Clinical trial results:
Multiple Ascending Dose (MAD) Phase I Study of the IGF-1R Antagonist R1507 Administered as an Intravenous Infusion in children and Adolescents with Advanced Solid Tumors

Summary

EudraCT number	2016-001046-26
Trial protocol	Outside EU/EEA
Global end of trial date	09 December 2011

Results information

Result version number	v1 (current)
This version publication date	17 June 2017
First version publication date	17 June 2017

Trial information

Trial identification

Sponsor protocol code	NO21200

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00560144
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 December 2011
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 December 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the doses of R1507, a monoclonal antibody to the Type I Insulin-like Growth Factor Receptor (IGF-1R), that achieve serum drug exposure levels (AUCs) in children and adolescents with advanced solid tumors that are equivalent to the exposures in adults at the adult recommended doses of 9 mg/kg administered on a weekly schedule and 16 mg/kg administered every 3 weeks. To determine the maximum tolerated doses (MTD) of R1507 in children and adolescents with advanced solid tumors IF dose-limiting toxicity (DLT) is observed in 2 or more subjects at any dose level on the weekly or every 3 week schedules.

Protection of trial subjects:

All study subjects were required to read and sign an informed consent form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 November 2007
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 34
Worldwide total number of subjects	34
EEA total number of subjects	0

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)	20
Adolescents (12-17 years)	14
Adults (18-64 years)	0
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 34 subjects were enrolled across six sites in the United States.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	R1507 16 mg/kg

Arm description:

Subjects received R1507 16 mg/kg body weight intravenously every 3 weeks until development of progressive disease or DLT that persisted or recurred after a dose reduction.

Arm type	Experimental
Investigational medicinal product name	R1507
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

R1507 16 mg/kg body weight intravenously every week.

Arm title	R1507 3 mg/kg

Arm description:

Subjects received R1507 3 mg/kg body weight intravenously every week until development of progressive disease or DLT that persisted or recurred after a dose reduction.

Arm type	Experimental
Investigational medicinal product name	R1507
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

R1507 3 mg/kg body weight intravenously every week.

Arm title	R1507 9 mg/kg

Arm description:

Subjects received R1507 9 mg/kg body weight intravenously every week until development of progressive disease or DLT that persisted or recurred after a dose reduction.

Arm type	Experimental
Investigational medicinal product name	R1507
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:
R1507 9 mg/kg body weight intravenously every week.

Number of subjects in period 1	R1507 16 mg/kg	R1507 3 mg/kg	R1507 9 mg/kg
Started	12	3	19
Completed	0	0	0
Not completed	12	3	19
Study Terminated by Sposor	3	-	-
Failure to Return	-	-	1
Insufficient Therapeutic Response	9	3	18

Baseline characteristics

Reporting groups	
Reporting group title	R1507 16 mg/kg
Reporting group description:	
Subjects received R1507 16 mg/kg body weight intravenously every 3 weeks until development of progressive disease or DLT that persisted or recurred after a dose reduction.	
Reporting group title	R1507 3 mg/kg
Reporting group description:	
Subjects received R1507 3 mg/kg body weight intravenously every week until development of progressive disease or DLT that persisted or recurred after a dose reduction.	
Reporting group title	R1507 9 mg/kg
Reporting group description:	
Subjects received R1507 9 mg/kg body weight intravenously every week until development of progressive disease or DLT that persisted or recurred after a dose reduction.	

Reporting group values	R1507 16 mg/kg	R1507 3 mg/kg	R1507 9 mg/kg
Number of subjects	12	3	19
Age Categorical Units: Subjects			
Children (2-11 years)	5	2	13
Adolescents (12-17 years)	7	1	6
Age Continuous Units: years			
arithmetic mean	12.8	10	9.3
standard deviation	± 3.17	± 5.57	± 4.45
Gender Categorical Units: Subjects			
Female	3	3	10
Male	9	0	9

Reporting group values	Total		
Number of subjects	34		
Age Categorical Units: Subjects			
Children (2-11 years)	20		
Adolescents (12-17 years)	14		
Age Continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender Categorical Units: Subjects			
Female	16		
Male	18		

End points

End points reporting groups

Reporting group title	R1507 16 mg/kg
Reporting group description:	
Subjects received R1507 16 mg/kg body weight intravenously every 3 weeks until development of progressive disease or DLT that persisted or recurred after a dose reduction.	
Reporting group title	R1507 3 mg/kg
Reporting group description:	
Subjects received R1507 3 mg/kg body weight intravenously every week until development of progressive disease or DLT that persisted or recurred after a dose reduction.	
Reporting group title	R1507 9 mg/kg
Reporting group description:	
Subjects received R1507 9 mg/kg body weight intravenously every week until development of progressive disease or DLT that persisted or recurred after a dose reduction.	

Primary: Total Number of Infusions of IGF-1R Antagonist R1507 Administered

End point title	Total Number of Infusions of IGF-1R Antagonist R1507 Administered[1]
End point description:	
End point type	Primary
End point timeframe:	
Up to 49 months	

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: No statistical analysis was performed for this end point.

End point values	R1507 16 mg/kg	R1507 3 mg/kg	R1507 9 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	3	19	
Units: number of infusions				
arithmetic mean (standard deviation)	5.08 (± 4.1)	4.33 (± 1.53)	11.21 (± 10.16)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Adverse Events

End point title	Percentage of Subjects with Adverse Events
End point description:	

An adverse event (AE) was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship to the study drug. An SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; Initial or prolonged inpatient hospitalization; Life-threatening experience (immediate risk of dying); Persistent or significant disability or incapacity; and congenital anomaly.

End point type	Secondary

End point timeframe:

From first dose of study drug up 30 days after the last dose of study drug administration (up to 49 months)

End point values	R1507 16 mg/kg	R1507 3 mg/kg	R1507 9 mg/kg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	3	19	
Units: subjects	11	3	19	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first dose of study drug up 30 days after the last dose of study drug administration (up to 49 months)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups	
Reporting group title	R1507 16 mg/kg
Reporting group description:	
Subjects received R1507 16 mg/kg body weight intravenously every 3 weeks until development of progressive disease or DLT that persisted or recurred after a dose reduction.	
Reporting group title	R1507 3 mg/kg
Reporting group description:	
Subjects received R1507 3 mg/kg body weight intravenously every week until development of progressive disease or DLT that persisted or recurred after a dose reduction.	
Reporting group title	R1507 9 mg/kg
Reporting group description:	
Subjects received R1507 9 mg/kg body weight intravenously every week until development of progressive disease or DLT that persisted or recurred after a dose reduction.	

Serious adverse events	R1507 16 mg/kg	R1507 3 mg/kg	R1507 9 mg/kg
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 12 (16.67%)	0 / 3 (0.00%)	4 / 19 (21.05%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	0 / 19 (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
Diarrhoea			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	0 / 19 (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			
Pain in extremity			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	0 / 19 (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
Hypercalcaemia			

subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	R1507 16 mg/kg	R1507 3 mg/kg	R1507 9 mg/kg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 12 (91.67%)	3 / 3 (100.00%)	19 / 19 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	2 / 19 (10.53%)
occurrences (all)	1	0	2
Pallor			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Hypotension			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Application site rash			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Asthenia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Catheter site erythema			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Chest pain			
subjects affected / exposed	2 / 12 (16.67%)	1 / 3 (33.33%)	1 / 19 (5.26%)
occurrences (all)	2	1	1
Catheter site pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	2
Fatigue			

subjects affected / exposed	5 / 12 (41.67%)	1 / 3 (33.33%)	7 / 19 (36.84%)
occurrences (all)	10	1	8
Chills			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	2
Injection site pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Irritability			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Mucosal inflammation			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	2
Oedema			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Oedema peripheral			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	2
Pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 3 (33.33%)	3 / 19 (15.79%)
occurrences (all)	0	1	3
Pyrexia			
subjects affected / exposed	1 / 12 (8.33%)	1 / 3 (33.33%)	5 / 19 (26.32%)
occurrences (all)	4	1	6
Reproductive system and breast disorders			
Testicular pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 12 (16.67%)	1 / 3 (33.33%)	6 / 19 (31.58%)
occurrences (all)	3	1	7
Dyspnoea			

subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	2
Epistaxis			
subjects affected / exposed	0 / 12 (0.00%)	2 / 3 (66.67%)	5 / 19 (26.32%)
occurrences (all)	0	2	6
Hiccups			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Nasal congestion			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Oropharyngeal pain			
subjects affected / exposed	3 / 12 (25.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	3	0	1
Pharyngeal disorder			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Pleural effusion			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Rhinitis allergic			
subjects affected / exposed	2 / 12 (16.67%)	0 / 3 (0.00%)	2 / 19 (10.53%)
occurrences (all)	2	0	2
Rhinorrhoea			
subjects affected / exposed	0 / 12 (0.00%)	1 / 3 (33.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Aggression			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Anger			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Confusional state			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0

Depression			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Hallucination			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Insomnia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	2 / 19 (10.53%)
occurrences (all)	1	0	2
Mood altered			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Psychomotor retardation			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Anxiety			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Investigations			
Alanine aminotransferase			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	2
Aspartate aminotransferase			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Blood albumin decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Blood bicarbonate decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Blood bilirubin			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Blood calcium decreased			

subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	2
Blood glucose increased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Blood lactate dehydrogenase			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Blood phosphorus decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Protein total increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Respiratory rate decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Weight decreased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Weight increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	2
Blood chloride decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			

Arthropod bite			
subjects affected / exposed	0 / 12 (0.00%)	1 / 3 (33.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Contusion			
subjects affected / exposed	2 / 12 (16.67%)	0 / 3 (0.00%)	2 / 19 (10.53%)
occurrences (all)	4	0	2
Ligament sprain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Muscle strain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Procedural pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Thermal burn			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Tachycardia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	2
Nervous system disorders			
Balance disorder			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Convulsion			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Dizziness			
subjects affected / exposed	2 / 12 (16.67%)	0 / 3 (0.00%)	2 / 19 (10.53%)
occurrences (all)	2	0	2
Dyskinesia			

subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	1 / 12 (8.33%)	2 / 3 (66.67%)	6 / 19 (31.58%)
occurrences (all)	1	2	7
Hemianopia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Iiird nerve disorder			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	4
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Somnolence			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Syncope			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	4 / 19 (21.05%)
occurrences (all)	0	0	8
Leukopenia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	2 / 19 (10.53%)
occurrences (all)	1	0	11
Neutropenia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Thrombocytopenia			
subjects affected / exposed	1 / 12 (8.33%)	1 / 3 (33.33%)	2 / 19 (10.53%)
occurrences (all)	1	1	2
Ear and labyrinth disorders			
Cerumen impaction			

subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Ear pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Eye disorders			
Eye swelling			
subjects affected / exposed	0 / 12 (0.00%)	1 / 3 (33.33%)	0 / 19 (0.00%)
occurrences (all)	0	1	0
Ocular surface disease			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Visual impairment			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Vitreous floaters			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Eyelid ptosis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	3 / 19 (15.79%)
occurrences (all)	1	0	5
Abdominal distension			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	2
Abdominal pain upper			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	3 / 12 (25.00%)	1 / 3 (33.33%)	2 / 19 (10.53%)
occurrences (all)	4	1	3
Diarrhoea			

subjects affected / exposed	3 / 12 (25.00%)	0 / 3 (0.00%)	6 / 19 (31.58%)
occurrences (all)	4	0	6
Dyspepsia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	3
Flatulence			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Dysphagia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Haematochezia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Lip blister			
subjects affected / exposed	2 / 12 (16.67%)	0 / 3 (0.00%)	0 / 19 (0.00%)
occurrences (all)	2	0	0
Lip ulceration			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Periodontal disease			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	3 / 12 (25.00%)	1 / 3 (33.33%)	3 / 19 (15.79%)
occurrences (all)	3	1	6
Rectal lesion			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	2 / 12 (16.67%)	1 / 3 (33.33%)	6 / 19 (31.58%)
occurrences (all)	2	1	9
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1

Hyperbilirubinaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Decubitus ulcer			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	2
Dermatitis contact			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Dry skin			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Eczema			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Erythema			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Exfoliative rash			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Pruritus			
subjects affected / exposed	2 / 12 (16.67%)	0 / 3 (0.00%)	4 / 19 (21.05%)
occurrences (all)	2	0	4
Rash			
subjects affected / exposed	2 / 12 (16.67%)	0 / 3 (0.00%)	4 / 19 (21.05%)
occurrences (all)	4	0	9
Rash maculo-papular			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Rash papular			

subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Skin ulcer			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Skin exfoliation			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Alopecia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Skin disorder			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Skin hypopigmentation			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 12 (25.00%)	0 / 3 (0.00%)	3 / 19 (15.79%)
occurrences (all)	4	0	8
Back pain			
subjects affected / exposed	3 / 12 (25.00%)	0 / 3 (0.00%)	2 / 19 (10.53%)
occurrences (all)	3	0	2
Bone pain			
subjects affected / exposed	3 / 12 (25.00%)	0 / 3 (0.00%)	0 / 19 (0.00%)
occurrences (all)	3	0	0
Flank pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Joint stiffness			

subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Muscle atrophy			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Muscle contracture			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Muscle spasms			
subjects affected / exposed	0 / 12 (0.00%)	1 / 3 (33.33%)	4 / 19 (21.05%)
occurrences (all)	0	1	8
Muscular weakness			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	2 / 19 (10.53%)
occurrences (all)	1	0	2
Musculoskeletal pain			
subjects affected / exposed	2 / 12 (16.67%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	2	0	1
Myalgia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	2
Neck pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	2 / 19 (10.53%)
occurrences (all)	1	0	2
Pain in extremity			
subjects affected / exposed	3 / 12 (25.00%)	1 / 3 (33.33%)	1 / 19 (5.26%)
occurrences (all)	6	2	2
Pain in jaw			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal chest pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	2 / 19 (10.53%)
occurrences (all)	1	0	2
Infections and infestations			
Bronchitis viral			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0

Cellulitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Conjunctivitis infective			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Gastroenteritis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Infection			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Otitis media			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Otitis media acute			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Paronychia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	3
Periorbital cellulitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Peritonsillar abscess			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Pharyngitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Respiratory tract infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1

Rhinitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	0 / 19 (0.00%)
occurrences (all)	1	0	0
Sinusitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	2 / 19 (10.53%)
occurrences (all)	0	0	2
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 12 (16.67%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	2	0	1
Hyperglycaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Hyperuricaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Hypoglycaemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	1	0	1
Vitamin d deficiency			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1
Decreased appetite			
subjects affected / exposed	4 / 12 (33.33%)	0 / 3 (0.00%)	4 / 19 (21.05%)
occurrences (all)	4	0	6
Hypokalaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 19 (5.26%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 September 2007	Amendment B updated the table of subject assessments, and the schedules of safety and pharmacokinetics assessments.
15 October 2007	Amendment C clarified the target population in the protocol synopsis.
30 July 2008	Amendment D clarified addition of a new dosing cohort/ schedule of 16 mg/kg every 3 weeks (q3W). Clarified which safety and routine lab assessments were to be done under each dosing schedule (once weekly [qW] or q3W). Clarified the objectives to indicate that a 16 mg/kg q3W dosing schedule would also be used in addition to the qW schedule to determine maximum tolerated dose (if dose-limiting toxicity were observed in ≥ 2 or more subjects) and also determine serum drug exposure levels in children as it was done in adults using the same schedule. Added text regarding the difference in dose reduction guidelines per each schedule (qW and q3W) for subjects who experienced dose-limiting toxicity.
16 September 2008	Amendment E included that lymphocyte phenotyping (assessments of CD3, CD4, CD8, CD19 and CD16/CD56) would be drawn at screening for all subjects.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported