Clinical trial results:
Multi-Center, Open-Label, Randomized Study of Anti-CCR4 Monoclonal Antibody KW-0761 or Investigator's Choice in Subjects with Previously Treated Adult T-cell Leukemia-Lymphoma (ATL)

Summary

EudraCT number	2011-005738-20
Trial protocol	BE GB FR
Global end of trial date	10 February 2017

Results information

Result version number	v1 (current)
This version publication date	25 February 2018
First version publication date	25 February 2018

Trial information

Trial identification

Sponsor protocol code	0761-009

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01626664
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Kyowa Kirin Pharmaceutical Development, Inc
Sponsor organisation address	212 Carnegie Center, Princeton, United States, 08540
Public contact	Clinical Trial Information, Kyowa Hakko Kirin Pharma, Inc., +1 6099191100, KKD.KW-0761@kyowakirin.com
Scientific contact	Clinical Trial Information, Kyowa Hakko Kirin Pharma, Inc., +1 6099191100, KKD.KW-0761@kyowakirin.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 March 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 March 2016
Global end of trial reached?	Yes
Global end of trial date	10 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To estimate overall response rate of KW-0761 for subjects with relapsed or refractory ATL.

Protection of trial subjects:

The study was conducted in accordance with the principles of the Declaration of Helsinki, the International Conference on Harmonization (ICH) consolidated guideline E6 - Good Clinical Practice (GCP) and any applicable national and local laws and regulations. Subjects were provided with written and oral information about the study (aims, methods, anticipated benefits, potential hazards and insurance arrangements). No procedures were conducted until informed consent was provided. The protocol included wording for the treatment of skin rash and hypersensitivity-like reactions (wording regarding premedication prior to KW-0761 infusion was also included in the protocol).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 August 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 13
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Brazil: 3
Country: Number of subjects enrolled	Peru: 7
Country: Number of subjects enrolled	United States: 39
Worldwide total number of subjects	71
EEA total number of subjects	22

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0

Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	57
From 65 to 84 years	14
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment opened in August 2012 and closed in May 2015.

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in the trial. Subjects that met all inclusion/exclusion criteria as per protocol were eligible for entry into the study. A total of 95 subjects were screened, of which 24 failed the screening process. 71 patients were therefore enrolled into the study.

Period 1

Period 1 title	Randomized
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Mogamulizumab (KW-0761)

Arm description:

anti-CCR4 monoclonal antibody KW-0761 (mogamulizumab)

Arm type	Experimental
Investigational medicinal product name	Mogamulizumab
Investigational medicinal product code	KW-0761
Other name	POTELIGEO®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1.0 mg/kg weekly x 4 in cycle 1 then every other week until progression

Arm title	Investigator's Choice

Arm description:

Comparator is investigator's choice of pralatrexate or gemcitabine plus oxaliplatin or DHAP

Arm type	Active comparator
Investigational medicinal product name	Pralatrexate
Investigational medicinal product code	
Other name	Folotyn
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

30 mg/m2 weekly for 3 weeks followed by 1 week of no therapy until progression

Investigational medicinal product name	gemcitabine plus oxaliplatin
Investigational medicinal product code	
Other name	Gemzar, Eloxatin, GemOx
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

gemcitabine 1000 mg/m2, followed by oxaliplatin 100 mg/m2 every 2 weeks until progression

Investigational medicinal product name	DHAP
Investigational medicinal product code	
Other name	Decadron, Dexasone, Baycadron, Platinol, Depocyt, Ara-C
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

dexamethasone 40 mg on Day 1-4, cisplatin 100 mg/m2 on Day 1 followed by 2 doses of cytarabine 2000 mg/m2 every 4 weeks until progression

Number of subjects in period 1	Mogamulizumab (KW-0761)	Investigator's Choice
Started	47	24
Completed	47	24

Period 2

Period 2 title	Crossover
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	IC Original then Crossover to mogamulizumab

Arm description:

Subjects who were randomized to the Investigator’s Choice regimen could be crossed over to receive mogamulizumab upon disease progression and with permission from the Medical Monitor.

Arm type	Experimental
Investigational medicinal product name	Mogamulizumab
Investigational medicinal product code	KW-0761
Other name	POTELIGEO®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1.0 mg/kg weekly x 4 in cycle 1x then every other week until progression

Number of subjects in period 2	IC Original then Crossover to mogamulizumab
Started	18
Completed	18

Baseline characteristics

Reporting groups	
Reporting group title	Mogamulizumab (KW-0761)
Reporting group description: anti-CCR4 monoclonal antibody KW-0761 (mogamulizumab)	
Reporting group title	Investigator's Choice
Reporting group description: Comparator is investigator's choice of pralatrexate or gemcitabine plus oxaliplatin or DHAP	

Reporting group values	Mogamulizumab (KW-0761)	Investigator's Choice	Total
Number of subjects	47	24	71
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	35	22	57
From 65-84 years	12	2	14
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	55	49	
full range (min-max)	22 to 82	24 to 80	-
Gender categorical Units: Subjects			
Female	23	14	37
Male	24	10	34

Subject analysis sets	
Subject analysis set title	Mogamulizumab (0761) (intent to treat)
Subject analysis set type	Intention-to-treat
Subject analysis set description: Patients who were randomized to KW-0761	
Subject analysis set title	Investigator's Choice (intent to treat)
Subject analysis set type	Intention-to-treat
Subject analysis set description: Subjects who were randomized to investigator's choice	
Subject analysis set title	Crossover (intent to treat)
Subject analysis set type	Intention-to-treat
Subject analysis set description: Randomized to Investigator's choice and cross over to KW-0761	
Subject analysis set title	Mogamulizumab (0761) (safety)

Subject analysis set type	Safety analysis
Subject analysis set description: Subjects randomized to mogamulizumab (0761)	
Subject analysis set title	Investigator's Choice (safety)
Subject analysis set type	Safety analysis
Subject analysis set description: Randomized to investigator's choice	
Subject analysis set title	Crossover (safety)
Subject analysis set type	Safety analysis
Subject analysis set description: Randomized to Investigator's choice and cross over to KW-0761	

Reporting group values	Mogamulizumab (0761) (intent to treat)	Investigator's Choice (intent to treat)	Crossover (intent to treat)
Number of subjects	47	24	18
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	35	22	17
From 65-84 years	12	2	1
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	55.0	49.0	46.8
full range (min-max)	22 to 82	24 to 80	24 to 65
Gender categorical Units: Subjects			
Female	23	14	10
Male	14	10	8

Reporting group values	Mogamulizumab (0761) (safety)	Investigator's Choice (safety)	Crossover (safety)
Number of subjects	47	24	18
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	35	22	17
From 65-84 years	12	2	1
85 years and over	0	0	0

Age continuous Units: years			
arithmetic mean	55.0	49.0	46.8
full range (min-max)	22 to 82	24 to 80	24 to 65
Gender categorical Units: Subjects			
Female	23	14	10
Male	14	10	8

End points

End points reporting groups

Reporting group title	Mogamulizumab (KW-0761)
Reporting group description: anti-CCR4 monoclonal antibody KW-0761 (mogamulizumab)	
Reporting group title	Investigator's Choice
Reporting group description: Comparator is investigator's choice of pralatrexate or gemcitabine plus oxaliplatin or DHAP	
Reporting group title	IC Original then Crossover to mogamulizumab
Reporting group description: Subjects who were randomized to the Investigator’s Choice regimen could be crossed over to receive mogamulizumab upon disease progression and with permission from the Medical Monitor.	
Subject analysis set title	Mogamulizumab (0761) (intent to treat)
Subject analysis set type	Intention-to-treat
Subject analysis set description: Patients who were randomized to KW-0761	
Subject analysis set title	Investigator's Choice (intent to treat)
Subject analysis set type	Intention-to-treat
Subject analysis set description: Subjects who were randomized to investigator's choice	
Subject analysis set title	Crossover (intent to treat)
Subject analysis set type	Intention-to-treat
Subject analysis set description: Randomized to Investigator's choice and cross over to KW-0761	
Subject analysis set title	Mogamulizumab (0761) (safety)
Subject analysis set type	Safety analysis
Subject analysis set description: Subjects randomized to mogamulizumab (0761)	
Subject analysis set title	Investigator's Choice (safety)
Subject analysis set type	Safety analysis
Subject analysis set description: Randomized to investigator's choice	
Subject analysis set title	Crossover (safety)
Subject analysis set type	Safety analysis
Subject analysis set description: Randomized to Investigator's choice and cross over to KW-0761	

Primary: Overall Response Rate

End point title	Overall Response Rate[1]
End point description: The data entered is based on an independent reviewer assessment. The table comparing independent reviewer to investigator assessment, which also includes crossover patients, is attached.	
End point type	Primary
End point timeframe: Every 8 weeks	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analysis was utilized for this primary endpoint.

End point values	Mogamulizumab (0761) (intent to treat)	Investigator's Choice (intent to treat)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	47	24		
Units: 71				
Complete Response	2	0		
Uncertified Complete Response	0	0		
Partial Response	11	2		
Stable Disease	0	4		
Relapsed Disease or Progressive Disease	16	13		
Not Assessable	18	5		
Overall Response Rate (Confirmed and Unconfirmed)	13	2		
Overall Response Rate Confirmed	5	0		

Attachments (see zip file)	Best Overall Response to Treatment/Best Overall Response to

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival: Randomized Treatment (Intent to Treat Set)

End point title	Progression-free Survival: Randomized Treatment (Intent to Treat Set)

End point description:

End point type	Secondary

End point timeframe:

From date of randomization until the date of first documented progression, start of alternative therapy, or date of death from any cause, whichever came first, up to 36 months

End point values	Mogamulizumab (0761) (intent to treat)	Investigator's Choice (intent to treat)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	47	24		
Units: 71				
median (confidence interval 95%)				
Progression-free Survival (months)	0.97 (0.87 to 1.33)	0.90 (0.77 to 2.73)		
Subjects (%) Alive Without Progression: 1 Month	47.5 (31.6 to 61.9)	44.1 (22.8 to 63.4)		
Subjects (%) Alive Without Progression: 2 Months	29.8 (16.6 to 44.2)	33.0 (14.2 to 53.3)		
Subjects (%) Alive Without Progression: 3 Months	24.4 (12.4 to 38.5)	26.4 (9.4 to 47.3)		

Subjects (%) Alive Without Progression: 4 Months	18.3 (7.9 to 32.1)	13.2 (2.4 to 33.5)		
Subjects (%) Alive Without Progression: 5 Months	18.3 (7.9 to 32.1)	0 (0 to 0)		
Subjects (%) Alive Without Progression: 6 Months	12.2 (4.0 to 25.1)	0 (0 to 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (Intent-to-Treat Set)

End point title	Overall Survival (Intent-to-Treat Set)

End point description:

Overall survival analysis was confounded by the crossover of 75% of Investigator's Choice subjects to mogamulizumab as this analysis was based upon the randomized treatment assignment.

End point type	Secondary

End point timeframe:

up to 36 months

End point values	Mogamulizumab (0761) (intent to treat)	Investigator's Choice (intent to treat)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	47	24		
Units: 71				
median (confidence interval 95%)				
Overall Survival (OS) (months)	4.90 (2.77 to 15.37)	6.87 (2.87 to 24.37)		
Subjects (%) Alive for at Least 1 Month	87.0 (73.2 to 93.9)	91.7 (70.6 to 97.8)		
Subjects (%) Alive for at Least 2 Months	75.6 (60.3 to 85.7)	79.2 (57.0 to 90.8)		
Subjects (%) Alive for at Least 3 Months	59.1 (43.1 to 72.0)	70.8 (48.4 to 84.9)		
Subjects (%) Alive for at Least 4 Months	54.3 (38.5 to 67.7)	66.7 (44.3 to 81.7)		
Subjects (%) Alive for at Least 5 Months	49.5 (33.9 to 63.3)	54.2 (32.7 to 71.4)		
Subjects (%) Alive for at Least 6 Months	44.3 (29.1 to 58.5)	54.2 (32.7 to 71.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of Life assessments

End point title	Quality of Life assessments

End point description:

There were no meaningful differences between the mogamulizumab and Investigator’s Choice groups in the FACT-Lym Total or subscale scores, and no indication of a decrement in quality of life associated with mogamulizumab. However, given the small initial sample size and very limited number of subjects with assessments beyond the first few cycles, it is difficult to draw any conclusions.

End point type	Secondary

End point timeframe:

up to 36 months

End point values	Mogamulizumab (0761) (intent to treat)	Investigator's Choice (intent to treat)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	47	24		
Units: 71	47	24		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From pre-treatment visit until 90 days after the last dose.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	15.0

Reporting groups	
Reporting group title	Mogamulizumab (KW-0761)
Reporting group description: -	
Reporting group title	Investigator's Choice
Reporting group description: -	
Reporting group title	Crossover
Reporting group description: Patients in this group crossed over to mogamulizumab after progressing on investigator's choice.	

Serious adverse events	Mogamulizumab (KW-0761)	Investigator's Choice	Crossover
Total subjects affected by serious adverse events			
subjects affected / exposed	26 / 47 (55.32%)	10 / 24 (41.67%)	9 / 18 (50.00%)
number of deaths (all causes)	30	10	12
number of deaths resulting from adverse events	10	1	2
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 47 (2.13%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease progression			
subjects affected / exposed	2 / 47 (4.26%)	0 / 24 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	1 / 47 (2.13%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multi-organ failure			

subjects affected / exposed	2 / 47 (4.26%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 1
Pyrexia			
subjects affected / exposed	2 / 47 (4.26%)	0 / 24 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 47 (2.13%)	0 / 24 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 47 (2.13%)	0 / 24 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	1 / 47 (2.13%)	0 / 24 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pulmonary toxicity			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	2 / 47 (4.26%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 1

Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 47 (2.13%)	0 / 24 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Amylase increased			
subjects affected / exposed	0 / 47 (0.00%)	1 / 24 (4.17%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 47 (2.13%)	1 / 24 (4.17%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bilirubin conjugated increased			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood lactate dehydrogenase increased			

subjects affected / exposed	0 / 47 (0.00%)	1 / 24 (4.17%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lipase increased			
subjects affected / exposed	0 / 47 (0.00%)	1 / 24 (4.17%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urine ketone body present			
subjects affected / exposed	1 / 47 (2.13%)	0 / 24 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	1 / 47 (2.13%)	0 / 24 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	1 / 47 (2.13%)	0 / 24 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	1 / 47 (2.13%)	0 / 24 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	2 / 47 (4.26%)	0 / 24 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Myocarditis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 24 (4.17%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 47 (0.00%)	1 / 24 (4.17%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osmotic demyelination syndrome			
subjects affected / exposed	1 / 47 (2.13%)	0 / 24 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral sensorimotor neuropathy			
subjects affected / exposed	1 / 47 (2.13%)	0 / 24 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 47 (0.00%)	1 / 24 (4.17%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tremor			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 47 (2.13%)	0 / 24 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Leukocytosis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 24 (4.17%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 47 (0.00%)	2 / 24 (8.33%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 47 (2.13%)	0 / 24 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	1 / 47 (2.13%)	1 / 24 (4.17%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 47 (2.13%)	0 / 24 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 24 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Ileitis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 24 (4.17%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 47 (2.13%)	1 / 24 (4.17%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	2 / 47 (4.26%)	1 / 24 (4.17%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	0 / 47 (0.00%)	1 / 24 (4.17%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain of skin			
subjects affected / exposed	1 / 47 (2.13%)	0 / 24 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pruritus			
subjects affected / exposed	0 / 47 (0.00%)	1 / 24 (4.17%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin hypopigmentation			
subjects affected / exposed	1 / 47 (2.13%)	0 / 24 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin ulcer			
subjects affected / exposed	1 / 47 (2.13%)	0 / 24 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 47 (2.13%)	0 / 24 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Flank pain			
subjects affected / exposed	1 / 47 (2.13%)	1 / 24 (4.17%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Mobility decreased			
subjects affected / exposed	1 / 47 (2.13%)	0 / 24 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	1 / 47 (2.13%)	0 / 24 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	1 / 47 (2.13%)	0 / 24 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Catheter site infection			
subjects affected / exposed	1 / 47 (2.13%)	0 / 24 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 24 (4.17%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridial infection			
subjects affected / exposed	1 / 47 (2.13%)	0 / 24 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytomegalovirus infection			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Empyema			
subjects affected / exposed	1 / 47 (2.13%)	0 / 24 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Infective thrombosis			

subjects affected / exposed	1 / 47 (2.13%)	0 / 24 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 47 (2.13%)	0 / 24 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oropharyngeal candidiasis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 24 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	1 / 47 (2.13%)	0 / 24 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	3 / 47 (6.38%)	0 / 24 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	3 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	2 / 2	0 / 0	0 / 0
Post procedural sepsis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 24 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	2 / 47 (4.26%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 47 (2.13%)	0 / 24 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Urosepsis			

subjects affected / exposed	1 / 47 (2.13%)	0 / 24 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 47 (0.00%)	1 / 24 (4.17%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	7 / 47 (14.89%)	4 / 24 (16.67%)	2 / 18 (11.11%)
occurrences causally related to treatment / all	0 / 7	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	1 / 47 (2.13%)	0 / 24 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	1 / 47 (2.13%)	0 / 24 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lactic acidosis			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour lysis syndrome			
subjects affected / exposed	1 / 47 (2.13%)	0 / 24 (0.00%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Mogamulizumab (KW-0761)	Investigator's Choice	Crossover
Total subjects affected by non-serious adverse events			
subjects affected / exposed	45 / 47 (95.74%)	24 / 24 (100.00%)	18 / 18 (100.00%)
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 47 (2.13%)	2 / 24 (8.33%)	0 / 18 (0.00%)
occurrences (all)	1	2	0
Flushing			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Hypertension			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Hypotension			
subjects affected / exposed	4 / 47 (8.51%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	4	0	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	3 / 18 (16.67%)
occurrences (all)	0	0	3
Chest pain			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Chills			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2
Fatigue			
subjects affected / exposed	5 / 47 (10.64%)	4 / 24 (16.67%)	1 / 18 (5.56%)
occurrences (all)	8	4	1
Gait disturbance			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2
Malaise			

subjects affected / exposed	0 / 47 (0.00%)	3 / 24 (12.50%)	0 / 18 (0.00%)
occurrences (all)	0	3	0
Mucosal inflammation			
subjects affected / exposed	0 / 47 (0.00%)	2 / 24 (8.33%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Oedema peripheral			
subjects affected / exposed	8 / 47 (17.02%)	4 / 24 (16.67%)	3 / 18 (16.67%)
occurrences (all)	8	4	3
Pain			
subjects affected / exposed	3 / 47 (6.38%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	3	0	1
Pyrexia			
subjects affected / exposed	4 / 47 (8.51%)	6 / 24 (25.00%)	3 / 18 (16.67%)
occurrences (all)	4	18	3
Reproductive system and breast disorders			
Sexual dysfunction			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Atelectasis			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Cough			
subjects affected / exposed	7 / 47 (14.89%)	2 / 24 (8.33%)	1 / 18 (5.56%)
occurrences (all)	7	2	1
Dyspnoea			
subjects affected / exposed	5 / 47 (10.64%)	3 / 24 (12.50%)	2 / 18 (11.11%)
occurrences (all)	5	3	2
Dyspnoea exertional			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Epistaxis			

subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Lung disorder			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Pleural effusion			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Productive cough			
subjects affected / exposed	3 / 47 (6.38%)	1 / 24 (4.17%)	0 / 18 (0.00%)
occurrences (all)	3	1	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 47 (0.00%)	2 / 24 (8.33%)	3 / 18 (16.67%)
occurrences (all)	0	2	3
Confusional state			
subjects affected / exposed	3 / 47 (6.38%)	0 / 24 (0.00%)	2 / 18 (11.11%)
occurrences (all)	3	0	2
Hallucination			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Insomnia			
subjects affected / exposed	5 / 47 (10.64%)	2 / 24 (8.33%)	1 / 18 (5.56%)
occurrences (all)	5	2	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 47 (6.38%)	2 / 24 (8.33%)	0 / 18 (0.00%)
occurrences (all)	4	12	0
Amylase increased			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	2
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 47 (10.64%)	2 / 24 (8.33%)	2 / 18 (11.11%)
occurrences (all)	5	13	2
Bilirubin conjugated increased			

subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 47 (4.26%)	3 / 24 (12.50%)	1 / 18 (5.56%)
occurrences (all)	2	8	1
Blood bicarbonate decreased			
subjects affected / exposed	3 / 47 (6.38%)	0 / 24 (0.00%)	0 / 18 (0.00%)
occurrences (all)	3	0	0
Blood bilirubin increased			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	3 / 18 (16.67%)
occurrences (all)	0	0	3
Blood creatine increased			
subjects affected / exposed	5 / 47 (10.64%)	2 / 24 (8.33%)	1 / 18 (5.56%)
occurrences (all)	5	2	1
Blood lactate dehydrogenase increased			
subjects affected / exposed	6 / 47 (12.77%)	1 / 24 (4.17%)	1 / 18 (5.56%)
occurrences (all)	7	1	1
Blood urea increased			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Lipase increased			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	3
Neutrophil count decreased			
subjects affected / exposed	2 / 47 (4.26%)	4 / 24 (16.67%)	1 / 18 (5.56%)
occurrences (all)	3	4	2
Platelet count decreased			
subjects affected / exposed	5 / 47 (10.64%)	2 / 24 (8.33%)	0 / 18 (0.00%)
occurrences (all)	5	11	0
Platelet count increased			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Transaminases increased			
subjects affected / exposed	0 / 47 (0.00%)	2 / 24 (8.33%)	0 / 18 (0.00%)
occurrences (all)	0	3	0

Urine output decreased			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Weight decreased			
subjects affected / exposed	2 / 47 (4.26%)	2 / 24 (8.33%)	0 / 18 (0.00%)
occurrences (all)	2	2	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Head injury			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Infusion related reaction			
subjects affected / exposed	21 / 47 (44.68%)	0 / 24 (0.00%)	8 / 18 (44.44%)
occurrences (all)	23	0	8
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Tachycardia			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 47 (10.64%)	3 / 24 (12.50%)	1 / 18 (5.56%)
occurrences (all)	6	3	2
Headache			
subjects affected / exposed	4 / 47 (8.51%)	7 / 24 (29.17%)	0 / 18 (0.00%)
occurrences (all)	4	7	0
Somnolence			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	10 / 47 (21.28%)	3 / 24 (12.50%)	6 / 18 (33.33%)
occurrences (all)	13	10	11
Leukopenia			
subjects affected / exposed	3 / 47 (6.38%)	1 / 24 (4.17%)	0 / 18 (0.00%)
occurrences (all)	3	1	0
Leukocytosis			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2
Neutropenia			
subjects affected / exposed	4 / 47 (8.51%)	4 / 24 (16.67%)	2 / 18 (11.11%)
occurrences (all)	10	8	3
Pancytopenia			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Thrombocytopenia			
subjects affected / exposed	6 / 47 (12.77%)	3 / 24 (12.50%)	2 / 18 (11.11%)
occurrences (all)	8	5	3
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 47 (2.13%)	2 / 24 (8.33%)	2 / 18 (11.11%)
occurrences (all)	1	2	3
Abdominal pain			
subjects affected / exposed	7 / 47 (14.89%)	2 / 24 (8.33%)	2 / 18 (11.11%)
occurrences (all)	7	2	2
Constipation			
subjects affected / exposed	6 / 47 (12.77%)	5 / 24 (20.83%)	1 / 18 (5.56%)
occurrences (all)	7	5	1
Diarrhoea			
subjects affected / exposed	3 / 47 (6.38%)	7 / 24 (29.17%)	2 / 18 (11.11%)
occurrences (all)	3	9	2
Diarrhoea haemorrhagic			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Dry mouth			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1

Gastrooesophageal reflux disease			
subjects affected / exposed	3 / 47 (6.38%)	1 / 24 (4.17%)	0 / 18 (0.00%)
occurrences (all)	3	2	0
Haematochezia			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	6 / 47 (12.77%)	9 / 24 (37.50%)	0 / 18 (0.00%)
occurrences (all)	7	11	0
Obstruction gastric			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	4 / 47 (8.51%)	7 / 24 (29.17%)	1 / 18 (5.56%)
occurrences (all)	6	7	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Blood blister			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Dermatitis acneiform			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Drug eruption			
subjects affected / exposed	9 / 47 (19.15%)	0 / 24 (0.00%)	4 / 18 (22.22%)
occurrences (all)	15	0	6
Dry skin			
subjects affected / exposed	3 / 47 (6.38%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	3	0	1
Ecchymosis			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Hyperhidrosis			

subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Pruritus			
subjects affected / exposed	3 / 47 (6.38%)	0 / 24 (0.00%)	0 / 18 (0.00%)
occurrences (all)	3	0	0
Rash			
subjects affected / exposed	3 / 47 (6.38%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	4	0	1
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Renal failure acute			
subjects affected / exposed	3 / 47 (6.38%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	3	0	1
Renal impairment			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 47 (6.38%)	1 / 24 (4.17%)	2 / 18 (11.11%)
occurrences (all)	4	1	2
Back pain			
subjects affected / exposed	3 / 47 (6.38%)	1 / 24 (4.17%)	0 / 18 (0.00%)
occurrences (all)	3	1	0
Bone pain			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Flank pain			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Groin pain			

subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Muscular weakness			
subjects affected / exposed	3 / 47 (6.38%)	1 / 24 (4.17%)	2 / 18 (11.11%)
occurrences (all)	4	1	2
Myalgia			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	3
Pain in extremity			
subjects affected / exposed	6 / 47 (12.77%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	6	0	1
Infections and infestations			
Aspergillosis			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Candidiasis			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Clostridium colitis			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Folliculitis			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Haemophilus infection			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Lower respiratory tract infection			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Lung infection			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Oral candidiasis			
subjects affected / exposed	3 / 47 (6.38%)	1 / 24 (4.17%)	0 / 18 (0.00%)
occurrences (all)	3	1	0

Pneumonia			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	3 / 47 (6.38%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	3	0	1
Urinary tract infection			
subjects affected / exposed	2 / 47 (4.26%)	2 / 24 (8.33%)	0 / 18 (0.00%)
occurrences (all)	2	2	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	4 / 47 (8.51%)	4 / 24 (16.67%)	1 / 18 (5.56%)
occurrences (all)	4	4	1
Dehydration			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	3 / 18 (16.67%)
occurrences (all)	0	0	3
Diabetes mellitus			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Hypercalcaemia			
subjects affected / exposed	5 / 47 (10.64%)	4 / 24 (16.67%)	3 / 18 (16.67%)
occurrences (all)	7	8	3
Hyperglycaemia			
subjects affected / exposed	3 / 47 (6.38%)	0 / 24 (0.00%)	0 / 18 (0.00%)
occurrences (all)	4	0	0
Hyperkalaemia			
subjects affected / exposed	4 / 47 (8.51%)	1 / 24 (4.17%)	0 / 18 (0.00%)
occurrences (all)	8	1	0
Hypernatraemia			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	3
Hyperuricaemia			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	1 / 18 (5.56%)
occurrences (all)	0	0	1
Hypoalbuminaemia			

subjects affected / exposed	2 / 47 (4.26%)	2 / 24 (8.33%)	2 / 18 (11.11%)
occurrences (all)	3	5	5
Hypokalaemia			
subjects affected / exposed	4 / 47 (8.51%)	3 / 24 (12.50%)	3 / 18 (16.67%)
occurrences (all)	4	5	4
Hypomagnesaemia			
subjects affected / exposed	4 / 47 (8.51%)	3 / 24 (12.50%)	4 / 18 (22.22%)
occurrences (all)	4	7	5
Hyponatraemia			
subjects affected / exposed	0 / 47 (0.00%)	0 / 24 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2
Hypophosphataemia			
subjects affected / exposed	3 / 47 (6.38%)	3 / 24 (12.50%)	2 / 18 (11.11%)
occurrences (all)	5	10	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 April 2012	• Changed the primary objective from PFS to estimation of ORR in the mogamulizumab treatment group. Progression-free survival and duration of response were made secondary objectives for the mogamulizumab and Investigator's Choice groups. • Specified that all primary analyses would be based on the Independent Review Committee response assessment for the mogamulizumab group in the ITT population. • Included additional surveillance for autoimmune syndrome development.
03 August 2012	Addressed comments from regulatory authority review and added additional safety testing as follows: Excluded subjects with smoldering subtype of ATL; Added pregnancy testing prior to each treatment cycle; Specified exclusion of any subjects with contraindication to any of the comparators; Specified when dose adjustments were required for weight change; Added thyroid function tests to monitor autoimmune development.
04 March 2013	• Modified the Inclusion/Exclusion Criteria to: Allow subjects with Gilbert's syndrome to be exempt from bilirubin requirement (Inclusion Criterion 9a); Allow subjects who were hepatitis C antibody-positive but hepatitis C quantitative-PCR-negative to be enrolled (Exclusion Criterion 5); Specify that only testing for hepatitis B surface antigen was required (Exclusion Criterion 6) and if the result was positive, the subject was to be excluded; Exclude subjects with QTc interval > 470 msec (Exclusion Criterion 10g). • Specified the permissible dosing interval for mogamulizumab administration during the first treatment cycle. • Allowed subjects with progressive disease in 1 disease compartment to continue to be treated on study, after consultation with the Kyowa Kirin Pharmaceutical Development, Inc. (KKD) Medical Monitor, for a period of up to 8 weeks as actual signs of objective progression may precede subsequent demonstration of an overall response. • Collected serum samples for analysis of anti-mogamulizumab antibodies in subjects who experienced an infusion reaction and clarified the infusion duration (i.e., 1 to 2 hours) in these subjects. • Specified that in cases where PET was not available, a conventional CT with contrast may be performed. • Specified that in this study disease progression and lymphopenia should not be considered AEs.
12 March 2013	• Modified Exclusion Criterion 6 to exclude subjects with active hepatitis B infection and minimize the risk of reactivation in subjects with a history of hepatitis B. • Modified Table 7.1.1-1 to include testing for hepatitis B virus DNA quantitative by polymerase chain reaction.

14 October 2013	• Excluded subjects with lymphoma or acute subtypes who had received > 2 prior systemic therapy regimens, and who did not achieve a response (CR or PR) or maintain SD for a minimum of 12 weeks on the most recent prior therapy (Exclusion Criterion 2). • Reduced the washout period from 2 weeks to 1 week for subjects treated with interferon-α and/or zidovudine and instructed the Investigator to contact the Medical Monitor to discuss the washout period for interferon-α, zidovudine, anti-neoplastic chemotherapy, radiation, immunotherapy, or investigational medications in subjects with rapidly progressive malignant disease. • Allowed subjects with rapidly progressive malignant disease to be crossed over to mogamulizumab with less than a 2-week washout period, if approved by the Medical Monitor, to maximize the opportunity for subjects to receive timely subsequent treatment in the setting of this aggressive disease. • Allowed subjects to receive influenza vaccination that consisted of killed virus. • Reduced the number of follow-up scans in subjects with the chronic subtype of ATL in cases where the subjects did not have evidence of ATL on the PET/CT at baseline. These subjects were required to undergo follow-up PET/CT scans to confirm a CR and/or if progressive disease was suspected in a compartment that could best be assessed by PET/CT. Due to the more indolent nature of the chronic subtype, regularly scheduled radiographs in the absence of symptoms of progression were unnecessary.
21 April 2014	• Provided updated safety information for mogamulizumab based on Edition 10 of the Investigator's Brochure. • Removed the immunogenicity assessment during the follow-up period since the sample was collected at the End-of-Treatment visit. • Allowed a subject who had been on a stable dose of medium or low potency topical corticosteroids for at least 4 weeks prior to the Pre-treatment Visit to be enrolled. The subject could continue therapy at the same dosage during the study; however, the Investigator was to attempt to taper the use to the lowest dosage tolerable (Exclusion Criterion 19). • Recommended premedication with acetaminophen or paracetamol orally and diphenhydramine 50 mg iv (or equivalent anti-histamine) for all subjects before the first mogamulizumab infusion. For subjects who experienced an infusion-related reaction, premedication was recommended prior to every subsequent infusion. • Specified that any subject who experienced a Grade 4 infusion reaction was to be discontinued from the study. • Required recording of medication taken during follow-up if used to treat an AE or was temporally associated with an AE and may have a causal relationship. • Specified that paraffin blocks or fresh tissue samples were preferred for determination of CCR4 expression. As KKD is developing a companion diagnostic assay, the remainder of the skin biopsy specimens was to be archived. Since unstained slides may have a shorter stability period, it was not recommended that they be submitted for this purpose. • In order to assess the PK exposure-response relationship for mogamulizumab, subjects who crossed over to mogamulizumab were also to undergo the collection of serum samples. • Updated the definition of relapsed or progressive disease in subjects with disease in the peripheral blood. The minimum threshold of disease was established as > 5% of abnormal cells; because of possible variability in the determination in subjects with blood disease changes only, a subseque
02 September 2015	• Clarified that subjects would be contacted by telephone every 30 days (± 7 days) up to 90 days (± 7 days) after the last dose of study medication or initiation of alternative therapy, whichever came first, to confirm and document any new onset AEs or toxicities. This instruction did not preclude an Investigator from reporting any AE occurring at any time after completion of the study if a causal relationship to study drug was suspected. • Revised the Exposure-response Analysis section to reflect the current plan for presenting the exposure-response data analysis. This study provides descriptive statistics on the PK data. Data from previously performed studies would be used to develop the model and data from this study (0761-009) would be incorporated into the analysis. Conclusions on exposure-response results are developed in a supplemental PK report based on the 31 Mar 2016 clinical cut-off.

28 April 2016	• Added a new protocol section, i.e., Study Procedures for Ongoing Subjects at the Time of Cutoff for Primary Analysis to define study criteria for continued treatment, clarify subject assessments to be performed by the Investigator, and specify relevant data collection required for subjects continuing to receive mogamulizumab at the clinical data cut-off date to be in accordance with Standard of Care at the Investigative site. • Specified blood/serum sample collection times for immunogenicity and natural ligand measurements (i.e., to be collected every 8 weeks during treatment) for subjects continuing to receive mogamulizumab at the clinical data cut-off date.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported