body temperature moved between 36.0 °C to 37.0 °C.

Jun/15/2016: Mogamulizumab 60 mg/day was administered. Body temperature moved in the range from 36.0 °C to 37.0 °C.

Jun/16/2016: Body temperature moved between 36.0 °C to 37.0 °C.

Jun/17/2016: Body temperature remained at 36.0 °C. Since the subject became symptomatically stable, he was discharged.

Jun/22/2016: On outpatient examination, the course was noted to be without pyrexia. Mogamulizumab 60 mg/day was administered.

Jun/29/2016: On outpatient examination, body temperature was around 36 °C. Tumour continuously showed a tendency towards enlargement. From the beginning of the subsequent week, etoposide + prednisone + vincristine + cyclophosphamide + doxorubicin (EPOCH) chemotherapy was scheduled to be initiated. The subject was recovering from the tumour associated fever.

Investigator's opinion on causality to the study drug:

Laryngeal haemorrhage: "Not related" to the study drug.
Comments: The event was due to aggravation of the underlying disease. It was clear that intraoral bleeding (laryngeal) occurred because of arterial rupture secondary to tumour enlargement. Therefore, the causality between the study drug and the event could be ruled out.

Tumour associated fever: "Not related" to the study drug.
Comments: Pyrexia was noted prior to initiation of the study drug, which was consistent with tumour associated fever. After initiation of the study drug, pyrexia subsided, which was possibly owing to the pre-treatment with dexamethasone. Following completion of the study drug, pyrexia recurred. Obvious focus of infection could not be located by the blood culture and imaging tests. However, since the subject was susceptible to infection, infection-induced pyrexia could not be ruled out. Furthermore, cytomegalovirus antigenemia was positive; pyrexia was also likely to be due to cytomegalovirus infection. However, given the fact that aggravation of underlying disease became clear on May/23/2016, it was appropriate to consider retrospectively that the pyrexia on and after May/15/2016 was also tumour associated fever. Therefore, the causality between the event and the study drug could be ruled out. Upon re-evaluation, the causality was thereby revised."

Study:	E7777-J081-205
Subject ID:	10011002
Age, race, sex:	6[redacted] years, Japanese, Male
Medical history: (MedDRA Preferred Term)	Extranodal marginal zone B-cell lymphoma (MALT type)
Current medical conditions: (MedDRA Preferred Term)	Anaemia, Electrocardiogram QT prolonged, Haemorrhoids, Hepatitis B surface antibody positive, Hypoalbuminaemia, Insomnia, Lymphopenia, Peripheral sensory neuropathy
Concomitant medications:	ACICLOVIR(1), BACTRIM(2), CEFEPIME(3), CHLORPHENAMINE(4), CHLORPHENAMINE(5), CHLORPHENAMINE(6), DEXAMETHASONE(7), FUROSEMIDE(8), FUROSEMIDE(9), FUROSEMIDE(10), GANCICLOVIR(11), GRANISETRON(12), HYDROCORTISONE(13), LANSOPRAZOLE(14), MAGNESIUM OXIDE(15), NERIPROCT(16), PARACETAMOL(17), PENTAMIDINE(18), PLATELETS(19), PLATELETS(20), PREDNISOLONE(21), SALBUTAMOL(22), SODIUM PICOSULFATE(23), VALGANCICLOVIR(24), ZOLPIDEM(25)
Date of first dose/last dose of study drug (Study Day):	16 MAY 2016 / 20 MAY 2016 (Study Day 5)
Other events: (MedDRA Preferred Term)	Insomnia, Weight increased, Constipation, Alanine aminotransferase increased, Aspartate aminotransferase increased, Fatigue, Pyrexia, Thrombocytopenia, Anaemia, Cytomegalovirus chorioretinitis
Date of diagnosis:	01 DEC 2014
Disease Histology:	Angioimmunoblastic T-cell lymphoma (PTCL)

Serious adverse events (Investigator term/MedDRA preferred term):	CMV retinitis / Cytomegalovirus chorioretinitis
Dose at or prior to adverse event onset:	9 µg/kg
Start date of adverse event (Study Day)/ outcome date of adverse event (Study Day):	15 JUN 2016 (Study Day 31) / 07 NOV 2016 (Study Day 176)
TEAE?	Yes
Serious criteria:	Requires inpatient hospitalization or prolongation of existing hospitalization, Persistent or significant disability or incapacity
Outcome:	RECOVERED/RESOLVED WITH SEQUELAE
Study drug action taken/other action taken:	DRUG WITHDRAWN / Treatment given and Withdrawn from study
Concomitant medications (used until the start date):	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 25
Relationship of event:	RELATED

Serious adverse events (Investigator term/MedDRA preferred term):	Thrombocytopenia / Thrombocytopenia
Dose at or prior to adverse event onset:	9 µg/kg
Start date of adverse event (Study Day)/ outcome date of adverse event (Study Day):	25 MAY 2016 (Study Day 10) / 20 JUL 2016 (Study Day 66)
TEAE?	Yes
Serious criteria:	Requires inpatient hospitalization or prolongation of existing hospitalization
Outcome:	RECOVERED/RESOLVED
Study drug action taken/other action taken:	DRUG WITHDRAWN / Treatment given and Withdrawn from study
Concomitant medications (used until the start date):	3, 4, 7, 8, 9, 12, 13, 15, 16, 17, 23, 25
Relationship of event:	RELATED

Narrative

A 6[redacted]-year-old male received DENILEUKIN DIFTITOX as a participant in a clinical trial Protocol # E7777-J081-205: "A Phase 2 Study of E7777 in Patients with Relapsed or Refractory Peripheral T-cell Lymphoma and Cutaneous T-cell Lymphoma."

May/02/2016: Informed consent was obtained.

May/16/2016: The subject initiated treatment with E7777 (denileukin diftitox) 9 μg/kg on Days 1 to 5 of each 3-week cycle. Lab data confirmed platelets at 19.4 × 10^4/μL.

May/20/2016: Cycle 1 Day 5: Five-day continuous administration of the study drug was completed. The study drug was discontinued.

May/23/2016: Lab data confirmed decreased platelets at 8.0 × 10^4/μL.

May/24/2016: The subject experienced thrombocytopenia. Cytomegalovirus (CMV) C7-horseradish peroxidase (HRP) test was performed; 0/50000 cells was confirmed.

May/25/2016: Lab data confirmed decreased platelets at 2.4 × 10^4/μL.

May/26/2016: Lab data confirmed decreased platelets at 1.8 × 10^4/μL, which was reported as a Grade 4 thrombocytopenia, and the subject was hospitalized. Enhanced platelet consumption associated with immunological mechanism was suspected; thus, co-suspect prednisolone (PSL) 1 mg/kg was initiated (60 mg/day). Histopathological findings of bone marrow aspiration was significant for: Bone marrow clot; Cell component: about 40% normal cell bone marrow; Hematopoietic cells in all three components; lymphoid cell aggregates dispersedly seen; Megakaryocyte count within normal limits, without hemophagocytosis.

May/28/2016: Lab data confirmed decreased platelets at 2.9 × 10^4/μL. Platelet Concentrate, Leukocytes Reduced (concentrated human blood platelet) 10 units were administered.

May/30/2016: Exudate in the left fundus was pointed out based on the ophthalmological examination. Lab data confirmed decreased platelets at 2.4 × 10^4/μL. Platelet Concentrate, Leukocytes Reduced 10 units were administered.

Jun/03/2016: Lab data confirmed decreased platelets at 3.3 × 10^4/μL.

Jun/08/2016: Lab data confirmed decreased platelets at 5.6 × 10^4/μL. Because of the adverse events, the subject was withdrawn from the study.

Jun/09/2016: Visual field disorder was gradually aggravated. PSL was decreased to 40 mg/day.

Jun/13/2016: It was pointed out that exudate in the left fundus showed a tendency towards expansion based on the ophthalmological examination.

Jun/14/2016: CMV C7-HRP test was performed.

Jun/15/2016: It was determined decreased platelets associated with the study drug occurred. As empiric treatment, ganciclovir 600 mg/day was initiated. The blood test performed on Jun/14/2016 confirmed CMV antigenemia (CMV C7-HRP 281/50000 cells). Cytomegalovirus retinitis (Grade 3) was diagnosed, deemed a persistent disability by the investigator and prolonging hospitalization.

Jun/16/2016: PSL was decreased to 30 mg/day.

Jun/20/2016: An ophthalmological examination showed no aggravation of the exudative lesion in the left fundus as compared with the findings at the previous visit.

Jun/21/2016: Valixa (valganciclovir hydrochloride) 450 mg twice a day was initiated.

Jun/23/2016: PSL was decreased to 20 mg/day and continued.

Jun/29/2016: Valixa was reduced to 450 mg once a day.

Jun/30/2016: Oral Fluconazole (FLCZ) as prophylaxis was initiated.

Jul/05/2016: Treatment was continued with Valixa at a maintenance dose of 450 mg once a day. After that, the subject was regularly followed up in cooperation with the department of ophthalmology.

Jul/06/2016: Lab data confirmed platelet count of $19.7 \times 10^4/\mu L$.

Jul/20/2016: Lab data confirmed platelet count of $17.2 \times 10^4/\mu L$. Based on the result, the event of decreased platelets was assessed as recovered to Grade 0. Thrombocytopenia reported as recovered.

Sep/27/2016: As salvage chemotherapy, ifosfamide, carboplatin, etoposide (ICE) chemotherapy was initiated. After a total of 2 cycles were performed, partial response (PR) was achieved.

Nov/07/2016: Ophthalmological examination revealed subsidence of cytomegalovirus retinitis. However, a scar remained on the left fundus, and the subject had irreparable visual field defect as a sequelae. The cytomegalovirus retinitis (Grade 3) recovered with sequelae.

Investigator's opinion on causality to the study drug:

Cytomegalovirus retinitis: "Related" to the study medication.

Comments: The major cause of the event was likely to be high-dose steroid use. However, influence of E7777 on cell-mediated immunity was unknown. Given the clinical course, the causality of the study drug to the event could not be ruled out.

Thrombocytopenia: "Related" to the study medication.

Comments: Platelets rapidly decreased in the subject with E7777 starting from Cycle 1 Day 11. The potential causes of the decreased platelets were as follows: 1) direct toxicity of E7777, 2) autoimmune thrombocytopenia, an accompanying disease of underlying disease, 3) progression of bone marrow infiltration. However, the similar event with the study drug had rarely reported, indicating that 1) was less likely. Based on the clinical course, 2) was most suspected. On the other hand, any of the three assumptions could not be completely ruled out. A multitude of the causes, instead of a single one, might have been involved.

Even though the mechanism of the event was associated with any of the above three, it was apparent that the event rapidly occurred with E7777. Therefore, the causality of the study drug to the event was assessed as probably related.

Sponsor's opinion on causality (only if it differs from the investigator's opinion):

Cytomegalovirus retinitis: Given the subjects age, underlying malignancy and considering the concurrent use of co-suspect medication prednisolone (causes immunosuppression), we would consider the event of cytomegalovirus retinitis as "Not Related" to the study medication.

Study:	E7777-J081-205
Subject ID:	10021001
Age, race, sex:	7[redacted] years, Japanese, Male
Medical history: (MedDRA Preferred Term)	-
Current medical conditions: (MedDRA Preferred Term)	Back pain, Cataract, Gastrooesophageal reflux disease, Hypertension, Seasonal allergy
Concomitant medications:	AMLODIPINE(1), AMLODIPINE(2), BACTRIM(3), DEXAMETHASONE(4), DEXAMETHASONE(5), DEXAMETHASONE(6), DEXCHLORPHENIRAMINE(7), DEXCHLORPHENIRAMINE(8), DEXCHLORPHENIRAMINE(9), EPERISONE(10), FLUCONAZOLE(11), FUROSEMIDE(12), FUROSEMIDE(13), GRANISETRON(14), GRANISETRON(15), GRANISETRON(16), LANSOPRAZOLE(17), LOXOPROFEN(18), LOXOPROFEN(19), MAGNESIUM OXIDE(20), MINOFIT(21), NEO NICHIPHAGEN C(22), PARACETAMOL(23), PARACETAMOL(24), PARACETAMOL(25), PARACETAMOL(26), PARACETAMOL(27), REBAMIPIDE(28), URSODEOXYCHOLIC ACID(29), URSODEOXYCHOLIC ACID(30), ZOLEDRONIC ACID(31), ZOLPIDEM(32)
Date of first dose/last dose of study drug (Study Day):	16 MAY 2016 / 30 JUN 2016 (Study Day 46)
Other events: (MedDRA Preferred Term)	Pain in extremity, Hypertension, Insomnia, Constipation, Weight increased, Lymphopenia, Thrombocytopenia, Electrocardiogram QT prolonged, Sinus bradycardia, Supraventricular extrasystoles, Brain natriuretic peptide increased, Musculoskeletal stiffness, Cardiomegaly, Pyrexia
Date of diagnosis:	16 JUN 2012
Disease Histology:	Peripheral T-cell lymphoma, NOS (PTCL)

Serious adverse events (Investigator term/MedDRA preferred term):	alanine aminotransferase increased / Alanine aminotransferase increased
Dose at or prior to adverse event onset:	9 µg/kg
Start date of adverse event (Study Day)/ outcome date of adverse event (Study Day):	23 MAY 2016 (Study Day 8) / 10 JUN 2016 (Study Day 26)
TEAE?	Yes
Serious criteria:	Requires inpatient hospitalization or prolongation of existing hospitalization
Outcome:	RECOVERED/RESOLVED
Study drug action taken/other action taken:	DOSE NOT CHANGED / Treatment given
Concomitant medications (used until the start date):	1, 3, 4, 7, 11, 12, 14, 17, 20, 21, 23, 24, 31, 32
Relationship of event:	RELATED

Serious adverse events (Investigator term/MedDRA preferred term):	aspartate aminotransferase increased / Aspartate aminotransferase increased
Dose at or prior to adverse event onset:	9 µg/kg
Start date of adverse event (Study Day)/ outcome date of adverse event (Study Day):	23 MAY 2016 (Study Day 8) / 08 JUN 2016 (Study Day 24)
TEAE?	Yes
Serious criteria:	Requires inpatient hospitalization or prolongation of existing hospitalization
Outcome:	RECOVERED/RESOLVED
Study drug action taken/other action taken:	DOSE NOT CHANGED / Treatment given
Concomitant medications (used until the start date):	1, 3, 4, 7, 11, 12, 14, 17, 20, 21, 23, 24, 31, 32
Relationship of event:	RELATED

Narrative

A 7[redacted]-year-old male received DENILEUKIN DIFTITOX as a participant in a clinical trial Protocol # E7777-J081-205: "A Phase 2 Study of E7777 in Patients with Relapsed or Refractory Peripheral T-cell Lymphoma and Cutaneous T-cell Lymphoma."

May/02/2016: Informed consent was obtained.

May/08/2016: Subject commenced treatment with co-suspect PO Calonal (acetaminophen) 600 mg three times daily for pain in thigh and co-suspect PO rebamipide 100 mg three times daily for gastritis prophylaxis.

May/16/2016: The subject initiated treatment with E7777 (denileukin diftitox) 9 µg/kg on Days 1 to 5 of each 3-week cycle. Subject commenced treatment with co-suspect PO Calonal 500 mg once daily, intravenous (IV) granisetron 3 mg daily (indication unknown) and IV Dexart (dexamethasone sodium phosphate) 6.6 mg daily (indication unknown).

May/19/2016: Calonal dose of 600 mg three times daily was discontinued. Subject received single dose of co-suspect zoledronic acid 4 mg IV for pain in thigh.

May/20/2016: Calonal dose of 500 mg once daily, IV granisetron 3 mg daily and IV Dexart 6.6 mg daily were discontinued.

May/23/2016: ALT increased to 202 and AST increased to 200. Therefore, the subject was placed under observation with prolonged hospitalization. The subject had mild malaise. Minofit (Stronger Neo-Minophagen C,-P) was administered as a liver supporting drug. An abdominal echogram was taken, which showed no apparent abnormalities in the hepatic parenchyma. Consequently, drug-induced hepatic function disorder was suspected. Study drug continuing as per protocol schedule and rebamipide maintained.

May/24/2016: ALT was 180, and AST was 139. Malaise showed an improving tendency. Examination showed: HBV antigen and antibody negative; HCV antigen and antibody negative.

May/26/2016: ALT was 198, and AST was 116.

May/27/2016: The subject was in stable condition, and lab data was hovering, without obvious aggravation. Thus, therapy was switched from drip infusion of Minofit to oral Glycyron and Urso (ursodeoxycholic acid), and the subject was discharged on the same day. Subsequently, the subject was placed under outpatient observation. The subject did not recover from the increased AST and increased ALT.

May/30/2016: The subject presented to the study site for the protocol-designated Visit. ALT was 207, and AST was 92.

Jun/05/2016: The subject was hospitalized for administration of the study drug.

Jun/06/2016: Administration of the study drug was judged to be feasible; thus, the therapy for Cycle 2 Day 1 was started. At a non-protocol-designated visit, blood test results were confirmed. ALT was 85, and AST was 33; hepatic function showed an improving tendency.

Jun/08/2016: ALT was 51, and AST was 15; hepatic function showed an improving tendency. The subject recovered from the increased AST. The subject was recovering from the increased ALT.

Jun/10/2016: ALT was 37. AST was 15. Hepatic function recovered. The subject recovered from the increased ALT. Bradycardia was noted; therefore, the administration for Cycle 2 Day 5 on the same day was suspended.
Jun/13/2016: ALT was 29, AST was 21. No abnormalities were noted on the hepatic function related data.

Investigator's opinion on causality to the study drug:

Alanine aminotransferase increased and aspartate aminotransferase increased: "Related" to the study medication.
Comments: Based on the onset timing and administration timing, the causality between the study drug and the event could not be ruled out. Also, the causality between the zoledronic acid the event could not be ruled out.

Study:	E7777-J081-205
Subject ID:	10021002
Age, race, sex:	5[redacted] years, Japanese, Female
Medical history: (MedDRA Preferred Term)	-
Current medical conditions: (MedDRA Preferred Term)	Anaemia, Constipation, Dry skin, Duodenal ulcer, Gastric ulcer, Gastrooesophageal reflux disease, Hepatic function abnormal, Uterine leiomyoma, Vitreous floaters
Concomitant medications:	BACTRIM(1), CEFEPIME(2), DEXAMETHASONE(3), DEXCHLORPHENIRAMINE(4), ESOMEPRAZOLE(5), ESOMEPRAZOLE(6), FEXOFENADINE(7), FLUCONAZOLE(8), FUROSEMIDE(9), GRANISETRON(10), GUAIAZULENE(11), HEPARINOID(12), HYDROCORTISONE(13), MAGNESIUM OXIDE(14), MINOFIT(15), NEO NICHIPHAGEN C(16), OLOPATADINE(17), PARACETAMOL(18), PARACETAMOL(19), PIP/TAZO(20), PREDNISOLONE(21), RESTAMIN CORTIZON(22), SODIUM PICOSULFATE(23), STELAMIN(24), URSODEOXYCHOLIC ACID(25), VEEN D(26)
Date of first dose/last dose of study drug (Study Day):	14 NOV 2016 / 18 NOV 2016 (Study Day 5)
Other events: (MedDRA Preferred Term)	Weight increased, Lymphopenia, Haemorrhoids, Folliculitis, Drug hypersensitivity, Decreased appetite, Cancer pain, Dysgeusia, Fatigue, Hypoacusis
Date of diagnosis:	01 MAR 2016
Disease Histology:	Peripheral T-cell lymphoma, NOS (PTCL)

Serious adverse events (Investigator term/MedDRA preferred term):	alanine aminotransferase increased / Alanine aminotransferase increased
Dose at or prior to adverse event onset:	9 µg/kg
Start date of adverse event (Study Day)/ outcome date of adverse event (Study Day):	21 NOV 2016 (Study Day 8) / 24 NOV 2016 (Study Day 11)
TEAE?	Yes
Serious criteria:	Requires inpatient hospitalization or prolongation of existing hospitalization
Outcome:	RECOVERING/RESOLVING
Study drug action taken/other action taken:	DOSE NOT CHANGED / Treatment given
Concomitant medications (used until the start date):	1, 2, 3, 4, 5, 8, 9, 10, 11, 12, 13, 14, 15, 18, 19, 20, 23, 25, 26
Relationship of event:	RELATED

Serious adverse events (Investigator term/MedDRA preferred term):	alanine aminotransferase increased / Alanine aminotransferase increased
Dose at or prior to adverse event onset:	9 µg/kg
Start date of adverse event (Study Day)/ outcome date of adverse event (Study Day):	24 NOV 2016 (Study Day 11) / 25 NOV 2016 (Study Day 12)
TEAE?	Yes
Serious criteria:	Requires inpatient hospitalization or prolongation of existing hospitalization
Outcome:	NOT RECOVERED/NOT RESOLVED
Study drug action taken/other action taken:	DOSE NOT CHANGED / Treatment given
Concomitant medications (used until the start date):	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14, 15, 18, 19, 20, 23, 25, 26
Relationship of event:	RELATED

Serious adverse events (Investigator term/MedDRA preferred term):	alanine aminotransferase increased / Alanine aminotransferase increased
Dose at or prior to adverse event onset:	9 µg/kg
Start date of adverse event (Study Day)/ outcome date of adverse event (Study Day):	25 NOV 2016 (Study Day 12) / 12 DEC 2016 (Study Day 29)
TEAE?	Yes
Serious criteria:	Requires inpatient hospitalization or prolongation of existing hospitalization
Outcome:	RECOVERED/RESOLVED
Study drug action taken/other action taken:	DOSE NOT CHANGED / Treatment given
Concomitant medications (used until the start date):	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14, 15, 18, 19, 20, 21, 22, 23, 24, 25, 26
Relationship of event:	NOT RELATED

Serious adverse events (Investigator term/MedDRA preferred term):	aspartate aminotransferase increased / Aspartate aminotransferase increased
Dose at or prior to adverse event onset:	9 µg/kg
Start date of adverse event (Study Day)/ outcome date of adverse event (Study Day):	21 NOV 2016 (Study Day 8) / 22 NOV 2016 (Study Day 9)
TEAE?	Yes
Serious criteria:	Requires inpatient hospitalization or prolongation of existing hospitalization
Outcome:	RECOVERING/RESOLVING
Study drug action taken/other action taken:	DOSE NOT CHANGED / Treatment given
Concomitant medications (used until the start date):	1, 2, 3, 4, 5, 8, 9, 10, 11, 12, 13, 14, 15, 18, 19, 20, 23, 25, 26
Relationship of event:	RELATED

Serious adverse events (Investigator term/MedDRA preferred term):	aspartate aminotransferase increased / Aspartate aminotransferase increased
Dose at or prior to adverse event onset:	9 µg/kg
Start date of adverse event (Study Day)/ outcome date of adverse event (Study Day):	22 NOV 2016 (Study Day 9) / 24 NOV 2016 (Study Day 11)
TEAE?	Yes
Serious criteria:	Requires inpatient hospitalization or prolongation of existing hospitalization
Outcome:	RECOVERING/RESOLVING
Study drug action taken/other action taken:	DOSE NOT CHANGED / Treatment given
Concomitant medications (used until the start date):	1, 2, 3, 4, 5, 8, 9, 10, 11, 12, 13, 14, 15, 18, 19, 20, 23, 25, 26
Relationship of event:	RELATED

Serious adverse events (Investigator term/MedDRA preferred term):	aspartate aminotransferase increased / Aspartate aminotransferase increased
Dose at or prior to adverse event onset:	9 µg/kg
Start date of adverse event (Study Day)/ outcome date of adverse event (Study Day):	24 NOV 2016 (Study Day 11) / 25 NOV 2016 (Study Day 12)
TEAE?	Yes
Serious criteria:	Requires inpatient hospitalization or prolongation of existing hospitalization
Outcome:	NOT RECOVERED/NOT RESOLVED
Study drug action taken/other action taken:	DOSE NOT CHANGED / Treatment given
Concomitant medications (used until the start date):	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14, 15, 18, 19, 20, 23, 25, 26
Relationship of event:	RELATED

Serious adverse events (Investigator term/MedDRA preferred term):	aspartate aminotransferase increased / Aspartate aminotransferase increased
Dose at or prior to adverse event onset:	9 µg/kg
Start date of adverse event (Study Day)/ outcome date of adverse event (Study Day):	25 NOV 2016 (Study Day 12) / 28 NOV 2016 (Study Day 15)
TEAE?	Yes
Serious criteria:	Requires inpatient hospitalization or prolongation of existing hospitalization
Outcome:	RECOVERED/RESOLVED
Study drug action taken/other action taken:	DOSE NOT CHANGED / Treatment given
Concomitant medications (used until the start date):	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14, 15, 18, 19, 20, 21, 22, 23, 24, 25, 26
Relationship of event:	NOT RELATED

Serious adverse events (Investigator term/MedDRA preferred term):	fever / Pyrexia
Dose at or prior to adverse event onset:	9 µg/kg
Start date of adverse event (Study Day)/ outcome date of adverse event (Study Day):	20 NOV 2016 (Study Day 7) / 30 NOV 2016 (Study Day 17)
TEAE?	Yes
Serious criteria:	Requires inpatient hospitalization or prolongation of existing hospitalization
Outcome:	RECOVERED/RESOLVED
Study drug action taken/other action taken:	DOSE NOT CHANGED / Treatment given
Concomitant medications (used until the start date):	1, 2, 3, 4, 5, 8, 9, 10, 12, 13, 14, 18, 19, 23, 25
Relationship of event:	RELATED

Narrative

A 5[redacted]-year-old female received DENILEUKIN DIFTITOX as a participant in a clinical trial Protocol # E7777-J081-205: "A Phase 2 Study of E7777 in Patients with Relapsed or Refractory Peripheral T-cell Lymphoma and Cutaneous T-cell Lymphoma."

Nov/01/2016: Informed consent was obtained.

Nov/14/2016: The subject initiated treatment with E7777 (denileukin diftitox) 9 µg/kg on Days 1 to 5 of each 3-week cycle.

Nov/20/2016: Fever (between 37.0 °C and 37.9 °C) was noted; subject was hospitalized and an antibiotic of cefepime and an antipyretic of Calonal (acetaminophen) were started.

Nov/21/2016: Fever (between 37.0 °C and 37.9 °C) persisted; given suspected antibiotic-induced event, treatment was switched to suspect drug IV Tazopipe (tazobactam sodium/piperacillin sodium) (dose unknown) and continued. The subject experienced increased AST, Grade 3, and increased ALT Grade 3. Because of increased ALT (142) and AST (154), hospitalization was prolonged, to observe the condition. Mild malaise was present. A liversupporting drug, Minofit (Stronger Neo-Minophagen C-P), was initiated.

Nov/22/2016: Lab data showed ALT (142) and AST (131) Grade 2, and malaise resolved.

Nov/24/2016: Lab data showed ALT (97) Grade 2, and AST (72) Grade 1, indicating a tendency toward recovering. Drug allergy (Tazopipe as suspect drug) led to skin eruption and itchy sensation (non-serious). Tazopipe was thus discontinued. Fexofenadine treatment was initiated. Fever (between 37.0 °C and 38.0 °C) persisted.

Nov/25/2016: Lab data showed increased ALT (130) and AST (110) again. The influence of the antibiotic of Tazopipe was suspected to be the cause of the increased ALT and AST. Skin eruption was aggravated. Treatment was switched from fexofenadine to prednisolone 20 mg. Fever (between 37.0 °C and 37.9 °C) was persistent.

Nov/26/2016: Without use of antipyretic, body temperature was stabilized at 36 °C. Partial aggravation of skin eruption was noted, and olopatadine hydrochloride was added to the treatment.

Nov/28/2016: The subject recovered from the increased AST. Lab data showed ALT 120 and AST 76, which showed an improving tendency. Lab data showed that the event remained as Grade 1. Since the AST value indicated Grade 1 at baseline, the date of recovery was assessed to be the same date. Skin eruption also showed a recovering tendency. Minofit was completed, and oral liver supporting drug was started.

Nov/30/2016: Lab data showed ALT 124 and AST 64, which showed a recovery tendency. Fever was absent. Skin eruption was also improving with continuous oral treatment. Given stabilized general condition, the subject was discharged on the same day. The subject was recovering from the increased ALT. The subject recovered from the fever. The case tracking was completed as of this report.

Dec/12/2016: Lab data showed ALT 49. The subject recovered from the increased ALT. Lab data showed that the event remained as Grade 1. Since the ALT value indicated Grade 1 at baseline, the date of recovery was assessed to be the same date.

Investigator's opinion on causality to the study drug:

Aspartate aminotransferase increased (prior to Nov/25/2016), alanine aminotransferase increased (prior to Nov/25/2016), pyrexia: "Related" to the study medication.

Comment: The increased AST and increased ALT from Nov/21 to Nov/24 were assessed to be related to the study drug.

Aspartate aminotransferase increased (from Nov/25/2016), alanine aminotransferase increased (from Nov/25/2016): "Not Related" to the study medication.

Comment: The increased AST and increased ALT from Nov/25 were considered to be due to antibiotic treatment; thus not related to the study drug.

Sponsor's opinion on causality (only if it differs from the investigator's opinion):

Aspartate aminotransferase increased, aspartate aminotransferase increased, pyrexia: Given that the events occurred approximately one week after the initiation of study drug, and that alanine aminotransferase increased and aspartate aminotransferase increased have been observed in patients previously treated with denileukin, there is at least a reasonable possibility of a causal relationship of study drug to the reported events of "pyrexia", "AST increased" and "ALT increased" and the events are therefore conservatively classified as "Related" to the study drug.

Study:	E7777-J081-205
Subject ID:	10021003
Age, race, sex:	6[redacted] years, Japanese, Male
Medical history: (MedDRA Preferred Term)	-
Current medical conditions: (MedDRA Preferred Term)	Choroidal detachment, Constipation, Dry eye, Haemorrhoids, Headache, Hypertriglyceridaemia, Hypoalbuminaemia, Insomnia, Malaise, Palmar-plantar erythrodysaesthesia syndrome, Psoriasis
Concomitant medications:	ALBUMIN HUMAN(1), ALBUMIN HUMAN(2), ATOVAQUONE(3), BETAMETHASONE(4), BROTIZOLAM(5), CEFEPIME(6), CEFEPIME(7), CLOBETASOL(8), CROTAMITON(9), DAIVOBET(10), DEQUALINIUM(11), DEXAMETHASONE(12), DEXCHLORPHENIRAMINE(13), DIFLUCORTOLONE(14), DIQUAFOSOL(15), ESCHERICHIA COLI(16), FEXOFENADINE(17), FOSFOCOL FIDES(18), FUROSEMIDE(19), GRANISETRON(20), HACHIAZULE /00523101/(21), LIDOCAINE(22), LORAZEPAM(23), LOXOPROFEN(24), MAGNESIUM OXIDE(25), MEROPENEM(26), METHYLPREDNISOLONE(27), METHYLPREDNISOLONE(28), METHYLPREDNISOLONE(29), METOCLOPRAMIDE(30), MINOFIT(31), NEO NICHIPHAGEN C(32), NEO NICHIPHAGEN C(33), PARACETAMOL(34), PARACETAMOL(35), PREDNISOLONE(36), RABEPRAZOLE(37), SODIUM CHLORIDE(38), SODIUM CHLORIDE(39), SODIUM PICOSULFATE(40), TRIBENOSIDE(41), ZOLPIDEM(42)
Date of first dose/last dose of study drug (Study Day):	30 JUL 2018 / 03 AUG 2018 (Study Day 5)
Other events: (MedDRA Preferred Term)	Rash maculo-papular, Aspartate aminotransferase increased, Blood creatine phosphokinase increased, Hypophosphataemia, Lymphopenia, Alanine aminotransferase increased, Nausea, Pyrexia, Blood creatinine increased, Gamma-glutamyltransferase increased, Hypertriglyceridaemia, Hypoalbuminaemia, Laryngeal pain, Weight decreased, Sinus tachycardia
Date of diagnosis:	31 MAY 2017
Disease Histology:	Peripheral T-cell lymphoma, NOS (PTCL)

Serious adverse events (Investigator term/MedDRA preferred term):	Alanin aminotransferase increased / Alanine aminotransferase increased
Dose at or prior to adverse event onset:	9 µg/kg
Start date of adverse event (Study Day)/ outcome date of adverse event (Study Day):	06 AUG 2018 (Study Day 8) / 07 AUG 2018 (Study Day 9)
TEAE?	Yes
Serious criteria:	Requires inpatient hospitalization or prolongation of existing hospitalization
Outcome:	RECOVERING/RESOLVING
Study drug action taken/other action taken:	DOSE NOT CHANGED / Treatment given
Concomitant medications (used until the start date):	1, 2, 3, 5, 6, 7, 9, 10, 12, 13, 14, 15, 16, 17, 19, 20, 21, 23, 24, 25, 30, 31, 34, 35, 37, 38, 39, 40, 41, 42
Relationship of event:	RELATED

Serious adverse events (Investigator term/MedDRA preferred term):	Alanin aminotransferase increased / Alanine aminotransferase increased
Dose at or prior to adverse event onset:	9 µg/kg
Start date of adverse event (Study Day)/ outcome date of adverse event (Study Day):	07 AUG 2018 (Study Day 9) / 13 AUG 2018 (Study Day 15)
TEAE?	Yes
Serious criteria:	Requires inpatient hospitalization or prolongation of existing hospitalization
Outcome:	NOT RECOVERED/NOT RESOLVED
Study drug action taken/other action taken:	DOSE NOT CHANGED / Treatment given
Concomitant medications (used until the start date):	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 23, 24, 25, 26, 27, 30, 31, 34, 35, 37, 38, 39, 40, 41, 42
Relationship of event:	RELATED

Serious adverse events (Investigator term/MedDRA preferred term):	Alanin aminotransferase increased / Alanine aminotransferase increased
Dose at or prior to adverse event onset:	9 µg/kg
Start date of adverse event (Study Day)/ outcome date of adverse event (Study Day):	13 AUG 2018 (Study Day 15) / 15 AUG 2018 (Study Day 17)
TEAE?	Yes
Serious criteria:	Requires inpatient hospitalization or prolongation of existing hospitalization
Outcome:	NOT RECOVERED/NOT RESOLVED
Study drug action taken/other action taken:	DOSE NOT CHANGED / Treatment given
Concomitant medications (used until the start date):	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 23, 24, 25, 26, 27, 28, 29, 30, 31, 34, 35, 37, 38, 39, 40, 41, 42
Relationship of event:	NOT RELATED

Serious adverse events (Investigator term/MedDRA preferred term):	Alanin aminotransferase increased / Alanine aminotransferase increased
Dose at or prior to adverse event onset:	9 µg/kg
Start date of adverse event (Study Day)/ outcome date of adverse event (Study Day):	15 AUG 2018 (Study Day 17) / 17 AUG 2018 (Study Day 19)
TEAE?	Yes
Serious criteria:	Requires inpatient hospitalization or prolongation of existing hospitalization
Outcome:	RECOVERING/RESOLVING
Study drug action taken/other action taken:	DOSE NOT CHANGED / Treatment given
Concomitant medications (used until the start date):	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 23, 24, 25, 26, 27, 28, 29, 30, 31, 34, 35, 37, 38, 39, 40, 41, 42
Relationship of event:	NOT RELATED

Serious adverse events (Investigator term/MedDRA preferred term):	Aspartate aminotransferase increased / Aspartate aminotransferase increased
Dose at or prior to adverse event onset:	9 µg/kg
Start date of adverse event (Study Day)/ outcome date of adverse event (Study Day):	06 AUG 2018 (Study Day 8) / 07 AUG 2018 (Study Day 9)
TEAE?	Yes
Serious criteria:	Requires inpatient hospitalization or prolongation of existing hospitalization
Outcome:	RECOVERING/RESOLVING
Study drug action taken/other action taken:	DOSE NOT CHANGED / Treatment given
Concomitant medications (used until the start date):	1, 2, 3, 5, 6, 7, 9, 10, 12, 13, 14, 15, 16, 17, 19, 20, 21, 23, 24, 25, 30, 31, 34, 35, 37, 38, 39, 40, 41, 42
Relationship of event:	RELATED

Serious adverse events (Investigator term/MedDRA preferred term):	Aspartate aminotransferase increased / Aspartate aminotransferase increased
Dose at or prior to adverse event onset:	9 µg/kg
Start date of adverse event (Study Day)/ outcome date of adverse event (Study Day):	07 AUG 2018 (Study Day 9) / 13 AUG 2018 (Study Day 15)
TEAE?	Yes
Serious criteria:	Requires inpatient hospitalization or prolongation of existing hospitalization
Outcome:	NOT RECOVERED/NOT RESOLVED
Study drug action taken/other action taken:	DOSE NOT CHANGED / Treatment given
Concomitant medications (used until the start date):	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 23, 24, 25, 26, 27, 30, 31, 34, 35, 37, 38, 39, 40, 41, 42
Relationship of event:	RELATED

Serious adverse events (Investigator term/MedDRA preferred term):	Aspartate aminotransferase increased / Aspartate aminotransferase increased
Dose at or prior to adverse event onset:	9 µg/kg
Start date of adverse event (Study Day)/ outcome date of adverse event (Study Day):	13 AUG 2018 (Study Day 15) / 15 AUG 2018 (Study Day 17)
TEAE?	Yes
Serious criteria:	Requires inpatient hospitalization or prolongation of existing hospitalization
Outcome:	RECOVERING/RESOLVING
Study drug action taken/other action taken:	DOSE NOT CHANGED / Treatment given
Concomitant medications (used until the start date):	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 23, 24, 25, 26, 27, 28, 29, 30, 31, 34, 35, 37, 38, 39, 40, 41, 42
Relationship of event:	NOT RELATED

Serious adverse events (Investigator term/MedDRA preferred term):	Aspartate aminotransferase increased / Aspartate aminotransferase increased
Dose at or prior to adverse event onset:	9 µg/kg
Start date of adverse event (Study Day)/ outcome date of adverse event (Study Day):	15 AUG 2018 (Study Day 17) / 17 AUG 2018 (Study Day 19)
TEAE?	Yes
Serious criteria:	Requires inpatient hospitalization or prolongation of existing hospitalization
Outcome:	RECOVERING/RESOLVING
Study drug action taken/other action taken:	DOSE NOT CHANGED / Treatment given

Concomitant medications (used until the start date):	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 23, 24, 25, 26, 27, 28, 29, 30, 31, 34, 35, 37, 38, 39, 40, 41, 42
Relationship of event:	NOT RELATED

Serious adverse events (Investigator term/MedDRA preferred term):	skin disorder medicamentosa / Drug eruption
Dose at or prior to adverse event onset:	9 µg/kg
Start date of adverse event (Study Day)/ outcome date of adverse event (Study Day):	07 AUG 2018 (Study Day 9) / 20 SEP 2018 (Study Day 53)
TEAE?	Yes
Serious criteria:	Requires inpatient hospitalization or prolongation of existing hospitalization
Outcome:	RECOVERED/RESOLVED
Study drug action taken/other action taken:	DOSE NOT CHANGED / Treatment given
Concomitant medications (used until the start date):	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 23, 24, 25, 26, 27, 30, 31, 34, 35, 37, 38, 39, 40, 41, 42
Relationship of event:	RELATED

Narrative

A 6[redacted]-year-old male received DENILEUKIN DIFTITOX as a participant in a clinical trial Protocol # E7777-J081-205: "A Phase 2 Study of E7777 in Patients with Relapsed or Refractory Peripheral T-cell Lymphoma and Cutaneous T-cell Lymphoma."

Jul/30/2018: The subject initiated treatment with E7777 (denileukin diftitox) 9 µg/kg on Days 1 to 5 of each 3-week cycle.

Aug/01/2018: The subject experienced increased AST, requiring/prolonging hospitalization.

Aug/02/2018: Alb: 3.1 g/dL. Albuminar (human serum albumin) 12.5 g was administered.

Aug/03/2018: Alb: 3.2 g/dL. Albuminar 12.5 g was administered. Study drug discontinued (last administration on this date).

Aug/05/2018: The subject had pyrexia of 38.4 °C. Antibiotic treatment was initiated.

Aug/06/2018: The subject received IV cefepime dihydrochloride hydrate, 3 grams twice per day, for infection prophylaxis. Alb: 2.8 g/dL. Albuminar 12.5 g was administered. AST was 205, ALT was 153. Since hospitalization was prolonged due to increased ALT and increased AST, the events were assessed as serious adverse events (SAEs). Liver supporting drug was initiated.

Aug/07/2018: The subject experienced skin disorder medicamentosa. The subject had redness with facial oedema and papule involving the neck to precordia, abdomen, back, then to extremities. Given the possibility of drug-induced event due to cefepime (CFPM), the antibiotic regimen was switched to meropenem (MEPM). Skin disorder medicamentosa was diagnosed and considered as an SAE, and thus, steroid therapy with prednisolone (PSL)

1 mg/kg/day was started. Lab data showed tendency toward recovery (AST: 81, ALT: 90).

Aug/08/2018: PSL 1000 mg/day was administered.

Aug/10/2018: AST and ALT were considered to be improving with the value at 42 and 57, respectively.

Aug/11/2018: PSL 1 mg/kg/day was administered.

Aug/13/2018: The subject experienced increased AST and increased ALT requiring/prolonging hospitalization. AST and ALT increased to 180 and 185, respectively. Recurrent increase in AST and ALT was noted. Drug-induced liver disorder due to steroid was also suspected. The course was observed with continuation of the liver supporting drug.

Aug/16/2018: PSL 0.5 mg/kg/day was administered.

Aug/17/2018: Given the withdrawal of the informed consent, the subject dropped out of the study (last administration date of the study drug: Aug/03/2018).

Aug/20/2018: Lab data improved (AST: 43, ALT: 92) and the liver supporting drug was changed to oral drug. Despite dose decrease of PSL, the skin eruption was improving. PSL was changed to oral prednisolone 30 mg.

Aug/21/2018: The subject was discharged since the condition became stable.

Aug/29/2018: The subject recovered from the increased AST (onset date: Aug/01/2018), increased ALT (onset date: Aug/03/2018), increased AST (onset date: Aug/13/2018), and increased ALT (onset date: Aug/13/2018). AST level was 30 and ALT level was 31.

Aug/30/2018: Prednisolone was decreased to 15 mg.

Sep/06/2018: Prednisolone was decreased to 10 mg and oral Glycyron was completed.

Sep/14/2018: Prednisolone was decreased to 5 mg.

Sep/20/2018: Prednisolone was terminated. The subject recovered from the skin disorder medicamentosa.

Investigator's opinion on causality to the study drug:

Aspartate aminotransferase increased (prior to Aug/13/2018), alanine aminotransferase increased (prior to Aug/13/2018), and drug eruption: "Related" to the study medication.
Comments: The events were suspected to be drug-induced liver disorder, and thus, the causality was assessed as "related.

Aspartate aminotransferase increased (from Aug/13/2018), alanine aminotransferase increased (from Aug/13/2018): "Not related" to the study medication.
Comments: The events were not related to the study drug (the steroid therapy was considered to be involved in the onset of the events).

Sponsor's opinion on causality (only if it differs from the investigator's opinion):

Aspartate aminotransferase increased, alanine aminotransferase increased: Given the short latency to onset of the events after initiating the study medication, recovery after stopping the study medication and considering that elevations in transaminases have been previously observed in subjects treated with the study medication, the events increased are classified as "Related" to the study medication.

Study:	E7777-J081-205
Subject ID:	10031001
Age, race, sex:	7[redacted] years, Japanese, Female
Medical history: (MedDRA Preferred Term)	Cholelithiasis, Eosinophilic pneumonia, Herpes zoster, Hyperthyroidism, Pneumonia
Current medical conditions: (MedDRA Preferred Term)	Body tinea, Bundle branch block right, Dry eye, Glossodynia, Pruritus
Concomitant medications:	BETAMETHASONE(1), CARBOHYDRATES NOS W/POTASSIUM CHLORIDE/SODIUM(2), DEXAMETHASONE(3), DEXAMETHASONE(4), DEXAMETHASONE(5), DEXAMETHASONE(6), DEXAMETHASONE(7), DEXCHLORPHENIRAMINE(8), DEXCHLORPHENIRAMINE(9), DEXCHLORPHENIRAMINE(10), DEXCHLORPHENIRAMINE(11), DEXCHLORPHENIRAMINE(12), DEXCHLORPHENIRAMINE(13), DEXTROMETHORPHAN(14), DIPHENHYDRAMINE(15), DIPHENHYDRAMINE(16), ESOMEPRAZOLE(17), ETIZOLAM(18), FLAVINE ADENINE DINUCLEOTIDE(19), HYALURONIC ACID(20), HYDROCORTISONE(21), L-CARBOCYSTEINE(22), MAGNESIUM OXIDE(23), MINOFIT(24), MINOFIT(25), NEO NICHIPHAGEN C(26), NEO NICHIPHAGEN C(27), OLOPATADINE(28), OLOPATADINE(29), PARACETAMOL(30), PARACETAMOL(31), PARACETAMOL(32), PARACETAMOL(33), PARACETAMOL(34), PARACETAMOL(35), PIPERACILLIN W/TAZOBACTAM /01606301/(36), RAMOSETRON(37), RAMOSETRON(38), RAMOSETRON(39), RAMOSETRON(40), RAMOSETRON(41), SENNOSIDE A+B(42), URSODEOXYCHOLIC ACID(43)
Date of first dose/last dose of study drug (Study Day):	18 APR 2016 / 15 JUL 2016 (Study Day 89)
Other events: (MedDRA Preferred Term)	Constipation, Cough, Lymphopenia, Pneumonia, Dermatosis, Eczema eyelids
Date of diagnosis:	04 AUG 2010
Disease Histology:	Peripheral T-cell lymphoma, NOS (PTCL)

Serious adverse events (Investigator term/MedDRA preferred term):	Alanine aminotransferase increased / Alanine aminotransferase increased
Dose at or prior to adverse event onset:	9 µg/kg
Start date of adverse event (Study Day)/ outcome date of adverse event (Study Day):	25 APR 2016 (Study Day 8) / 16 MAY 2016 (Study Day 29)
TEAE?	Yes
Serious criteria:	Requires inpatient hospitalization or prolongation of existing hospitalization
Outcome:	RECOVERED/RESOLVED
Study drug action taken/other action taken:	DOSE NOT CHANGED / Treatment given
Concomitant medications (used until the start date):	1, 2, 3, 8, 9, 15, 18, 19, 20, 23, 24, 25, 26, 30, 31, 37, 42, 43
Relationship of event:	RELATED

Serious adverse events (Investigator term/MedDRA preferred term):	Aspartate aminotransferase increased / Aspartate aminotransferase increased
Dose at or prior to adverse event onset:	9 µg/kg
Start date of adverse event (Study Day)/ outcome date of adverse event (Study Day):	25 APR 2016 (Study Day 8) / 04 MAY 2016 (Study Day 17)
TEAE?	Yes
Serious criteria:	Requires inpatient hospitalization or prolongation of existing hospitalization
Outcome:	RECOVERED/RESOLVED
Study drug action taken/other action taken:	DOSE NOT CHANGED / Treatment given
Concomitant medications (used until the start date):	1, 2, 3, 8, 9, 15, 18, 19, 20, 23, 24, 25, 26, 30, 31, 37, 42, 43
Relationship of event:	RELATED

Narrative

A 7[redacted]-year-old female received DENILEUKIN DIFTITOX as a participant in a clinical trial Protocol # E7777-J081-205: "A Phase 2 Study of E7777 in Patients with Relapsed or Refractory Peripheral T-cell Lymphoma and Cutaneous T-cell Lymphoma."

Apr/18/2016: The subject initiated treatment with E7777 (denileukin diftitox) 9 µg/kg on Days 1 to 5 of each 3-week cycle.

Apr/22/2016: Administrations of the study drug in 5 consecutive days were finished.

Apr/25/2016: The subject experienced increased AST and increased ALT requiring initial/prolonged hospitalization. Lab data showed: WBC 6.7 × 10^3/µL, Hb 12.7 g/dL, PLT 18.2 × 10^4/µL, TP 6.3 g/dL, Alb 3.3 g/dL, AST 157 U/L, ALT 191 U/L, LDH 355 U/L, ALP 396 U/L, γ-GTP 114 U/L, Na 139 mEq/L, K 5.3 mEq/L, Cl 101 mEq/L, Ca 8.4 mg/dL, CRP 0.66 mg/dL. Anorexia was present. An ultrasound of the abdomen showed no abnormalities. Although discharge was scheduled for the same day, given the presence of increased transaminases Grade 3, liver supporting drugs (Adelavin, Glycyron, Stronger Neo-Minophagen C P 20 mL) were added to the treatment, and the subject was placed under inpatient observation.

May/02/2016: Since transaminases showed a tendency to improve, intravenous drip infusion of liver supporting drugs (Adelavin, Stronger Neo-Minophagen C P 20 mL) was discontinued.

May/04/2016: The subject recovered from the increased AST.

May/05/2016: After the discontinuation of intravenous drip infusion of liver supporting drugs, increased AST and increased ALT were not noted. Therefore, the subject was discharged on the same day.

May/16/2016: The subject recovered from the ALT increased.

Investigator's opinion on causality to the study drug:

Alanine aminotransferase increased, aspartate aminotransferase increased: "Related" to the study medication.

Comments: The likelihood of liver disorder associated with the past history or the on-going concomitant drugs was low. In addition, the adverse events occurred on treatment Day 8, consistent with the report on the onset timing in the previous phase. Based on the above, the increased AST and increased ALT in this case were likely to be related to the study drug.

Study:	E7777-J081-205
Subject ID:	10031008
Age, race, sex:	6[redacted] years, Japanese, Male
Medical history: (MedDRA Preferred Term)	-
Current medical conditions: (MedDRA Preferred Term)	Atelectasis, Constipation, Dry eye, Nephrolithiasis, Pruritus, Renal cyst
Concomitant medications:	ALBUMIN HUMAN(1), BACTRIM(2), BETAMETHASONE(3), CAMOSTAT(4), CEFEPIME(5), CLOBETASOL(6), DESLORATADINE(7), DEXAMETHASONE(8), DEXAMETHASONE(9), DEXAMETHASONE(10), DEXCHLORPHENIRAMINE(11), DEXCHLORPHENIRAMINE(12), DIFLUPREDNATE(13), DIQUAFOSOL(14), HEPARINOID(15), MINOFIT(16), NEO NICHIPHAGEN C(17), NEO NICHIPHAGEN C(18), NEO NICHIPHAGEN C(19), PARACETAMOL(20), PARACETAMOL(21), RAMOSETRON(22), RAMOSETRON(23), SODIUM PICOSULFATE(24), URSODEOXYCHOLIC ACID(25), URSODEOXYCHOLIC ACID(26), URSODEOXYCHOLIC ACID(27), VITAMEDIN INTRAVENOUS(28)
Date of first dose/last dose of study drug (Study Day):	20 AUG 2018 / 13 SEP 2018 (Study Day 25)
Other events: (MedDRA Preferred Term)	Hypoalbuminaemia, Lymphopenia, Aspartate aminotransferase increased, Alanine aminotransferase increased, Myalgia, Decreased appetite, Malaise, Nausea, Lipase increased, Hepatic function abnormal, Amylase increased, Blood alkaline phosphatase increased, Gamma-glutamyltransferase increased, Proteinuria
Date of diagnosis:	11 JUL 2017
Disease Histology:	Primary cutaneous gamma-delta T-cell lymphoma (CTCL)

Serious adverse events (Investigator term/MedDRA preferred term):	Hepatic function disorder / Hepatic function abnormal
Dose at or prior to adverse event onset:	9 µg/kg
Start date of adverse event (Study Day)/ outcome date of adverse event (Study Day):	31 AUG 2018 (Study Day 12) / 04 SEP 2018 (Study Day 16)
TEAE?	Yes
Serious criteria:	Requires inpatient hospitalization or prolongation of existing hospitalization
Outcome:	RECOVERING/RESOLVING
Study drug action taken/other action taken:	DOSE NOT CHANGED / Treatment given
Concomitant medications (used until the start date):	1, 2, 5, 6, 7, 8, 9, 11, 13, 15, 16, 20, 22, 24, 25, 26
Relationship of event:	RELATED

Narrative

A 6[redacted]-year-old male received DENILEUKIN DIFTITOX as a participant in a clinical trial Protocol # E7777-J081-205: "A Phase 2 Study of E7777 in Patients with Relapsed or Refractory Peripheral T-cell Lymphoma and Cutaneous T-cell Lymphoma."

Aug/20/2018: The subject initiated treatment with E7777 (denileukin diftitox) 9 µg/kg (631.8 µg) on Days 1 to 5 of each 3-week cycle.

Aug/24/2018: Increased AST (Grade 1) developed. Last dose of study drug in Cycle 1 was administered.

Aug/25/2018: Increased ALT (Grade 1) developed.