Clinical trial results:
A Phase III, Multicenter, Open-Label Study to Assess Efficacy, Safety, Pharmacokinetics and Immunogenicity of Abatacept Administered Intravenously in Japanese Children and Adolescents with Active Juvenile Idiopathic Arthritis Who Have a History of an Inadequate Response or Intolerance to Methotrexate or Biologics

Summary

EudraCT number	2016-000940-32
Trial protocol	Outside EU/EEA
Global end of trial date	

Results information

Result version number	v1 (current)
This version publication date	16 February 2019
First version publication date	16 February 2019

Trial information

Trial identification

Sponsor protocol code	IM101365

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussée de la Hulpe 185, Brussels, Belgium, 1170
Public contact	EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation,, clinical.trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.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	Interim
Date of interim/final analysis	30 January 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to assess the primary efficacy as assessed by American College of Rheumatology (ACR) Pediatric (Ped) 30 response rate at Day 113 in Japanese active polyarticular-course Juvenile idiopathic arthritis (JIA) subjects.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 September 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Japan: 20
Worldwide total number of subjects	20
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)	11
Adolescents (12-17 years)	9
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:

23 participants were enrolled and 20 participants were treated. Reason for non-treatment was that 3 participants no longer met study criteria.

Period 1

Period 1 title	Short Term Treatment Period (to Week 16)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Abatacept

Arm description:

Abatacept 10 mg/kg (for body weight less than 75 kg), 750 mg (for body weight between 75 and 100 kg), and 1g (for body weight above 100kg) intravenous infusion on Week 0 (Day 1), Week 2 (Day 15), Week 4 (Day 29) and every 4 weeks (28 days) thereafter up to the end of the study

Arm type	Experimental
Investigational medicinal product name	Abatacept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

10 mg/kg per infusion for
subjects weighing < 75 kg, 750 mg for subjects weighing 75 to 100 kg and 1000 mg for subjects weighing >100 kg.
Subjects were to be dosed on Day 1 (Week 0), Day 15 (Week 2), Day 29 (Week 4) and every 28 days thereafter for
the duration of the study.

Number of subjects in period 1	Abatacept
Started	20
Completed	20

Period 2

Period 2 title	Long Term Treatment Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Abatacept

Arm description:

Abatacept 10 mg/kg (for body weight less than 75 kg), 750 mg (for body weight between 75 and 100 kg), and 1g (for body weight above 100kg) intravenous infusion on Week 0 (Day 1), Week 2 (Day 15), Week 4 (Day 29) and every 4 weeks (28 days) thereafter up to the end of the study

Arm type	Experimental

No investigational medicinal product assigned in this arm

Number of subjects in period 2	Abatacept
Started	20
Completed	16
Not completed	4
Subject Request to Discontinue	1
Lack of efficacy	3

Baseline characteristics

Reporting groups	
Reporting group title	Abatacept
Reporting group description:	
Abatacept 10 mg/kg (for body weight less than 75 kg), 750 mg (for body weight between 75 and 100 kg), and 1g (for body weight above 100kg) intravenous infusion on Week 0 (Day 1), Week 2 (Day 15), Week 4 (Day 29) and every 4 weeks (28 days) thereafter up to the end of the study	

Reporting group values	Abatacept	Total	
Number of subjects	20	20	
Age Categorical Units: Subjects			
<=18 years	20	20	
Between 18 and 65 years	0	0	
>=65 years	0	0	
Age Continuous Units: years			
arithmetic mean	10.2		
standard deviation	± 3.24	-	
Sex: Female, Male Units: Subjects			
Female	15	15	
Male	5	5	
Race/Ethnicity, Customized			
Japan			
Units: Subjects			
Japanese	20	20	

End points

End points reporting groups

Reporting group title	Abatacept
Reporting group description:	
Abatacept 10 mg/kg (for body weight less than 75 kg), 750 mg (for body weight between 75 and 100 kg), and 1g (for body weight above 100kg) intravenous infusion on Week 0 (Day 1), Week 2 (Day 15), Week 4 (Day 29) and every 4 weeks (28 days) thereafter up to the end of the study	
Reporting group title	Abatacept
Reporting group description:	
Abatacept 10 mg/kg (for body weight less than 75 kg), 750 mg (for body weight between 75 and 100 kg), and 1g (for body weight above 100kg) intravenous infusion on Week 0 (Day 1), Week 2 (Day 15), Week 4 (Day 29) and every 4 weeks (28 days) thereafter up to the end of the study	

Primary: Percentage of Participants Experiencing a American College of Rheumatology (ACR) Pediatric 30 response at Week 16

End point title	Percentage of Participants Experiencing a American College of Rheumatology (ACR) Pediatric 30 response at Week 16[1]
End point description:	
American College of Rheumatology (ACR) pediatric (PED) 30 response was defined as '≥30% improvement' and '≥3 of the 6 Juvenile Idiopathic Arthritis (JIA) core set' and ≥30% worsening in not more than 1 of the 6 JIA core set variables. JIA core set variables defined as the number of active joints, number of joints with Limit of Motion (LOM), physician's global assessment of disease severity, patient global assessment of overall well being, parent assessment of physical function, and acute phase reactant value. A non-responder imputation was applied.	
End point type	Primary
End point timeframe:	
Week 16 (Day 113)	
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: Only summary statistics planned for this endpoint.	

End point values	Abatacept			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: percentage of participants				
number (confidence interval 95%)	90.0 (68.3 to 98.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Experiencing a American College of Rheumatology Pediatric 50, 70, 90 Response or Inactive Disease at Week 16

End point title	Percentage of Participants Experiencing a American College of Rheumatology Pediatric 50, 70, 90 Response or Inactive Disease at Week 16

End point description:

ACR PED 50 response is defined as '≥50% improvement' and '≥3 of the 6 Juvenile Idiopathic Arthritis (JIA) core set' and ≥30% worsening in not more than 1 of the 6 JIA core set variables. ACR PED 70 response is defined as '≥70% improvement' and '≥3 of the 6 JIA core set' and ≥30% worsening in not more than 1 of the 6 JIA core set variables. ACR PED 90 response is defined as '≥90% improvement' and '≥3 of the 6 JIA core set' and ≥30% worsening in not more than 1 of the 6 JIA core set variables. Inactive disease status is defined as no active joints, physician's global assessment of disease severity equal or less than 10mm and C-reactive protein (CRP) within normal limits (0.3 mg/dL). A non-responder imputation is applied. mm=millimeter; mg/dL=milligrams/deciliter

End point type	Secondary

End point timeframe:

Week 16 (Day 113)

End point values	Abatacept			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: percentage of participants				
number (confidence interval 95%)				
ACR PED 50	75.0 (50.9 to 91.3)			
ACR PED 70	70.0 (45.7 to 88.1)			
ACR PED 90	35.0 (15.4 to 59.2)			
Inactive Disease	25.0 (8.7 to 49.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Median Percentage of Improvement from Baseline in Physical Function as Assessed by the Childhood Health Assessment Questionnaire (CHAQ) Disability Index at Week 16

End point title	Median Percentage of Improvement from Baseline in Physical Function as Assessed by the Childhood Health Assessment Questionnaire (CHAQ) Disability Index at Week 16

End point description:

Physical function was evaluated using the disability section of the Childhood Health Assessment Questionnaire (CHAQ). The questionnaire was derived from the adult HAQ. The disability section assessed physical functions in 8 domains: dressing and grooming, arising, eating, walking, hygiene, reach, grip and common activities. The questions were evaluated on a 4-point scale: 0 = without any difficulty, 1 = with some difficulty, 2 = with much difficulty and 3 =unable to do. Higher scores indicate greater dysfunction. A disability index was calculated as the mean of the 8 functional scales. The percentage of Improvement from baseline was calculated using the following equation: (Baseline value - Post-baseline value) / Baseline value x 100.

End point type	Secondary

End point timeframe:

Week 16 (Day 113)

End point values	Abatacept			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: percentage of improvement from baseline				
median (inter-quartile range (Q1-Q3))	43.18 (0.00 to 100.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Death, Serious Adverse Events (SAEs), Drug-Related SAEs, Discontinuation Due to Drug-Related SAEs, Drug-Related Adverse Events (AEs), and Discontinuation Due to Drug-Related AEs During the Short Term Period

End point title	Number of Participants With Death, Serious Adverse Events (SAEs), Drug-Related SAEs, Discontinuation Due to Drug-Related SAEs, Drug-Related Adverse Events (AEs), and Discontinuation Due to Drug-Related AEs During the Short Term Period

End point description:

AE=any new unfavorable symptom, sign, or disease or worsening of a preexisting condition that may not have a causal relationship with treatment. SAE=a medical event that at any dose results in death, persistent or significant disability/incapacity, or drug dependency/abuse; is life-threatening, an important medical event, or a congenital anomaly/birth defect; or requires or prolongs hospitalization. SAEs also include hospitalizations for elective surgical procedures. Drug-related=related or missing relationship to study drug. Data includes all events from the date of the first dose of the study drug up to 56 days post the last dose of the study drug in the short-term period or start of the long-term period, whichever occurred first.

End point type	Secondary

End point timeframe:

Day 1 up to 56 days post Week 16 (Day 113); approximately 6 months

End point values	Abatacept			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: participants				
Death	0			
SAEs	2			
Drug-Related SAEs	1			
Discontinuation Due to Drug-Related SAEs	0			
Drug-Related AEs	5			
Discontinuation Due to Drug-Related AEs	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum observed concentration (Cmax) of Abatacept During the Short Term Period

End point title	Maximum observed concentration (Cmax) of Abatacept During the Short Term Period

End point description:

Cmax was obtained from the serum concentration versus time data after intravenous administration of abatacept. Blood samples were collected at 0 hour (pre-dose) on Days 15 and 29 and at 0 hour (pre-dose) and 0.5 hours (post dose) on Days 57, 85, and 113. A blood sample was also collected on an interim visit that occurred on any day between Day 92 and Day 110. ug/mL=micrograms/milliliter

End point type	Secondary

End point timeframe:

9 time points up to Week 16 (Day 113)

End point values	Abatacept			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: ug/mL				
geometric mean (geometric coefficient of variation)				
Day 57	163.13 (± 26.22)			
Day 85	172.43 (± 23.15)			
Day 113	167.85 (± 18.42)			

Statistical analyses

No statistical analyses for this end point

Secondary: Trough observed concentration (Ctrough) of Abatacept During the Short Term Period

End point title	Trough observed concentration (Ctrough) of Abatacept During the Short Term Period

End point description:

Blood samples were collected at 0 hour (pre-dose) on Days 15 and 29 and at 0 hour (pre-dose) and 0.5 hours (post dose) on Days 57, 85, and 113. A blood sample was also collected on an interim visit that occurred on any day between Day 92 and Day 110. ug/mL=micrograms/milliliter

End point type	Secondary

End point timeframe:

9 time points up to Week 16 (Day 113)

End point values	Abatacept			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: ug/mL				
geometric mean (geometric coefficient of variation)				
Day 15	25.50 (± 27.61)			
Day 29	38.64 (± 29.08)			
Day 57	17.24 (± 36.63)			
Day 85	16.79 (± 40.01)			
Day 113	15.56 (± 36.61)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Positive Immunogenicity During the Short Term Period

End point title	Number of Participants with Positive Immunogenicity During the Short Term Period

End point description:

A positive immunogenicity response for 'Cytotoxic T-lymphocyte antigen (CTLA4), Immunoglobulin (Ig)', 'Ig and/or Junction Region', respectively = (1) missing baseline immunogenicity measurement and positive analytical laboratory reported immunogenicity response post-baseline (2) negative baseline immunogenicity response and positive analytical laboratory reported immunogenicity response post-baseline (3) positive baseline immunogenicity response and positive analytical laboratory reported immunogenicity response post-baseline with titer value strictly greater than the baseline titer value. Assessment based on assay cutpoint value. Serum samples were collected prior to study medication at Week 0 (Day 1), Week 8 (Day 57), and Week 16 (Day 113) in the short term period. Participants who early discontinued from the study or complete and did not switch to commercial abatacept had a serum sample collected on final visit or early termination visit, 28, 84 and 168 days after the last dose.

End point type	Secondary

End point timeframe:

Day 1 up to Week 16 (Day 113)

End point values	Abatacept			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: participants	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During cumulative period: from first dose date up to 56 days beyond last dose. In LT period up to 56 days beyond the last dose of study medication in the ST period for participants not entering the LT period

Adverse event reporting additional description:

Study Start: August 2013; Study Reached PE Completion: Study DBL October 2016

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Abatacept

Reporting group description:

Abatacept 10 mg/kg (for body weight less than 75 kg), 750 mg (for body weight between 75 and 100 kg), and 1g (for body weight above 100kg) intravenous infusion on Week 0 (Day 1), Week 2 (Day 15), Week 4 (Day 29) and every 4 weeks (28 days) thereafter up to the end of the study.

Serious adverse events	Abatacept		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 20 (30.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Musculoskeletal and connective tissue disorders			
Juvenile idiopathic arthritis			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Varicella			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral tonsillitis			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Enterocolitis Viral			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Abatacept		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 20 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Skin papilloma			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Vascular disorders			
Haemorrhage			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	4		
Injection site swelling			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Non-cardiac chest pain			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Hypothermia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Oedema			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Chest Pain			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Immune system disorders			
Allergy to arthropod sting			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Seasonal allergy			
subjects affected / exposed	5 / 20 (25.00%)		
occurrences (all)	5		
Reproductive system and breast disorders			
Balanoposthitis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Dysmenorrhoea			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Upper respiratory tract inflammation			
subjects affected / exposed	5 / 20 (25.00%)		
occurrences (all)	5		
Epistaxis			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Rhinorrhoea			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Rhinitis allergic			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Allergic Bronchitis			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Oropharyngeal Pain			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Psychiatric disorders			
Attention Deficit/Hyperactivity Disorder			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Nightmare			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Bone density decreased			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Influenza B Virus Test Positive			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Streptococcus Test Positive			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Arthropod sting			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Frostbite			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Limb injury			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Radius fracture			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Contusion			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	4		
Joint dislocation			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Ligament sprain			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Excoriation			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Wound			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Arthropod bite			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Eye contusion			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 20 (35.00%)		
occurrences (all)	7		
Restless legs syndrome			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Dizziness Postural			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		

Hypoaesthesia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Intercostal Anemia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Eye disorders			
Conjunctivitis allergic			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Dry eye			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Scleritis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Ocular Hyperaemia			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	5 / 20 (25.00%)		
occurrences (all)	5		
Toothache			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Haemorrhoids			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Stomatitis			
subjects affected / exposed	7 / 20 (35.00%)		
occurrences (all)	7		
Abdominal pain			

subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Dental caries			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	4		
Vomiting			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Abdominal pain upper			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Enterocolitis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Aphthous ulcer			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Constipation			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Irritable Bowel Syndrome			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Acne			
subjects affected / exposed	5 / 20 (25.00%)		
occurrences (all)	5		
Asteatosis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		

Rash			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Dermatitis			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Purpura			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Skin ulcer			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Ingrowing nail			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Alopecia			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Dry skin			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 20 (25.00%)		
occurrences (all)	5		
Tendonitis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Arthritis			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Back pain			

subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Joint swelling			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Neck pain			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Juvenile Idiopathic Arthritis			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Pain in Extremity			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Muscle Fatigue			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Musculoskeletal Pain			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Infections and infestations			
Pharyngitis			
subjects affected / exposed	12 / 20 (60.00%)		
occurrences (all)	12		
Otitis externa			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Otitis media acute			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	3 / 20 (15.00%)		
occurrences (all)	3		
Upper respiratory tract infection			
subjects affected / exposed	4 / 20 (20.00%)		
occurrences (all)	4		

Cystitis				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Enteritis infectious				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Oral candidiasis				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Tonsillitis				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Viral pharyngitis				
subjects affected / exposed	3 / 20 (15.00%)			
occurrences (all)	3			
Viral rash				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Angular cheilitis				
subjects affected / exposed	2 / 20 (10.00%)			
occurrences (all)	2			
Bronchitis				
subjects affected / exposed	5 / 20 (25.00%)			
occurrences (all)	5			
Gastroenteritis				
subjects affected / exposed	4 / 20 (20.00%)			
occurrences (all)	4			
Varicella				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Influenza				
subjects affected / exposed	10 / 20 (50.00%)			
occurrences (all)	10			
Nasopharyngitis				
subjects affected / exposed	17 / 20 (85.00%)			
occurrences (all)	17			

Oral herpes				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Tinea infection				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Conjunctivitis				
subjects affected / exposed	3 / 20 (15.00%)			
occurrences (all)	3			
Gastroenteritis viral				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Enterocolitis viral				
subjects affected / exposed	2 / 20 (10.00%)			
occurrences (all)	2			
Herpes simplex				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Hordeolum				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Paronychia				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Folliculitis				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Furuncle				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Hand-Foot-And-Mouth Disease				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			
Herpangina				
subjects affected / exposed	1 / 20 (5.00%)			
occurrences (all)	1			

Herpes Virus Infection subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Mycoplasma Infection subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Oesophageal Candidiasis subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Otitis Media subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Viral Tonsillities subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Metabolism and nutrition disorders			
Hypoglycaemia subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		
Obesity subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 January 2016	Update the secondary objectives and the exploratory objectives. Other changes incorporated revision of contraceptive methods and the internal organization change

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported