Aug/28/2018: Anorexia, nausea and malaise were present.

Aug/30/2018: Anorexia, nausea and malaise showed a tendency of improvement.

Aug/31/2018: Due to chills and nausea, the subject was emergently transported to the study site. The body temperature was 38.8 °C. The subject experienced hepatic function disorder. Laboratory test revealed hepatic function disorder Grade 2, for which liver supporting drug Stronger Neo-Minophagen C P (monoammonium glycyrrhizinate/glycine/aminoacetic acid/L-cysteine hydrochloride hydrate) and Cefepime Dihydrochloride (cefepime dihydrochloride hydrate) were added to the treatment and the subject was determined to be hospitalized for course observation. Since there was also a possibility of infection, detailed general bacteria test was being performed.

Sep/01/2018: The subject became afebrile and the hepatic enzyme levels were improving.

Sep/02/2018: Anorexia, nausea and malaise resolved.

Sep/04/2018: Intravenous drip infusion of the liver supporting drug g Stronger Neo-Minophagen C P and Cefepime Dihydrochloride were discontinued, and another liver supporting drug (Glycyron (monoammonium glycyrrhizinate/glycine/aminoacetic acid/ DL-methionine)) was added to the treatment. After the condition was checked by abdominal ultrasonography, the subject was determined to be discharged on the same day.

Sep/10/2018: Since the hepatic enzyme levels returned to normal, the event of hepatic function disorder was considered to have resolved.

Investigator's opinion on causality to the study drug:

Hepatic function abnormal: "Related" to the study medication.
Comments: It was considered unlikely that an onset of liver disorder was associated with the subject's underlying disease or concomitant drugs. In addition, the timing of the peak of the adverse event was on day 12 of the study drug treatment, which was consistent with the information (on the peak timing of the fluctuation of AST/ALT) in the reports submitted in the previous phase. Given these, the hepatic function disorder in this case was considered to be related to the study drug.

Study:	E7777-J081-205
Subject ID:	10041001
Age, race, sex:	5[redacted] years, Japanese, Male
Medical history: (MedDRA Preferred Term)	-
Current medical conditions: (MedDRA Preferred Term)	-
Concomitant medications:	APREPITANT(1), APREPITANT(2), APREPITANT(3), APREPITANT(4), APREPITANT(5), APREPITANT(6), APREPITANT(7), APREPITANT(8), BETAMETHASONE(9), CHLORPHENAMINE(10), CHLORPHENAMINE(11), CHLORPHENAMINE(12), CHLORPHENAMINE(13), CLOBETASOL(14), DEXAMETHASONE(15), DEXAMETHASONE(16), DEXAMETHASONE(17), DEXAMETHASONE(18), DEXAMETHASONE(19), DEXAMETHASONE(20), DEXAMETHASONE(21), DEXAMETHASONE(22), DEXCHLORPHENIRAMINE(23), DEXCHLORPHENIRAMINE(24), DEXCHLORPHENIRAMINE(25), DEXCHLORPHENIRAMINE(26), DEXCHLORPHENIRAMINE(27), FENOFIBRATE(28), GENTAMICIN(29), GRANISETRON(30), GRANISETRON(31), GRANISETRON(32), GRANISETRON(33), GRANISETRON(34), GRANISETRON(35), GRANISETRON(36), GRANISETRON(37), HEPARINOID(38), HYDROXYZINE(39), HYOSCINE(40), LEVOFLOXACIN(41), METOCLOPRAMIDE(42), METOCLOPRAMIDE(43), OLOPATADINE(44), PARACETAMOL(45), PARACETAMOL(46), PARACETAMOL(47), PARACETAMOL(48), PARACETAMOL(49), PARACETAMOL(50), PARACETAMOL(51), PARACETAMOL(52), PARACETAMOL(53)
Date of first dose/last dose of study drug (Study Day):	30 MAY 2016 / 28 OCT 2016 (Study Day 152)
Other events: (MedDRA Preferred Term)	Alanine aminotransferase increased, Aspartate aminotransferase increased, Hypertriglyceridaemia, Hypoalbuminaemia, Abdominal pain upper, Gamma-glutamyltransferase increased, Lymphopenia, Capillary leak syndrome, Facial pain
Date of diagnosis:	2000
Disease Histology:	Mycosis fungoides (CTCL)

Serious adverse events (Investigator term/MedDRA preferred term):	capillary leak syndrome / Capillary leak syndrome
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):	17 JUL 2016 (Study Day 49) / 25 JUL 2016 (Study Day 57)
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, 9, 10, 11, 14, 15, 16, 17, 23, 24, 30, 31, 32, 38, 39, 40, 41, 42, 44, 45, 46, 47
Relationship of event:	RELATED

Serious adverse events (Investigator term/MedDRA preferred term):	Lymphopenia / Lymphopenia
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 JUN 2016 (Study Day 8) / 13 JUN 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 / None
Concomitant medications (used until the start date):	1, 9, 14, 15, 23, 24, 30, 38, 39, 40, 41, 44, 45
Relationship of event:	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."

May/06/2016: Informed consent was obtained.

May/23/2016: WBC 7030 and lymphocytes 10.0% were confirmed.

May/30/2016: The subject initiated treatment with E7777 (denileukin diftitox) 9 µg/kg on Days 1 to 5 of each 3-week cycle for mycosis fungoides.

Jun/03/2016: Subject completed Cycle 1, day 5 continuous administration of study treatment. WBC 12860 and lymphocytes 4.0% were confirmed.

Jun/06/2016: WBC 8080 and lymphocytes 2.0% were confirmed. The subject experienced lymphopenia (Grade 4) and hospitalization had to be prolonged; thus the event was evaluated as serious.

Jun/10/2016: WBC 6510 and lymphocytes 3.0% were confirmed. Hospitalization continued.

Jun/13/2016: WBC 7330 and lymphocytes 24.0 % were confirmed.

Jun/14/2016: Lab data returned to the normal levels with favourable progress; thus the subject was discharged. The subject recovered from the lymphopenia (Grade 4). Study drug continuing per protocol schedule.

Jul/11/2016: Cycle 3 Day 1: The study drug was initiated.

Jul/15/2016: Cycle 3 Day 5: The study drug administered for 5 consecutive days was completed.

Jul/17/2016: Nausea (Grade 2) occurred without vomiting, due to capillary leak syndrome (Grade 2). Lab data showed blood pressure 91/55.

Jul/18/2016: Nausea persisted. Oral Primperan (metoclopramide) was administered. Lab data showed blood pressure 86/69.

Jul/19/2016: Lab data showed blood pressure 115/82 and Albumin 2.9 g/dL. The series of the events that occurred on and after Jul/17 were evaluated as capillary leak syndrome (Grade 2). Because of the intense symptoms such as nausea, hospitalization had to be prolonged; thus, the event was assessed as SAE. Nausea persisted, which was symptomatically intense. Oral Primperan was administered three times a day.

Jul/20/2016: Nausea started to subside with Oral Primperan, and the subject was thereby discharged.

Jul/25/2016: Cycle 3 Day 15: The subject visited the study site, which was scheduled on the protocol. Lab data showed blood pressure 106/74 and Albumin 3.8 g/dL. Given resolution of nausea, capillary leak syndrome (Grade 2) was assessed as recovered. The study drug was continued per protocol schedule.

Investigator's opinion on causality to the study drug:

Capillary leak syndrome: "Related" to the study medication.

Given the presence of capillary leak syndrome-associated symptoms such as decreased blood pressure and nausea, prolonged hospitalization was decided. After administration of the study drug, the symptoms were noted. Based on the course between the administration and the event onset as well as the past reports, there was a rational possibility that the study drug was related to the event.

Lymphopenia: "Related" to the study medication.

Given the decreased lymphocytes as Grade 4, the course had to be carefully observed for possible infection; thus prolonged hospitalization was decided. On Day 8 of the administration of the study drug, rapid decrease was noted. Furthermore, based on the course from the administration to the onset of the decreased lymphocytes as well as the past report, there assumed a rational possibility in the causality between the study drug and the event.

Study:	E7777-J081-205
Subject ID:	10041002
Age, race, sex:	6[redacted] years, Japanese, Female
Medical history: (MedDRA Preferred Term)	-
Current medical conditions: (MedDRA Preferred Term)	Cataract, Diabetes mellitus, Hyperlipidaemia, Lid lag
Concomitant medications:	ALCLOMETASONE(1), APREPITANT(2), APREPITANT(3), APREPITANT(4), APREPITANT(5), APREPITANT(6), APREPITANT(7), APREPITANT(8), BENZETHONIUM(9), CEFDINIR(10), CHLORPHENAMINE(11), CHLORPHENAMINE(12), CHLORPHENAMINE(13), CHLORPHENAMINE(14), CHLORPHENAMINE(15), CHLORPHENAMINE(16), CHLORPHENAMINE(17), CLARITHROMYCIN(18), CLOBETASOL(19), DEXAMETHASONE(20), DEXAMETHASONE(21), DEXAMETHASONE(22), DEXAMETHASONE(23), DEXAMETHASONE(24), DEXAMETHASONE(25), DEXAMETHASONE(26), DEXAMETHASONE(27), DIFLUPREDNATE(28), DIQUAFOSOL(29), FLEBOBAG RING LACT(30), FLUOROMETHOLONE(31), GENTAMICIN(32), GENTAMICIN(33), GRANISETRON(34), GRANISETRON(35), GRANISETRON(36), GRANISETRON(37), GRANISETRON(38), GRANISETRON(39), GRANISETRON(40), HYDROXYZINE(41), INSULIN ASPART(42), LEVOCETIRIZINE(43), LEVOFLOXACIN(44), LULICONAZOLE(45), MAGNESIUM OXIDE(46), METOCLOPRAMIDE(47), METOCLOPRAMIDE(48), NADIFLOXACIN(49), NEO-MEDROL EYE-EAR(50), OFLOXACIN(51), PARACETAMOL(52), PARACETAMOL(53), PARACETAMOL(54), PARACETAMOL(55), PARACETAMOL(56), PARACETAMOL(57), PARACETAMOL(58), PARACETAMOL(59), PREDNISOLONE(60), PROBUCOL(61), REBAMIPIDE(62), REPAGLINIDE(63), SALICYLIC ACID(64), SULFADIAZINE(65), TENELIGLIPTIN(66), UREA(67), WHITE SOFT PARAFFIN(68)
Date of first dose/last dose of study drug (Study Day):	11 JUL 2016 / 18 NOV 2016 (Study Day 131)
Other events: (MedDRA Preferred Term)	Wound, Skin infection, Alanine aminotransferase increased, Aspartate aminotransferase increased, Pyrexia, Lymphopenia, Gingivitis, Constipation
Date of diagnosis:	18 JUN 1999
Disease Histology:	Mycosis fungoides (CTCL)

Serious adverse events (Investigator term/MedDRA preferred term):	Capillary leak Syndrome / Capillary leak syndrome
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):	18 JUL 2016 (Study Day 8) / 08 AUG 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, 11, 19, 20, 21, 28, 29, 31, 34, 41, 43, 44, 45, 47, 49, 50, 51, 52, 60, 61, 63, 64, 65, 66, 67, 68
Relationship of event:	RELATED

Serious adverse events (Investigator term/MedDRA preferred term):	Lymphopenia / Lymphopenia
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):	19 JUL 2016 (Study Day 9) / 21 JUL 2016 (Study Day 11)
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 / None
Concomitant medications (used until the start date):	1, 2, 11, 19, 20, 21, 28, 29, 31, 34, 41, 43, 44, 45, 47, 49, 50, 51, 52, 60, 61, 63, 64, 65, 66, 67, 68
Relationship of event:	RELATED

Serious adverse events (Investigator term/MedDRA preferred term):	Squamous cell carcinoma of skin / Squamous cell carcinoma of skin
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):	17 NOV 2016 (Study Day 130) / -
TEAE?	Yes
Serious criteria:	Requires inpatient hospitalization or prolongation of existing hospitalization
Outcome:	NOT RECOVERED/NOT 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, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68
Relationship of event:	NOT RELATED

Narrative

A 6[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."

Jun/10/2016: Informed consent was obtained for Study #E7777.

Jul/08/2016: A screening test was performed. Lab data showed Alb 3.7, WBC of 8090, 5.5% lymphocytes, total lymphocytes of 445.

Jul/11/2016: Day 1 of Cycle 1 was started. Blood pressure was 128/69. The study drug 9 µg/kg/day was initiated.

Jul/15/2016: On Day 5 of Cycle 1, a 5-day consecutive treatment was completed. Lab data showed Alb 3.0.

Jul/18/2016: Nausea occurred. The subject experienced capillary leak syndrome (Grade 3). Primperan (metoclopramide) was orally administered.

Jul/19/2016: Given intense symptoms such as capillary leak syndrome-associated nausea, course observation was decided with prolonged hospitalization, based on which the event was assessed as SAE. Lab data showed Alb 2.9. The subject experienced lymphopenia (Grade 4). Laboratory results showed

WBC of 9120, 2.0% lymphocytes, total lymphocytes of 182. The subject had lymphopenia (Grade 4) requiring prolongation of hospitalization; thus, the event was considered as a serious adverse event (SAE).

Jul/20/2016: Fluid replacement was initiated because of a decline in dietary intake, decreased blood pressure with 83/58, and others. Lactec was started for decreased meal intake (Grade 3).

Jul/21/2016: Laboratory results showed WBC of 10490, 9.5% lymphocytes, total lymphocytes of 997, Alb 2.6, bloodpressure 97/67. The subject recovered from the lymphopenia (Grade 4).

Jul/22/2016: Lab data showed blood pressure 81/49.

Jul/23/2016: Oedema appeared on the extremities. Lab data showed blood pressure 94/55. The meal intake gradually increased and Lactec was completed.

Jul/24/2016: Lab data showed an improving tendency of blood pressure with 115/64.

Jul/25/2016: The nausea tended to improve gradually. Laboratory results showed Alb 2.4, WBC of 8420, 9.0% lymphocytes, total lymphocytes of 758. The lymphopenia were considered as "resolved" in accordance with the normal lab values mentioned above as well as the lab values on Jul/21/2016.

Jul/26/2016: The subject had a favorable meal intake with no recurrent nausea. Fluid replacement was not necessary. The subject was placed under observation by continuing treatment with Primperan. The subject did not recover from the nausea. Action taken with study drug reported as dose maintained.

Jul/27/2016: Lab data showed Alb 2.4. No further decrease was noted in the albumin levels, with an improving tendency of blood pressure and nausea. Since general condition started to be recovering, the subject was discharged.

Aug/01/2016: The subject visited the study site for initiation of therapy on Day 1 of Cycle 2. Lab data indicated recovery of Alb to 3.0. While oedema on the upper extremity subsided, the condition on the lower extremity persisted. Capillary leak syndrome was assessed as "not completely recovered"; thus, administration of the study drug was decided to be postponed. The subject did not recover from the capillary leak syndrome (Grade 3).

Aug/08/2016: The subject visited the study site for initiation of therapy on Day 1 of Cycle 2. Lab data indicated recovery of Alb to 3.7. Furthermore, blood pressure improved, oedema disappeared, and general condition was favourable, based on which capillary leak syndrome was considered to have been completely cured. The subject recovered from the capillary leak syndrome (Grade 3).

Nov/14/2016: Cycle 6 Day 1 was started.

Nov/17/2016: The subject experienced squamous cell carcinoma of skin (Grade 3). A line of small masses were noted on the right upper arm. Spinocellular carcinoma affected by the previous radiotherapy or/and phototherapy was

alternative possibility in the differential diagnosis. A biopsy of the mass in the right upper arm was performed.

Nov/18/2016: Cycle 6 Day 5 was completed. Last dose of study drug was administered.

Nov/28/2016: Cycle 6 Day 15: the biopsy of the mass in the right upper arm yielded a pathological diagnosis of squamous cell carcinoma of skin. Hospitalization was scheduled for Dec/02 to perform resection. Biopsies of other parts in the entire body would be additionally performed. The event was reported to sponsor, who decided the subject's withdrawal from the study given possible influence on evaluation of skin lesion by resection. On the same day, the subject underwent some of the tests designated to be done at the time of withdrawal.

Nov/29/2016: The remaining designated tests were conducted. The subject did not recover from the squamous cell carcinoma of skin (Grade 3).

Dec/02/2016: After hospitalization, the subject with a diagnosis of squamous cell carcinoma of skin underwent excision of the relevant mass in the right upper arm. For biopsy, other than from the excised lesion, four specimens were obtained from the chest, lower abdomen, and thigh; two specimens from the head.

Dec/06/2016: After excision, the condition became stable; thus, the subject was discharged.

Dec/09/2016: The biopsy results of six out of the seven specimens from the regions including the excised lesion were consistent with a diagnosis of spinocellular carcinoma.

Dec/12/2016: The subject was hospitalized. Interferon therapy was initiated for mycosis fungoides. Topical Beselna (imiquimod) was tried for spinocellular carcinoma.

Dec/28/2016: After treatment, the conditions became stable; thus, the subject was discharged.

Jan/06/2017: Because erosion and pain as adverse events of Beselna were intense, Beselna was discontinued.

Jan/24/2017: Spinocellular carcinoma in the parietal region showed a tendency to expand. Thus, TS-1 (tegafur/gimeracil/oteracil potassium) was initiated.

Jun/16/2017: Because of pain in the hand and foot due to TS-1, TS-1 was suspended.

Jun/30/2017: Expansion of spinocellular carcinoma in the parietal region and enlargement of the metastatic lesion in the posterior side of the left auricle were noted. Thus, TS-1 was discontinued, and palliative approach with radiotherapy was decided.

Jul/27/2017: Amelioration of corneal ulcer was confirmed by an ophthalmologist. Subsequently, radiotherapy was initiated for spinocellular carcinoma (parietal region: a total of 30 Gy/10 doses, posterior side of the left auricle: a total of 30 Gy/10 doses).

Aug/09/2017: Radiotherapy for spinocellular carcinoma was completed.

Aug/24/2017: As for the spinocellular carcinoma in the parietal region and the posterior side of the left auricle, while no remarkable change was observed in the parietal region, its surrounding bank-shaped tumour elevation disappeared. However, the subject had pain from the erosion and ulcer of the unaffected skin surrounding the lesion, due to radiation skin disorder.

Sep/12/2017: No further favorable radiotherapy effect was expected for the spinocellular carcinoma in the parietal region. The subject did not recover from the squamous cell carcinoma of skin (Grade 3). Date unknown: The subject was dropped out from the study due to squamous cell carcinoma of skin.

Investigator's opinion on causality to the study drug:

Capillary leak syndrome: "Related" to the study drug.

Comments: Capillary leak syndrome (Grade 3): The subject became symptomatic after administration of the study drug. Considering the clinical course between the start of the study drug and the onset of the symptom as well as the contents of the previous reports, the event was rationally considered to be related to the study drug.

Lymphopenia: "Related" to the study drug.

Comments: Lymphocyte level abruptly decreased after the start of the study drug. Considering the clinical course between the start of the study drug and the onset of the decreased lymphocytes as well as the contents of the previous reports, the event was rationally considered to be related to the study drug.

Squamous cell carcinoma of skin: "Not Related" to the study drug.

Comments: Radiotherapy and/or phototherapy that had been received were highly likely to have affected the patient's condition.

Study:	E7777-J081-205
Subject ID:	10061001
Age, race, sex:	6[redacted] years, Japanese, Male
Medical history: (MedDRA Preferred Term)	Adrenal insufficiency, Spondylitic myelopathy
Current medical conditions: (MedDRA Preferred Term)	Benign prostatic hyperplasia, Chronic sinusitis, Colour blindness, Constipation, Diabetes mellitus, Diabetic nephropathy, Hypertension, Hyperuricaemia, Insomnia, Iron deficiency anaemia, Lumbar spinal stenosis, Macular degeneration, Neuralgia, Neurogenic bladder, Peripheral sensorimotor neuropathy, Pruritus, Radiation corneal injury, Rhinitis allergic, Sjogren's syndrome, Skin erosion, Skin ulcer, Tinea infection
Concomitant medications:	BACLOFEN(1), BENZBROMARONE(2), BETAMETHASONE(3), BETHANECHOL(4), BISACODYL(5), BROTIZOLAM(6), DEXAMETHASONE(7), DEXCHLORPHENIRAMINE(8), DIPHENHYDRAMINE(9), ENALAPRIL(10), EPINASTINE(11), EUFUSOL(12), EUFUSOL(13), FUROSEMIDE(14), GLYCEROL(15), GRANISETRON(16), HYALURONIC ACID(17), HYDROCORTISONE(18), HYDROCORTISONE(19), INSULIN HUMAN(20), IRON(21), ITRACONAZOLE(22), LANSOPRAZOLE(23), LEVOFLOXACIN(24), LOXOPROFEN(25), MAGNESIUM OXIDE(26), MECOBALAMIN(27), NEO NICHIPHAGEN C(28), NEUPHAGEN(29), NEUPHAGEN(30), PARACETAMOL(31), PARACETAMOL(32), PIOGLITAZONE(33), PREGABALIN(34), RED BLOOD CELLS(35), SENNOSIDE A+B(36), SENNOSIDE A+B(37), SILODOSIN(38), SODIUM PICOSULFATE(39), SOLITA-T1(40), SULFADIAZINE(41), TENELIGLIPTIN(42), TERBINAFINE(43), URSODEOXYCHOLIC ACID(44), VIDARABINE(45), ZINC(46)
Date of first dose/last dose of study drug (Study Day):	07 JUN 2016 / 11 JUN 2016 (Study Day 5)
Other events: (MedDRA Preferred Term)	Constipation, Hyperglycaemia, Anaemia, Lymphopenia, Hypoalbuminaemia, Malaise, Adrenal insufficiency, Pyrexia, Alanine aminotransferase increased, Aspartate aminotransferase increased, Gamma-glutamyltransferase increased, Thrombocytopenia, Renal impairment, Capillary leak syndrome, Generalised oedema, Weight increased, Blood alkaline phosphatase increased, Hyperkalaemia, Angular cheilitis
Date of diagnosis:	05 NOV 2007
Disease Histology:	Mycosis fungoides (CTCL)

Serious adverse events (Investigator term/MedDRA preferred term):	Capirally leak syndrome / Capillary leak syndrome
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 JUN 2016 (Study Day 15) / -
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 / None
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, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 38, 39, 40, 41, 42, 43, 44, 46
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/16/2016: Informed consent was obtained.

Jun/07/2016: The subject initiated Cycle 1 of E7777 (denileukin diftitox) 9 µg/kg (528.3 µg) on Days 1 to 5 of each 3-week cycle. Pre-treatment drugs of dexamethasone, d-chlorpheniramine maleate, granisetron hydrochloride, and acetaminophen were used.

Jun/11/2016: Pre-treatment drugs of dexamethasone, d-chlorpheniramine maleate, granisetron hydrochloride, and acetaminophen were continuously administered "uneventfully" until this date. Study drug was discontinued.

Jun/12/2016: The subject had a subjective symptom of malaise before going to sleep on Jun/11. Before going to sleep, the subject had pyrexia on Jun/12. Antibiotic treatment was initiated.

Jun/13/2016: Infection tests including chest radiography and blood culture assay were performed; however, with no marked infectious focus revealed, the cause of the pyrexia was unknown. Continuation of antibiotic treatment and administration of acetaminophen did not lead to defervescence. For possible relapse adrenal insufficiency and pyrexia due to immunization reaction associated with the drug completion of dexamethasone on Jun/11, intravenous hydrocortisone sodium succinate 0.5 DF (dosage form), as needed, considered a co-suspect drug, was initiated, which led to defervescence.

Jun/14/2016: After awakening pyrexia elevated again; hydrocortisone sodium succinate was re-administered, which led to defervescence. Insufficient intake of liquid and meal as well as mild decrease of kidney function was noted; thus, fluid replacement therapy was additionally performed.

Jun/15/2016: The onset for "Capillary leak syndrome" requiring hospitalization was reported. In the afternoon, pyrexia elevated again; hydrocortisone sodium succinate was re-administered, which led to defervescence. After initiation of the study drug, serum albumin decreased, accompanied by generalised oedema and weight increase.

Jun/16/2016: For elevated pyrexia, hydrocortisone sodium succinate was re-administered, which led to defervescence. Hypoalbuminaemia and oedema were persistent.

Jun/17/2016: Weight showed an increasing tendency; in an attempt to improve oedema, furosemide was initiated and fluid replacement therapy was completed. Slightly low serum cortisol was confirmed. Adrenal hypofunction could not be completely ruled out either. Therefore, intravenous injection of hydrocortisone sodium succinate was completed (subject received last dose of co-suspect medication on this date). Oral hydrocortisone was initiated for adrenal control. Pyrexia did not recur on and after Jun/16/2016.

Jun/18/2016: Face oedema was aggravated. Computed tomography (CT) of the neck to pelvis showed no findings suggestive of the cause of face oedema. Since insufficient meal intake and malaise improved, and adrenal insufficiency showed an improving tendency, along with face oedema as a possible adverse reaction of steroid treatment, oral hydrocortisone was discontinued.

Jun/20/2016: Face oedema improved. Furosemide was completed.

Jun/21/2016: Face oedema improved further. Serum albumins showed a tendency towards improvement, but the level was low as compared with the level before initiation of the study drug. Oedema and hypoalbuminaemia were assessed as the causes for prolongation of the initially planned hospitalization.

Jul/01/2016: Recovery or a tendency towards improvement was noted in the adverse events that occurred after administration of the study drug (such as pyrexia, oedema, hypoalbuminaemia, hepatic function disorder, aggravated renal function, decreased platelet count). However, upon comprehensive review, continuation of the study was considered difficult. Therefore, the subject was withdrawn from the study.

Jul/06/2016: The subject recovered from the oedema. Serum albumin level was lower than that prior to initiation of the study drug, but gradually improving, based on which discharge was possible. Consequently, the subject was discharged. The subject was recovering from the capillary leak syndrome.

Investigator's opinion on causality to the study drug:

Capillary leak syndrome: "Related" to the study medication.

Comments: Serum albumin had been lower than prior to initiation of the study drug, which became lower by debilitation due to pyrexia after administration. While oedema was possibly associated with an influence of steroid treatment, hypoalbuminaemia, decreased kidney function, and additional fluid replacement after administration of the study drug were also the likely causes. The above events were considered as those of "capillary leak syndrome", which occurred after administration of the study drug; thus, the causality of the event to the study drug could not be ruled out.

Study:	E7777-J081-205
Subject ID:	10061002
Age, race, sex:	6[redacted] years, Japanese, Male
Medical history: (MedDRA Preferred Term)	-
Current medical conditions: (MedDRA Preferred Term)	Blindness traumatic, Cerebral infarction, Constipation, Haemorrhoids, Hyperlipidaemia, Hypertension, Insomnia, Lipoma, Peripheral sensory neuropathy, Skin ulcer
Concomitant medications:	ACETYLSALICYLIC ACID(1), ACICLOVIR(2), ACICLOVIR(3), AMLODIPINE(4), ASPHAGEN(5), BACTRIM(6), BISACODYL(7), CANDESARTAN(8), CEFEPIME(9), DAIKENCHUTO(10), DEXAMETHASONE(11), DEXAMETHASONE(12), DEXAMETHASONE(13), DEXAMETHASONE(14), DEXAMETHASONE(15), DEXAMETHASONE(16), DEXAMETHASONE(17), DEXAMETHASONE(18), DEXCHLORPHENIRAMINE(19), DEXCHLORPHENIRAMINE(20), DEXCHLORPHENIRAMINE(21), DEXCHLORPHENIRAMINE(22), DEXCHLORPHENIRAMINE(23), DEXCHLORPHENIRAMINE(24), DEXCHLORPHENIRAMINE(25), DEXCHLORPHENIRAMINE(26), DEXCHLORPHENIRAMINE(27), DIFLUPREDNATE(28), DIFLUPREDNATE(29), ETIZOLAM(30), FUROSEMIDE(31), GENTAMICIN(32), GLUTATHIONE(33), GRANISETRON(34), GRANISETRON(35), GRANISETRON(36), GRANISETRON(37), GRANISETRON(38), GRANISETRON(39), GRANISETRON(40), GRANISETRON(41), GUAIAZULENE(42), GUAIAZULENE(43), HEPARINOID(44), HYDROCORTISONE(45), IRON(46), LANSOPRAZOLE(47), LOXOPROFEN(48), MAGNESIUM OXIDE(49), METHYLPREDNISOLONE(50), NEO NICHIPHAGEN C(51), NEO NICHIPHAGEN C(52), OLOPATADINE(53), PARACETAMOL(54), PARACETAMOL(55), PARACETAMOL(56), PARACETAMOL(57), PARACETAMOL(58), PARACETAMOL(59), PARACETAMOL(60), PARACETAMOL(61), PARACETAMOL(62), PARACETAMOL(63), PARACETAMOL(64), PARACETAMOL(65), POSTERISAN F(66), POTACOL R(67), PRAVASTATIN(68), PREGABALIN(69), SENNOSIDE A+B(70), SODIUM PICOSULFATE(71), SULFADIAZINE(72), TAIOZET(73), TEPRENONE(74), TRAMADOL(75), URSODEOXYCHOLIC ACID(76), WHITE SOFT PARAFFIN(77)
Date of first dose/last dose of study drug (Study Day):	12 SEP 2017 / 09 MAR 2018 (Study Day 179)
Other events: (MedDRA Preferred Term)	Leukocytosis, Lymphopenia, Alanine aminotransferase increased, Aspartate aminotransferase increased, Hypoalbuminaemia, Pyrexia, C-reactive protein increased, Thrombocytopenia, Anaemia, Weight increased, Oedema peripheral, Contrast media allergy, Post herpetic neuralgia, Pruritus
Date of diagnosis:	28 MAY 2016
Disease Histology:	Mycosis fungoides (CTCL)

Serious adverse events (Investigator term/MedDRA preferred term):	Herpes zoster / Herpes zoster
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):	18 FEB 2018 (Study Day 160) / 26 FEB 2018 (Study Day 168)
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, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 19, 20, 21, 22, 23, 24, 25, 26, 28, 29, 30, 31, 33, 34, 35, 36, 37, 38, 39, 40, 42, 44, 45, 46, 47, 49, 50, 51, 52, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 66, 67, 68, 69, 70, 71, 72, 76, 77
Relationship of event:	NOT 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/24/2017: Informed consent was obtained.

Sep/12/2017: The subject initiated treatment Cycle 1 with E7777 (denileukin diftitox) 9 µg/kg on Days 1 to 5 of each 3-week cycle. This was administered for five days until Day 5 on Sep/16/2017.

Feb/05/2018: Cycle 7 of the study drug treatment was administered. The study drug was administered for 5 days until Day 5 on Feb/09/2018, and the treatment was completed without any problems. Co-suspect Dexart (dexamethsone sodium phosphate) was initiated (until Feb/09/2018) for premedication of the study drug.

Feb/09/2018: Subject received the latest dose of study drug prior to the event. Co-suspect Dexart was discontinued.

Feb/15/2018: At the protocol-designed visit on Day 11 of Cycle 7, papule was noted on the left retroauricular region accompanied with mild pain. Therefore, the subject was scheduled to visit the dermatology department on Feb/19/2018.

Feb/18/2018: The onset date for the event "herpes zoster" requiring hospitalization/prolonged hospitalization. The subject was aware of aggravated pain and extensive skin eruption formation from the left side of the face to the neck, for which the subject visited the emergency outpatient department of the study site. Pyrexia of 38 °C and swelling of the left eyelid were present. In addition, papules and blisters with red halo from the head to the face, accumulated blisters from the left retroauricular region to the posterior neck, and aggregation of skin eruption (probably post-blister formation) on the upper palate were noted. Blister-like skin eruption was also noted on the few areas of the body trunk. Based on these findings, the subject was diagnosed as generalised herpes zoster and was hospitalized for

treatment. Intravenous administration of antiviral drug (aciclovir) was initiated. For the pain, oral analgesic drug was initiated.

Feb/19/2018: Qualitative analysis of varicella-zoster virus (VZV) antigen showed positive.

Feb/22/2018: An improvement tendency of the skin symptoms and pain was confirmed with continuous treatment with the intravenous antiviral drug (aciclovir) and oral analgesic drug. The scheduled protocol-designed examination (ophthalmological examination) was not conducted since the subject was under management of infection.

Feb/24/2018: For recurrent aggravated pain, dose of oral Lyrica (pregabalin) was increased.

Feb/25/2018: Intravenous treatment with antiviral drug (aciclovir) was completed.

Feb/26/2018: For neuralgia (the vicinity of the stellate ganglion as well as the pain sites in the face and neck) secondary to herpes zoster in the left neck, low-level laser irradiation and oral treatment with a drug for chronic pain (tramadol hydrochloride) were started. Since herpes zoster was almost healed, the subject was discharged. The event was reported as recovered. Study drug was continued.

Investigator's opinion on causality to the study drug:

Herpes zoster: "Not related" to the study medication.
Comments: In this case, immunosuppression due to the adrenal corticosteroid preparation (used as pre medication at the study drug administration) was considered to be involved in the onset of the event. Therefore, the causal relationship to the study drug could be ruled out.

Study:	E7777-J081-205
Subject ID:	10071001
Age, race, sex:	7[redacted] years, Japanese, Male
Medical history: (MedDRA Preferred Term)	-
Current medical conditions: (MedDRA Preferred Term)	Cataract, Cerebellar infarction, Diabetes mellitus, Dry skin, Hypertension, Tumour pain
Concomitant medications:	AMINIC /01983901/(1), AMINO ACIDS NOS W/CARBOHYDRATES NOS/07403701/(2), APIXABAN(3), APIXABAN(4), BACTRIM(5), BISOPROLOL(6), CARBOHYDRATES NOS W/POTASSIUM CHLORIDE/SODIUM(7), CARBOHYDRATES NOS W/POTASSIUM CHLORIDE/SODIUM(8), CEFTRIAXONE(9), DEXAMETHASONE(10), DEXCHLORPHENIRAMINE(11), ESOMEPRAZOLE(12), GLYCINE MAX(13), GUAIAZULENE(14), HEPARIN(15), HEPARINOID(16), HICALIQ(17), HYDROCORTISONE(18), HYDROCORTISONE(19), HYDROCORTISONE(20), LACTOBACILLUS CASEI(21), LACTOBACILLUS CASEI(22), LEVOFLOXACIN(23), LOPERAMIDE(24), LOXOPROFEN(25), LOXOPROFEN(26), LOXOPROFEN(27), MAGNESIUM SULFATE(28), METAMIZOLE(29), METAMIZOLE(30), METRONIDAZOLE(31), MIANSERIN(32), MINERIC 5(33), OFLOXACIN(34), OTHER ANTIDIARRHEALS(35), PARACETAMOL(36), POTASSIUM(37), POTASSIUM(38), POTASSIUM(39), POTASSIUM(40), RAMOSETRON(41), REBAMIPIDE(42), SITAGLIPTIN(43), SITAGLIPTIN(44), SODIUM CHLORIDE(45), TEPRENONE(46), TRAMADOL(47), URSODEOXYCHOLIC ACID(48), VITAMEDIN /00274301/(49), VITAMINS NOS(50), VOGLIBOSE(51), VOGLIBOSE(52), WHITE SOFT PARAFFIN(53), ZOLEDRONIC ACID(54)
Date of first dose/last dose of study drug (Study Day):	11 JUL 2016 / 15 JUL 2016 (Study Day 5)
Other events: (MedDRA Preferred Term)	Lymphopenia, Hypoalbuminaemia, Diarrhoea, Rash generalised, Vomiting, Pyrexia, Conjunctivitis, Perianal erythema, Delirium, Hypokalaemia, Ventricular arrhythmia
Date of diagnosis:	11 DEC 2015
Disease Histology:	Anaplastic large cell lymphoma (ALCL), ALK- (PTCL)

Serious adverse events (Investigator term/MedDRA preferred term):	Consciousness disturbed / Altered state of consciousness
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 JUL 2016 (Study Day 12) / 01 AUG 2016 (Study Day 22)
TEAE?	Yes
Serious criteria:	Requires inpatient hospitalization or prolongation of existing hospitalization
Outcome:	RECOVERED/RESOLVED
Study drug action taken/other action taken:	DRUG WITHDRAWN / Withdrawn from study
Concomitant medications (used until the start date):	3, 5, 10, 11, 12, 16, 25, 36, 41, 42, 43, 47, 48, 51
Relationship of event:	RELATED

Serious adverse events (Investigator term/MedDRA preferred term):	Consciusness disturbed / Altered state of consciousness
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 2016 (Study Day 36) / 18 AUG 2016 (Study Day 39)
TEAE?	Yes
Serious criteria:	Requires inpatient hospitalization or prolongation of existing hospitalization
Outcome:	RECOVERED/RESOLVED
Study drug action taken/other action taken:	NOT APPLICABLE / None
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, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54
Relationship of event:	NOT RELATED

Serious adverse events (Investigator term/MedDRA preferred term):	Neuropathy sensory peripheral / Peripheral sensory neuropathy
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 JUL 2016 (Study Day 12) / 17 AUG 2016 (Study Day 38)
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, 5, 10, 11, 12, 16, 25, 36, 41, 42, 43, 47, 48, 51
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."

Jun/23/2016: Informed consent was obtained.

Jul/11/2016: The subject initiated treatment with E7777 (denileukin diftitox) 9 µg/kg on Days 1 to 5 of each 3-week cycle.

Jul/15/2016: The study drug was discontinued.

Jul/20/2016: The subject was discharged. Immediately after returning home, the subject vomited.

Jul/21/2016: Malaise was enhanced. Skin eruption expanded. Diarrhoea was present.

Jul/22/2016: The onset for the events "peripheral sensory neuropathy Grade 3" and "altered state of consciousness Grade 2" was reported. Feelings of weakness in the extremities occurred, which made the subject almost bedridden. Swaying while walking and difficulty in speaking were present.

Jul/23/2016: The subject was bedridden throughout the day. Activities of daily living (ADL) were decreased, and the subject required assistance when he needed to move. Pyrexia was present.

Jul/24/2016: The subject remained bedridden, with poor response. Given difficulty in home care, the subject was hospitalized for detailed examination.

Jul/26/2016: In view of consciousness, while the level fluctuated, the subject easily opened the eyes in reaction to speech. Although the subject was able to converse, it took time to respond, with difficulty in speaking. Given fasting , continuous total parenteral nutrition was initiated. Rehabilitation intervention was initiated for peripheral sensory neuropathy disorder and motor difficulty in extremities. Continuation of the study was determined to be unfeasible. Consequently, the subject was withdrawn from the study. The event of disturbed consciousness was determined to be due to the study drug.

Jul/30/2016: Level of consciousness became alert. Difficulty in speaking was simultaneously showing recovering tendency.

//2016 No abnormalities were found on examination of cerebrospinal fluid and electromyography. Magnetic resonance imaging (MRI) and computed tomography (CT) showed no abnormality suggestive of the cause.

Aug/01/2016: General condition was stable. Meal intake was started. The disturbed consciousness Grade 2 was reported as recovered. Subject was initiated on Tetramide (mianserin hydrochloride) 10 mg for delirium and Biolactis (Lactobacillus case i) 60 mg for diarrhoea.

Aug/03/2016: Subject was initiated on Teprenone 50 mg daily for gastric prophylaxis.

Aug/04/2016: Subject was initiated on Slow-K (potassium chloride) 3600 mg for hypokalemia.

Aug/12/2016: Subject was initiated Maintate (bisoprolol fumarate) 1.25 mg for arrhythmia.

Aug/15/2016: Disturbed consciousness (second episode) was present during the night-time period of the previous day. Blood testing revealed high Ca. Subsequently, CT was performed to closely examine the suspected aggravation of tumour and central nervous system lesion. The findings showed no central nervous system lesion. There was an enlarged mass in the right lower neck, which was concluded to be the aggravated underlying disease. ADL was decreased. The subject was treated with Zometa (zoledronic acid hydrate) and Dexart (dexamethasone sodium phosphate) for the high Ca.

Aug/16/2016: The subject did not recover from the disturbed consciousness Grade 2.

Aug/17/2016: Neurologic examination was performed. In view of position sense disorder and ataxia of lower extremity, the conditions were almost within normal limits. As of this report, acute neurologic disorder that could lead to abasia was absent. The subject recovered from the peripheral sensory neuropathy Grade 3.

Aug/18/2016: The subject recovered from the disturbed consciousness Grade 2 (onset date Aug/15/2016). Ca showed a tendency towards low level. Given recovery of general condition, therapy (not specified) was resumed on the same day.

Investigator's opinion on causality to the study drug:

Altered state of consciousness (onset date of Jul/22/2016): "Related" to the study medication.

Comments: At the time of the initial onset of disturbed consciousness, Ca was within normal limits. Therefore, hypercalcaemia due to aggravated underlying disease was not the cause of the event.

Altered state of consciousness (onset date of Aug/15/2016): "Not related" to the study medication.

Comments: The event was considered to be owing to hypercalcaemia associated with aggravated underlying disease. Therefore, relationship to the study drug was ruled out.

Peripheral sensory neuropathy: "Related" to the study medication.

Comments: The cause of the onset of this event was examined closely, but the cause could not be identified. This is an event that occurred after administration of the study drug and improved after the study drug was discontinued, so a causal relationship to the study drug cannot be ruled out.

Study:	E7777-J081-205
Subject ID:	10101001
Age, race, sex:	3[redacted] years, Japanese, Male
Medical history: (MedDRA Preferred Term)	-
Current medical conditions: (MedDRA Preferred Term)	Constipation, Dry skin, Hepatic function abnormal, Hyperlipidaemia, Hypertension, Hypohidrosis
Concomitant medications:	AMLODIPINE(1), BACTRIM(2), BETAMETHASONE(3), CARBOHYDRATES NOS W/POTASSIUM CHLORIDE/SODIUM(4), CARVEDILOL(5), CHLORPHENAMINE(6), CHLORPHENAMINE(7), CHLORPHENAMINE(8), CHLORPHENAMINE(9), DEXAMETHASONE(10), DEXAMETHASONE(11), DEXAMETHASONE(12), DEXAMETHASONE(13), DEXAMETHASONE(14), DEXAMETHASONE(15), DEXAMETHASONE(16), DEXAMETHASONE(17), DIFLUPREDNATE(18), DIFLUPREDNATE(19), DL-METHIONINE W/GLYCINE/GLYCYRRHIZIC ACID(20), FLEBOBAG RING LACT(21), FUROSEMIDE(22), FUROSEMIDE(23), GLUC5% W/RINGER BAXTER(24), GRANISETRON(25), GRANISETRON(26), GRANISETRON(27), GRANISETRON(28), GRANISETRON(29), GRANISETRON(30), GRANISETRON(31), GRANISETRON(32), HEPARINOID(33), HYDROCORTISONE(34), HYDROCORTISONE(35), LEVOFLOXACIN(36), MAGNESIUM OXIDE(37), METOCLOPRAMIDE(38), PARACETAMOL(39), PARACETAMOL(40), PARACETAMOL(41), PARACETAMOL(42), PARACETAMOL(43), SENNOSIDE A+B(44), STRONG NEO-MINOPHAGEN C(45), STRONG NEO-MINOPHAGEN C(46), STRONG NEO-MINOPHAGEN C(47), URSODEOXYCHOLIC ACID(48)
Date of first dose/last dose of study drug (Study Day):	09 MAY 2016 / 07 OCT 2016 (Study Day 152)
Other events: (MedDRA Preferred Term)	Weight increased, Malaise, Nausea, Decreased appetite, Hypoalbuminaemia, Myalgia, Pyrexia, Pharyngeal inflammation
Date of diagnosis:	12 DEC 2006
Disease Histology:	Mycosis fungoides (CTCL)

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):	14 MAY 2016 (Study Day 6) / 30 MAY 2016 (Study Day 22)
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, 5, 6, 10, 18, 22, 25, 33, 34, 39, 45, 46
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):	14 MAY 2016 (Study Day 6) / 30 MAY 2016 (Study Day 22)
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, 5, 6, 10, 18, 22, 25, 33, 34, 39, 45, 46
Relationship of event:	RELATED

Narrative

A 3[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/01/2016: Informed consent was obtained.
Apr/14/2016: Another informed consent was obtained. Screening test was performed.
May/06/2016: The subject was hospitalized, as scheduled, prior to initiation of the study drug.
May/09/2016: The subject initiated treatment with E7777 (denileukin diftitox) 9 µg/kg on Days 1 to 5 of each 3-week cycle. Stronger Neo-Minophagen C as concomitant prophylactic treatment was initiated.
May/13/2016: The study drug was administered on Cycle 1 Day 5. Stronger Neo-Minophagen C was as concomitant prophylactic treatment was continued.
May/14/2016: The subject experienced increased AST (Grade 3) and increased ALT (Grade 3) (see labs) and was hospitalized. Stronger Neo-Minophagen C was continued.
May/16/2016: Blood test resulted in further increased AST/ALT (see labs), based on which hospitalization was determined to be prolonged. Given nausea and anorexia, oral intake decreased, due to which fluid replacement therapy was initiated. Malaise and myalgia of back and lower extremities were noted.
May/17/2016: Because pyrexia around 37.5 °C was noted, Solu-Cortef (hydrocortisone sodium succinate) 100 mg was administered.
May/18/2016: Blood test showed an improving tendency in AST and ALT levels (see labs). Fluid replacement therapy continued and Stronger Neo-Minophagen C were continued.
May/19/2016: Pyrexia subsided to 36's °C, and myalgia and malaise were mitigated.
May/21/2016: Appetite was regained, which increased oral intake; therefore, fluid replacement was reduced.
May/23/2016: Since AST and ALT levels further improved (see labs), Urso (ursodeoxycholic acid) and Glycyron were initiated. Pyrexia of 38.6 °C

was noted, but the findings by which infection was suspected, were not clear. Therefore, the course observation was decided and the subject was thus discharged. Stronger Neo-Minophagen C discontinued.

May/30/2016: AST and ALT levels further improved (31/93). Cycle 2 was started, and the following were assessed: the subject recovered from the increased AST; as for the increased ALT, ALT recovered to the same level as that of the pre-treatment. The subject was reported as recovered from the increased AST (Grade 3) and increased ALT (Grade 3).

Investigator's opinion on causality to the study drug:

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

Comments: Hepatic function disorder and mild hepatic steatosis were previously pointed out after Oxsoralen (methoxsalen) for treatment of the underlying disease. At the time of hospitalization before initiation of the study drug, AST and ALT were 33 and 57, respectively. The events were reportedly known as well as highly frequently-occurred adverse events; even though the events were known, the causality between the study drug and the events could not be ruled out.

Study:	E7777-J081-205
Subject ID:	10131001
Age, race, sex:	5[redacted] years, Japanese, Male
Medical history: (MedDRA Preferred Term)	-
Current medical conditions: (MedDRA Preferred Term)	Anaemia, Anogenital warts, Astigmatism, Cataract, Cheilitis, Cough, Dry eye, Eosinophil count increased, Glaucoma, Insomnia, Keratitis, Neutropenia, Pruritus, Thrombocytopenia
Concomitant medications:	AMBROXOL(1), AMINO ACIDS NOS W/CARBOHYDRATES NOS/07403701/(2), AUGMENTIN /00756801/(3), BACTRIM(4), BEPOTASTINE(5), BROTIZOLAM(6), CEFEPIME(7), CEFTRIAXONE(8), CHLORPHENAMINE(9), CHLORPHENAMINE(10), CHLORPHENAMINE(11), CHLORPHENAMINE(12), CHLORPHENAMINE(13), CHLORPHENAMINE(14), CHLORPHENAMINE(15), CHLORPHENAMINE(16), CHLORPHENAMINE(17), CHLORPHENAMINE(18), DEXAMETHASONE(19), DEXAMETHASONE(20), DEXAMETHASONE(21), DEXAMETHASONE(22), DEXAMETHASONE(23), DEXAMETHASONE(24), DEXAMETHASONE(25), DIFLUPREDNATE(26), DIMEMORFAN(27), DIPHENHYDRAMINE(28), DOMIPHEN(29), DOMIPHEN(30), EPINASTINE(31), FEXOFENADINE(32), FLURBIPROFEN(33), FLURBIPROFEN(34), FOLIC ACID(35), FUROSEMIDE(36), FUROSEMIDE(37), GRANISETRON(38), GRANISETRON(39), GRANISETRON(40), GRANISETRON(41), GRANISETRON(42), GUALENIC ACID(43), HEPARINOID(44), HEPARINOID(45), HYALURONIC ACID(46), HYDROXYZINE(47), LANSOPRAZOLE(48), LEVOFLOXACIN(49), LEVOFLOXACIN(50), LEVOFLOXACIN(51), LOXOPROFEN(52), LOXOPROFEN(53), LOXOPROFEN(54), MECOBALAMIN(55), METOCLOPRAMIDE(56), NEO NICHIPHAGEN C(57), OLANZAPINE(58), OSMOSAL /00501801/(59), OSMOSAL /00501801/(60), PARACETAMOL(61), PARACETAMOL(62), PARACETAMOL(63), PARACETAMOL(64), PARACETAMOL(65), PARACETAMOL(66), PARACETAMOL(67), PARACETAMOL(68), PARACETAMOL(69), PARACETAMOL(70), PARACETAMOL(71), PENTAZOCINE(72), PIP/TAZO(73), PIPERACILLIN W/TAZOBACTAM /01606301/(74), PLATELETS(75), RINGER-LACTATE(76), SENNOSIDE A+B(77), STRONG NEO-MINOPHAGEN C(78), SULPERAZON(79), VALGANCICLOVIR(80), VIDARABINE(81)
Date of first dose/last dose of study drug (Study Day):	10 APR 2017 / 04 AUG 2017 (Study Day 117)
Other events: (MedDRA Preferred Term)	Alanine aminotransferase increased, Aspartate aminotransferase increased, Neutropenia, Tumour associated fever, Lymphopenia, Nausea, Peripheral sensory neuropathy, Parotitis, Vomiting, Decreased appetite, Dehydration, Malaise, Thrombocytopenia, Gamma-glutamyltransferase increased, Oropharyngeal pain, Hypoalbuminaemia, Cytomegalovirus test positive, Upper respiratory tract infection, Amylase increased, Pyrexia, Proteinuria, Angular cheilitis, Upper respiratory tract inflammation, Colitis, Stomatitis
Date of diagnosis:	25 APR 2007
Disease Histology:	Angioimmunoblastic T-cell lymphoma (PTCL)

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):	19 JUN 2017 (Study Day 71) / 23 JUN 2017 (Study Day 75)
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, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 19, 20, 21, 22, 26, 27, 28, 29, 30, 31, 32, 35, 36, 38, 39, 40, 44, 46, 47, 48, 49, 52, 53, 55, 57, 58, 59, 61, 62, 63, 64, 65, 66, 73, 76, 78, 80, 81
Relationship of event:	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."

Mar/17/2017: Informed consent was obtained.

Apr/10/2017: The subject initiated treatment with E7777 (denileukin diftitox) 9 µg/kg (601 µg) on Days 1 to 5 of each 3-week cycle.

Jun/19/2017: On Day 8 of Cycle 3, the subject visited the study site on an outpatient basis. At 10:30, the subject had fever (Grade 2) of 39.4 °C. Oral Loxoprofen 60 mg was administered. At 11:40, the body temperature subsided to 37.8 °C. However, taking his safety into consideration, the subject was hospitalized. Drip infusion of Ceftriaxone Na (ceftriaxone sodium) was initiated. Blood culture test was performed, which showed a negative result. At 21:08, the subject had pyrexia of 38.6 °C. Oral Calonal (acetaminophen) 600 mg was administered.

Jun/20/2017: At 07:01, the subject had fever of 38.1 °C. Oral Calonal 600 mg was administered. Oral Levofloxacin 500 mg was initiated. At 09:46, the body temperature subsided to 35.8 °C. At 14:41, the subject had pyrexia of 37.6 °C. Oral Calonal 600 mg was administered. At 19:58, the body temperature subsided to 36.5 °C.

Jun/21/2017: At 06:34, the body temperature was 35.8 °C.

Jun/22/2017: At 06:21, the body temperature was 36.7 °C.

Jun/23/2017: At 07:17, the body temperature was 36.1 °C. Defervescence was maintained for three days. Consequently, the subject was discharged. Drip infusion of Ceftriaxone Na was completed. The tracking of the serious adverse event was completed as of this report. The subject recovered from the fever (Grade 2).

Aug/05/2017: The subject experienced abdominal pain due to suspected coliits (non-serious). The investigator deemed the suspected non serious colitis as related to the study drug.

Aug/15/2017: The subject recovered from the suspected colitis.

Investigator's opinion on causality to the study drug:

Fever: "Related" to the study medication.

Comments: The subject had repeatedly experienced pyrexia after the initiation of the study drug until the time of the report. Therefore, the study drug was considered to be related to the event.

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

Fever: Given the subjects underlying malignancy and considering that additional event details and circumstances were not provided, we would consider the event of pyrexia as "Not Related" to the study medication. Considering the recovery of the event after the treatment with antibiotics, suggestive of infectious etiology, in a subject with T cell lymphoma, that could be contributory.

Study:	E7777-J081-205
Subject ID:	10131002
Age, race, sex:	4[redacted] years, Japanese, Male
Medical history: (MedDRA Preferred Term)	-
Current medical conditions: (MedDRA Preferred Term)	Astigmatism, Dyslipidaemia, Pruritus, Seasonal allergy
Concomitant medications:	ATROPA BELLADONNA TOTAL ALKALOID EXTRACT W/CA(1), BEPOTASTINE(2), BROTIZOLAM(3), CHLORPHENAMINE(4), CHLORPHENAMINE(5), CHLORPHENAMINE(6), CHLORPHENAMINE(7), CHLORPHENAMINE(8), CHLORPHENAMINE(9), CHLORPHENAMINE(10), CHLORPHENAMINE(11), CLOBETASONE(12), CROTAMITON(13), DEXAMETHASONE(14), DEXAMETHASONE(15), DEXAMETHASONE(16), DEXAMETHASONE(17), DEXAMETHASONE(18), DEXAMETHASONE(19), DEXAMETHASONE(20), DEXAMETHASONE(21), DIFLUPREDNATE(22), GRANISETRON(23), GRANISETRON(24), GRANISETRON(25), GRANISETRON(26), GRANISETRON(27), GRANISETRON(28), GRANISETRON(29), GRANISETRON(30), MAGNESIUM OXIDE(31), NASAL /06166901/(32), NEO NICHIPHAGEN C(33), NEO NICHIPHAGEN C(34), PARACETAMOL(35), PARACETAMOL(36), PARACETAMOL(37), PARACETAMOL(38), PARACETAMOL(39), PARACETAMOL(40), PARACETAMOL(41), PARACETAMOL(42), ROSUVASTATIN(43), ROSUVASTATIN(44), SENNOSIDE A+B(45), STRONG NEO-MINOPHAGEN C(46), SULFADIAZINE(47), URSODEOXYCHOLIC ACID(48), URSODEOXYCHOLIC ACID(49), WHITE SOFT PARAFFIN(50), ZOLPIDEM(51)
Date of first dose/last dose of study drug (Study Day):	03 APR 2017 / 06 OCT 2017 (Study Day 187)
Other events: (MedDRA Preferred Term)	Skin erosion, Constipation, Decreased appetite, Malaise, Myalgia, Alanine aminotransferase increased, Aspartate aminotransferase increased, Gamma-glutamyltransferase increased, Hypoalbuminaemia, Vomiting, Blood alkaline phosphatase increased, Lipase increased, Insomnia, Blood creatine phosphokinase increased, Hypertension
Date of diagnosis:	25 APR 2016
Disease Histology:	Mycosis fungoides (CTCL)

Serious adverse events (Investigator term/MedDRA preferred term):	enlarged left groin lymph node / Lymphadenopathy
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):	04 JUL 2017 (Study Day 93) / 26 JUL 2017 (Study Day 115)
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 / None
Concomitant medications (used until the start date):	1, 2, 4, 5, 6, 7, 12, 13, 14, 15, 16, 17, 22, 23, 24, 25, 26, 31, 32, 33, 34, 35, 36, 37, 38, 43, 44, 45, 46, 47, 48, 49, 50, 51
Relationship of event:	NOT RELATED

Narrative

A 4[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."

Mar/21/2017: Signed informed consent form was obtained from the subject.

Mar/31/2017: Tumour assessment at baseline. Target lesion (1) inguinal nodes (right): 15mm×11mm (2) inguinal nodes (left): 20mm×10mm.

Apr/03/2017-Apr/07/2017: The subject initiated treatment with E7777 (denileukin diftitox) 9 µg/kg on Days 1 to 5 of each 3-week cycle.

May/08/2017-May/12/2017: The study drug 9 µg/kg was administered.

May/23/2017: Initial assessment of tumour response. Target lesion (1) inguinal nodes (right): 8mm×6mm (2) inguinal nodes (left): 8mm×7mm. Overall tumour response was assessed as partial response (PR) and the study was continued.

May/29/2017-Jun/02/2017: The study drug 9 µg/kg was administered.

Jun/19/2017-Jun/23/2017: The study drug 9 µg/kg was administered.

Jul/05/2017: Second assessment of tumour response. Target lesion (1) inguinal nodes (right): 9mm×6mm (2) inguinal nodes (left): 18mm×10mm. Enlarged left groin lymph node with redness was noted. Tenderness was also noted on palpation. At least 50% increase in the sum of products of diameters (SPD) was confirmed and thus the tumour response was assessed as progressive disease (PD); however detailed examination with biopsy was scheduled and the assessment was suspended.

Jul/10/2017: Biopsy of left inguinal nodes was performed.

Jul/20/2017: Pathology results showed peripheral T-cell lymphoma (PTCL) and the tumour response was assessed as PD.

Jul/21/2017: On physical examination, left groin nodes showed improvement tendency with no redness or tenderness on palpation. Repeat computerized tomography (CT) scan was scheduled for tumour response and the assessment was suspended.

Jul/25/2017: CT scan was performed.

Jul/26/2017: Reassessment of tumour response. Target lesion (1) inguinal nodes (right): 9mm×5mm (2) inguinal nodes (left): 15mm×6mm. Left groin nodes found on CT (Jul/05/2017) were considered to be transient inflammation. Overall tumour response was assessed as PR based on 30% increase in SPD and the study was continued. The enlarged left groin lymph node was reported as recovered.

Investigator's opinion on causality to the study drug:

Lymphadenopathy: "Not related" to the study medication.
Comments: On assessment of tumour response (Jul/05/2017), left groin nodes were noted

and thus overall response was initially assessed as PD. However, left groin nodes improved in the subsequent course and overall response was assessed as PR on reassessment (Jul/26/2017) and therefore the event was considered to be due to tumour enlargement associated with transient inflammation. Transient inflammation was likely to have occurred accidentally and therefore was considered unrelated to the study drug.

Study:	E7777-J081-205
Subject ID:	10141003
Age, race, sex:	3[redacted] years, Japanese, Female
Medical history: (MedDRA Preferred Term)	-
Current medical conditions: (MedDRA Preferred Term)	Alopecia, Conjunctivitis, Insomnia, Lymphopenia, Pruritus, Tumour associated fever, Uterine leiomyoma
Concomitant medications:	BETAMETHASONE(1), BILASTINE(2), CARBOHYDRATES NOS W/POTASSIUM CHLORIDE/SODIUM(3), CLOBETASOL(4), DEXAMETHASONE(5), DEXCHLORPHENIRAMINE(6), DEXCHLORPHENIRAMINE(7), DEXTROSE AND SODIUM CHLORIDE INJECTION(8), DICLOFENAC(9), EPINEPHRINE(10), ESOMEPRAZOLE(11), FENTANYL(12), FEXOFENADINE(13), FLUNITRAZEPAM(14), FLUOROMETHOLONE(15), FLURBIPROFEN(16), FUROSEMIDE(17), GENTAMICIN(18), HALOPERIDOL(19), HEPARIN(20), HEPARINOID(21), HYDROXYZINE(22), I.V. SOLUTIONS(23), KETOCONAZOLE(24), LANSOPRAZOLE(25), LEVOFLOXACIN(26), LOXOPROFEN(27), MAGNESIUM OXIDE(28), MENTHOL(29), METHYLPREDNISOLONE(30), MIDAZOLAM(31), NEO NICHIPHAGEN C(32), PARACETAMOL(33), PARACETAMOL(34), PENTAZOCINE(35), PREDNISOLONE(36), RAMOSETRON(37), RINGER-LACTATE(38), SENNOSIDE A+B(39), SODIUM BICARBONATE(40), SODIUM BICARBONATE(41), TEPRENONE(42), TRAMADOL(43), UNACID /00917901/(44), URSODEOXYCHOLIC ACID(45), WHITE SOFT PARAFFIN(46), ZOLPIDEM(47)
Date of first dose/last dose of study drug (Study Day):	13 NOV 2017 / 17 NOV 2017 (Study Day 5)
Other events: (MedDRA Preferred Term)	Constipation, Generalised oedema, Hypoalbuminaemia, Pain, Blood cholesterol increased, Hyperglycaemia, Hypertriglyceridaemia, Genital candidiasis, Hyperkalaemia, Thrombocytopenia
Date of diagnosis:	28 AUG 2017
Disease Histology:	Mycosis fungoides (CTCL)

Serious adverse events (Investigator term/MedDRA preferred term):	Capillary leak sybdrome / Capillary leak syndrome
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):	18 NOV 2017 (Study Day 6) / -
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 / None
Concomitant medications (used until the start date):	1, 2, 4, 5, 6, 7, 13, 15, 17, 18, 21, 26, 28, 29, 32, 33, 37, 39, 45, 46, 47
Relationship of event:	RELATED

Serious adverse events (Investigator term/MedDRA preferred term):	Drug-induced pneumonia / Pneumonia
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):	18 NOV 2017 (Study Day 6) / -
TEAE?	Yes
Serious criteria:	Requires inpatient hospitalization or prolongation of existing hospitalization
Outcome:	NOT RECOVERED/NOT 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, 13, 15, 17, 18, 21, 26, 28, 29, 32, 33, 37, 39, 45, 46, 47
Relationship of event:	RELATED

Serious adverse events (Investigator term/MedDRA preferred term):	rhabdomyolysis / Rhabdomyolysis
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 2017 (Study Day 9) / 23 NOV 2017 (Study Day 11)
TEAE?	Yes
Serious criteria:	Requires inpatient hospitalization or prolongation of existing hospitalization
Outcome:	NOT RECOVERED/NOT RESOLVED
Study drug action taken/other action taken:	NOT APPLICABLE / Treatment given
Concomitant medications (used until the start date):	1, 2, 3, 4, 5, 6, 7, 9, 11, 12, 13, 14, 15, 16, 17, 18, 21, 22, 25, 26, 27, 28, 29, 30, 32, 33, 34, 35, 36, 37, 38, 39, 42, 43, 44, 45, 46, 47
Relationship of event:	RELATED

Serious adverse events (Investigator term/MedDRA preferred term):	rhabdomyolysis / Rhabdomyolysis
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 NOV 2017 (Study Day 11) / 23 NOV 2017 (Study Day 11)
TEAE?	Yes
Serious criteria:	Death
Outcome:	FATAL
Study drug action taken/other action taken:	NOT APPLICABLE / Treatment given
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, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47
Relationship of event:	RELATED

Narrative

A 3[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."

Oct/17/2017: Informed consent was obtained.

Nov/13/2017: The subject initiated treatment with E7777 (denileukin diftitox) 9 μg/kg on Days 1 to 5 of each 3-week cycle. Glycyron and ursodeoxycholic acid were concomitantly used.

Nov/17/2017: On Day 5 of Cycle 1, the study drug was completed.

Nov/18/2017: Subject experienced drug-induced pneumonia Grade 3 and capillary leak syndrome Grade 3 requiring/prolonging hospitalization. Hypoalbuminaemia occurred. The subject had chief complaints of respiratory discomfort, oedema and malaise. Chest X-ray and computed tomography (CT) as well as blood test were performed, based on which pneumonia was suspected. Because of increased weight due to oedema, furosemide was initiated.

Nov/19/2017: Because of persistent respiratory discomfort, consultation with the pulmonary medicine department was made. Chest X-ray and CT were performed, which revealed worsening of the shadow in the bilateral lung fields and progression of respiratory failure. Predonine (prednisolone) 60 mg was administered and steroid pulse therapy as well as oxygen inhalation were initiated thereafter. Since the subject was considered to have developed drug-induced pneumonia, she was withdrawn from the study.

Nov/20/2017: For mild cardiomegaly and decreased albumin, consultation with the cardiovascular medicine department was made. Echocardiography was performed. Cardiac failure and pulmonary hypertension were excluded. A blood test was negative for beta-D-glucan and KL-6. Oral drugs except that/those as-needed were discontinued, and switched to an intravenous drug (s). Lasix 20 mg/2 mL and Yucion-S(ampicillin sodium/sulbactam sodium) 1.5 g were concomitantly administered.

Nov/21/2017: The subject experienced rhabdomyolysis. Capillary leak syndrome-triggered rhabdomyolysis, was suspected according to the blood test result, which showed increased CK and blood partially seen in the urine. Since the onset of renal failure was expected, consultation was made with the nephrology department. The subject had a chief complaint of generalised pain (mainly in the thighs). Pain relieving drug(s) was used, but with no effect. Computed tomography (CT) of the chest, abdomen and extremities was performed for differentiation from thrombosis, based on which deep vein thrombosis (DVT) was ruled out. Increase of the infusion volume was instructed. Due to poor pain control, consultation was made with the palliative care team. Drip infusion of Acelio (acetaminophen) 1000 mg and administration of oral Tramal (tramadol hydrochloride) 25 mg were instructed. Since no effect was noted with the two drugs, drip infusion of fentanyl (100 μg) was performed with an instruction that one-hour dosage should be administered at the time of pain. Steroid pulse therapy was completed. Oxygen inhalation was continued. The subject was placed under observation.

Nov/22/2017: High creatine kinase (CK) persisted. Myoglobinuria was highly likely based on the urine test result and the subject was diagnosed as

rhabdomyolysis. Pain and sedation control was continued with Fentanyl, Serenace (haloperidol), and midazolam. CMV infection test was negative.

Nov/23/2017: Early in the morning, heart rate rapidly decreased. The subject was found to have cardiac arrest. The subject's nurse called the duty doctor at the intensive care unit (ICU). Cardiac massage was started. Continuation of resuscitation was attempted, but with difficulty; the subject's family requested for discontinuation of resuscitation. The subject died of rhabdomyolysis Grade 5, cause of death reported as same. The subject did not recover from the drug-induced pneumonia Grade 3 or the capillary leak syndrome Grade 3. Autopsy was scheduled for Nov/24.

Nov/24/2017: Autopsy was performed. Findings at gross pathology showed multiple sites of haemorrhage from the muscle tissues in the fascia, with muscular discolouration. (see relevant Lab tests/data).

Investigator's opinion on causality to the study drug:

Rhabdomyolysis: "Related" to the study medication
Comments: Based on the autopsy diagnosis and report on findings, the following summary was made:

- Autopsy demonstrated myoglobin deposits in the renal tubules; the finding was consistent with rhabdomyolysis.

- As for atrophy of the right rectus femoris, the appearance might have been that of post-rhabdomyolysis.

- The direct death cause could not be made clear pathologically. Certain toxicity of the study drug or rapid change in the ion balance associated with rhabdomyolysis might have caused cardiac arrest.

In addition to the above, the onset was after initiation of the study drug, and the event was reported in ONTAK (E7272). Therefore, the causal relationship of the study drug to the event could not be ruled out.

Pneumonia: "Related" to the study medication
Comments: The event developed in an early stage after the initial administration of the study drug. Based on the consultations with the other departments, the causal relationship between the event and the study drug could not be ruled out.

Capillary leak syndrome: "Related" to the study medication
Comments: Based on the autopsy diagnosis and report on findings, capillary leak syndrome was likely to have been present locally. However, since the severity of generalised oedema was not high enough, generalised capillary leak syndrome was reported to be unlikely. However, the event developed after initiation of the study drug. Furthermore, the event was reported in 3 cases in the 205 trial. Therefore, although not the direct cause, the study drug

could not be ruled out as the causative agent. (Capillary leak syndrome developed in 3 out of 23 patients)

Study:	E7777-J081-205
Subject ID:	10191002
Age, race, sex:	8[redacted] years, Japanese, Male
Medical history: (MedDRA Preferred Term)	Gastric cancer, Thyroid neoplasm
Current medical conditions: (MedDRA Preferred Term)	Back pain, Cholelithiasis, Constipation, Gamma-glutamyltransferase increased, Pruritus, Rash
Concomitant medications:	ACICLOVIR(1), ALBUMIN HUMAN(2), AMINO ACIDS NOS W/ELECTROLYTES NOS/GLUCOSE/TH(3), AMINO ACIDS NOS W/ELECTROLYTES NOS/GLUCOSE/TH(4), BACTRIM(5), DEXAMETHASONE(6), DEXCHLORPHENIRAMINE(7), FUROSEMIDE(8), FUROSEMIDE(9), GRANISETRON(10), HEPARINOID(11), ITRACONAZOLE(12), LANSOPRAZOLE(13), LOXOPROFEN(14), MAGNESIUM OXIDE(15), PARACETAMOL(16), PARACETAMOL(17), PARACETAMOL(18), RINGER-LACTATE(19), SOLACET F(20), UNACID /00917901/(21), URSODEOXYCHOLIC ACID(22)
Date of first dose/last dose of study drug (Study Day):	28 AUG 2017 / 01 SEP 2017 (Study Day 5)
Other events: (MedDRA Preferred Term)	Aspartate aminotransferase increased, Blood alkaline phosphatase increased, Blood urea increased, Gamma-glutamyltransferase increased, Lymphopenia, Oedema peripheral, Thrombocytopenia, Alanine aminotransferase increased, Hypertriglyceridaemia, Hypoalbuminaemia, Vomiting, Leukopenia, Neutropenia, Blood lactate dehydrogenase increased, Tumour associated fever
Date of diagnosis:	09 FEB 2017
Disease Histology:	Peripheral T-cell lymphoma, NOS (PTCL)

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):	17 SEP 2017 (Study Day 21) / -
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, 3, 5, 6, 7, 8, 10, 11, 12, 13, 14, 15, 16, 17, 19, 22
Relationship of event:	NOT RELATED

Narrative

An 8[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/01/2017: Informed consent was obtained for the study of E7777.

Aug/28/2017: The subject initiated treatment with E7777 (denileukin diftitox) 9 µg/kg on Days 1 to 5 of each 3-week cycle.

Sep/01/2017: Subject received the last dose of E7777 (denileukin diftitox) 9 µg/kg.

Sep/17/2017: Fever, nausea, and feelings of weakness occurred at home. The nausea, vomiting, and feelings of weakness were likely to be due to fever. Consequently, the subject was emergently transported to a hospital. The subject had one episode of vomiting while in the ambulance. At 15:25, the subject was emergently hospitalized. He was in a hazy state. When hospitalized, the subject was placed on an oxygen mask. A blood test was performed. Body temperature was monitored throughout the day. At 16:27, a chest X-ray was taken with a portable X-ray machine. Acelio 0.5 vial was administered. The level of consciousness returned to normal. The subject received Solulact (lactated ringer's solution) 500 mL and intravenous infusion of B fluid (total electrolyte with amino acid and vitamin B1) 500 mL. Fever subsided, and the subject's level of consciousness improved. The oxygen saturation (SpO_2) improved; thus, the amount of oxygen given to the subject was reduced.

Sep/18/2017: Chest X-ray were performed (see labs). Blood and urine culture tests were performed (see labs). The subject received antibiotic of Unasyn-S (ampicillin sodium/sulbactam sodium) at two doses, Solulact 500 mL, and intravenous infusion of Bfluid 500 mL.

Sep/19/2017: It was the scheduled administration date on Day 1 of Cycle 2. However, the administration of the study drug was postponed. At 06:22, the body temperature was 36.1 °C. A blood test, urine collection, electrocardiogram, and X-ray were performed (results not provided). The subject received antibiotic of Unasyn-S and intravenous infusion of Bfluid 500 mL.

Sep/20/2017 - Sep/25/2017: The subject continued to receive antibiotic of Unasyn-S. The body temperature was in the range between 35 and 37 °C.

Sep/21/2017: A blood test was performed, which showed an improving tendency in the white blood cell count.

Sep/22/2017: Fluid replacement therapy was completed.

Sep/25/2017: A blood test was performed, which showed an improving tendency in the white blood cell count. Antimicrobial therapy was completed.

Sep/26/2017: Computed tomography (CT) was performed in search for the cause of the fever. The body temperature was in the range between 35 and 39 °C. The fever was of 39.8 °C, which was considered to be due to tumour associated fever. Event fever was not recovered.

Sep/27/2017: Impression of the findings on the CT scans obtained on Sep/26 did not suggest the cause of the fever. Tumor response was evaluated as progressive disease (PD) based on the new onset of lesion and tumour enlargement. Thus, the study drug was discontinued. The body temperature was in the range between 35 and 37 °C.

Sep/28/2017: The body temperature was in the range between 35 and 37 °C. The fever was suspected to be infectious, which however could not be determined. Symptomatic stability was considered to occur. The hospitalization would be continued for treatment of the underlying disease.

Investigator's opinion on causality to the study drug:

Fever: "Not related" to the study medication.
Comments: Upon review, since the fever was suspected to be infectious, the causality of the study drug to the event was ruled out

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）

Subject ID	性別	初回発現時年齢	MedDRA 基本語 (V22.0)	発現日 (Day)	発現時用量	持続期間	転帰	因果関係	治験薬の処置	重篤分類
20011004	男性	6[redacted]	急性汎発性発疹性膿疱症	11	9 µg/kg	26	軽快	おそらく関連あり	投与中断	入院
10051018	女性	7[redacted]	自己免疫障害	407	NA	NA	軽快	関連あり	該当せず	医学的に重要な事象
			毛細血管漏出症候群	8	9 µg/kg	14	回復	関連あり	投与中止	入院
20011005	男性	6[redacted]	発熱	22	9 µg/kg	1	回復	おそらく関連あり	投与中止	入院
10011007	男性	5[redacted]	悪性新生物進行	33	NA	NA	死亡	関連なし	該当せず	死亡
			脱水	21	NA	1	回復	関連なし	該当せず	入院
			下痢	21	NA	1	回復	関連あり	該当せず	入院
20011008	男性	7[redacted]	毛細血管漏出症候群	30	9 µg/kg	38	回復	おそらく関連あり	投与中止	入院，入院期間の延長
			注入に伴う反応	9	9 µg/kg	10	回復	関連あるかもしれない	投与中止	入院
			ブドウ球菌性菌血症	38	4.5 µg/kg	30	回復	関連なし	投与中止	入院期間の延長
10051022	女性	7[redacted]	急性腎障害	32	NA	22	死亡	関連あり	該当せず	死亡
			毛細血管漏出症候群	29	NA	NA	未回復	関連あり	該当せず	入院
			サイトメガロウイルス血症	35	NA	NA	未回復	関連あり	該当せず	入院期間の延長
			筋力低下	15	9 µg/kg	7	回復	関連あり	該当せず	入院
			低アルブミン血症	16	9 µg/kg	NA	軽快	関連あり	該当せず	入院
			低血圧	10	9 µg/kg	4	回復	関連あり	投与中止	入院
			肺炎	29	NA	NA	未回復	関連あり	該当せず	入院期間の延長
			頻脈	10	9 µg/kg	4	回復	関連あり	該当せず	入院
20011009	男性	4[redacted]	注入に伴う反応	1	9 µg/kg	22	回復	おそらく関連あり	投与中止	入院，入院期間の延長
20011013	男性	7[redacted]	譫妄	25	NA	15	回復（後遺症あり）	関連なし	投与中止	入院期間の延長
			悪心	24	9 µg/kg	16	回復	おそらく関連あり	投与中止	入院
			顔面骨骨折	2	9 µg/kg	6	回復（後遺症あり）	関連なし	投与中止	入院
			嘔吐	24	9 µg/kg	16	回復	おそらく関連あり	投与中止	入院
10101004	男性	3[redacted]	ブドウ球菌性敗血症	25	Not provided	NA	軽快	関連なし	投与中止	入院期間の延長

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）

Subject ID	性別	初回発現時年齢	MedDRA 基本語 (V22.0)	発現日 (Day)	発現時用量	持続期間	転帰	因果関係	治験薬の処置	重篤分類
20011012	男性	[redacted]	注入に伴う反応	30	9 µg/kg	4	回復	関連あるかもしれない	投与中止	入院
10131001	男性	[redacted]	毛細血管漏出症候群	5	9 µg/kg	NA	回復	関連あり	投与中止	入院
10081002	男性	[redacted]	腹痛	50	Not provided	3	回復（後遺症あり）	関連なし	投与中止	入院
			胆嚢炎	75	Not provided	NA	未回復	関連なし	該当せず	入院
			不全片麻痺	55	Not provided	8	回復（後遺症あり）	関連あり	投与中止	入院
10101005	男性	[redacted]	甲状腺炎	1 ヵ月	9 µg/kg	10	回復	関連あり	投与中止	入院
10111004	男性	[redacted]	急性呼吸不全	164	9 µg/kg	NA	死亡	関連なし	該当せず	死亡
			精神状態変化	127	9 µg/kg	NA	未回復	関連あり	該当せず	入院
			深部静脈血栓症	138	9 µg/kg	NA	未回復	関連なし	該当せず	入院期間の延長
			頭蓋内出血	143	9 µg/kg	NA	未回復	関連なし	該当せず	入院期間の延長
			JC ウイルス感染	141	9 µg/kg	NA	未回復	関連あり	該当せず	入院期間の延長
			外耳炎	124	9 µg/kg	NA	未回復	関連なし	投与中止	入院
			湿性咳嗽	141	9 µg/kg	NA	未回復	関連なし	該当せず	入院期間の延長
			耳帯状疱疹	127	9 µg/kg	NA	未回復	関連あり	該当せず	入院
			腹壁血腫	26	9 µg/kg	7	回復	関連なし	投与継続	入院
			脳幹卒中	152	9 µg/kg	NA	未回復	関連なし	該当せず	入院期間の延長
			痙攣発作	164	9 µg/kg	NA	死亡	関連なし	該当せず	死亡
			帯状疱疹性髄膜脳炎	127	9 µg/kg	NA	未回復	関連あり	該当せず	入院
10101008	男性	[redacted]	毛細血管漏出症候群	8	9 µg/kg	3	回復	関連あり	投与中止	入院
			注入に伴う反応	8	9 µg/kg	3	回復	関連あり	投与中止	入院
10181001	女性	[redacted]	急性腎障害	45	9 µg/kg	NA	軽快	関連なし	該当せず	入院
			毛細血管漏出症候群	12	9 µg/kg	NA	未回復	関連あり	投与中止	入院
			疼痛	45	9 µg/kg	NA	軽快	関連なし	該当せず	入院
			ブドウ球菌感染	35	9 µg/kg	NA	未回復	関連あり	該当せず	入院
			白血球増加症	45	9 µg/kg	NA	軽快	関連なし	該当せず	入院

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）

Subject ID	性別	初回発現時年齢	MedDRA 基本語 (V22.0)	発現日 (Day)	発現時用量	持続期間	転帰	因果関係	治験薬の処置	重篤分類
10181005	男性	4[redacted]	霧視	15	9 µg/kg	NA	不明	関連あり	投与中止	医学的に重要な事象
			毛細血管漏出症候群	9	9 µg/kg	NA	軽快	関連あり	投与中止	医学的に重要な事象，入院
10101006	女性	6[redacted]	末梢性浮腫	95	9 µg/kg	3	回復	関連あり	該当せず	入院
			血中アルカリホスファターゼ増加	95	9 µg/kg	3	回復	関連あり	該当せず	入院
			四肢痛	95	9 µg/kg	3	回復	関連なし	該当せず	入院
			敗血症	87	9 µg/kg	3	回復	関連なし	該当せず	入院
10121004	男性	6[redacted]	皮膚感染	154	9 µg/kg	2	回復	関連なし	投与中止	入院
10131004	男性	6[redacted]	悪寒	24	9 µg/kg	4	回復	関連あり	投与中止	入院
			敗血症	71	9 µg/kg	24	回復	関連なし	投与中止	入院
			頻脈	24	9 µg/kg	4	回復	関連あり	投与中断	入院
20021002	女性	6[redacted]	注入に伴う反応	3	9 µg/kg	33	回復	関連あり	投与中止	入院
			下気道感染	21	9 µg/kg	15	回復	関連なし	投与継続	入院
10011008	男性	7[redacted]	毛細血管漏出症候群	5	9 µg/kg	4	回復	関連あり	投与中止	入院
			注入に伴う反応	3	9 µg/kg	6	回復	関連あり	投与中止	入院
10141002	女性	6[redacted]	毛細血管漏出症候群	8	9 µg/kg	4	回復	関連あり	投与中止	入院
10051024	女性	5[redacted]	悪心	55	9 µg/kg	NA	未回復	関連なし	該当せず	入院
			敗血症性ショック	61	9 µg/kg	2	死亡	関連なし	該当せず	入院
10051025	男性	6[redacted]	胆嚢炎	37	9 µg/kg	NA	不明	関連なし	投与継続	入院
			食道炎	35	9 µg/kg	4	回復	関連なし	投与継続	入院
			非心臓性胸痛	35	9 µg/kg	1	回復	関連なし	投与継続	入院
			小腸閉塞	63	9 µg/kg	4	回復	関連なし	投与継続	入院
10121007	男性	6[redacted]	心嚢液貯留	121	9 µg/kg	4	回復	関連あり	該当せず	入院

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