



Clinical trial results:

-SPECIFIC 4 Patients: Study of Pediatric Efficacy and Safety with First-line use of Canakinumab An open-label canakinumab (ACZ885) dose reduction or dose interval prolongation efficacy and safety study in patients with Systemic Juvenile Idiopathic Arthritis (SJIA)

Summary

EudraCT number	2013-004867-29
Trial protocol	SE AT ES HU DE IT NL BE
Global end of trial date	25 April 2018

Results information

Result version number	v1 (current)
This version publication date	10 October 2018
First version publication date	10 October 2018

Trial information

Trial identification

Sponsor protocol code	CACZ885G2306
-----------------------	--------------

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Novartis Pharmaceuticals
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharmaceuticals, 41 613241111, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharmaceuticals, 41 613241111, Novartis.email@novartis.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	25 April 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	25 April 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate if at least 40% of patients in clinical remission (i.e., inactive disease for at least 24 weeks) on 4 mg/kg canakinumab (+/- concomitant NSAID only) were able to remain at a reduced canakinumab dose (2 mg/kg every 4 weeks) or prolonged canakinumab dose interval (4 mg/kg every 8 weeks) for at least 24 consecutive weeks in either treatment arm (Part II).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 November 2014
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	Austria: 3
Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	Brazil: 5
Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	France: 24
Country: Number of subjects enrolled	Germany: 18
Country: Number of subjects enrolled	Hungary: 13
Country: Number of subjects enrolled	Israel: 15
Country: Number of subjects enrolled	Italy: 10
Country: Number of subjects enrolled	Netherlands: 8
Country: Number of subjects enrolled	Poland: 5
Country: Number of subjects enrolled	Russian Federation: 31
Country: Number of subjects enrolled	Spain: 14
Country: Number of subjects enrolled	Sweden: 6
Country: Number of subjects enrolled	Turkey: 8
Country: Number of subjects enrolled	United States: 5

Worldwide total number of subjects	182
EEA total number of subjects	111

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)	112
Adolescents (12-17 years)	61
Adults (18-64 years)	9
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

182 enrolled but 16 qualified immediately for Part II & were randomized while 166 continued in Part I & were treated with canakinumab 4 mg/kg every 4 weeks until study end unless they discontinued, or until they qualified for Part II. Of these, 40 discontinued. Most frequent reason was lack of efficacy

Pre-assignment

Screening details:

75 patients (Cohort 1: 56 and Cohort 2: 20) qualified for Study Part II and were randomized to receive canakinumab at either a reduced dose (n=38) or a prolonged dose interval (n=37)

Period 1

Period 1 title	Part 1
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Part 1 Cohort 1

Arm description:

Participants from study CACZ885G2301E1, aged ≥ 2 to < 20 years at the time of the patient's first dose of canakinumab, who at the time of evaluation for participation in CACZ885G2306 were being treated with canakinumab 4mg/kg and had inactive disease

Arm type	Experimental
Investigational medicinal product name	canakinumab
Investigational medicinal product code	ACZ885
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

dose of canakinumab allowed was 300 mg, which was administered as 2 sc 150 mg injections, once every 4 weeks.

Arm title	PART 1: Cohort 2
------------------	------------------

Arm description:

Participants who at screening were aged ≥ 2 to < 20 years, had active SJIA (as per protocol), and were canakinumab treatment-naïve

Arm type	Experimental
Investigational medicinal product name	canakinumab
Investigational medicinal product code	ACZ885
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants from study CACZ885G2301E1, aged ≥ 2 to < 20 years at the time of the patient's first dose of canakinumab, who at the time of evaluation for participation in CACZ885G2306 were being treated with canakinumab 4mg/kg and had inactive disease Dose interval prologation All participants received canakinumab 4mg/kg (300 mg max) every 4 weeks in Part I of this study

Number of subjects in period 1 ^[1]	Part 1 Cohort 1	PART 1: Cohort 2
Started	68	98
Completed	61	65
Not completed	7	33
Consent withdrawn by subject	-	2
Adverse event, non-fatal	2	11
Study terminated by sponsor	-	1
New therapy for study indication	-	1
Lack of efficacy	5	17
Protocol deviation	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 182 enrolled but 16 qualified immediately for Part II & were randomized while 166 continued in Part I & were treated with canakinumab 4 mg/kg every 4 weeks until study end unless they discontinued, or until they qualified for Part II. Of these, 40 discontinued. Most frequent reason was lack of efficacy

75 patients (Cohort 1: 56 and Cohort 2: 20) qualified for Study Part II and were randomized to receive canakinumab at either a reduced dose (n=38) or a prolonged dose interval (n=37)

Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Part II Dose Reduction

Arm description:

canakinumab 4 mg/kg every 4 weeks until study end unless discontinuation occurred, or until they qualified & entered Part II

Arm type	Experimental
Investigational medicinal product name	Canakinumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

2 mg/kg q4 wks followed by 1 mg/kg q4 wk and drug discontinuation if appropriate.

Arm title	Part II Dose interval prolongation
------------------	------------------------------------

Arm description:

canakinumab 4 mg/kg every 4 weeks until study end unless discontinuation occurred, or until they qualified & entered Part II

Arm type	Experimental
----------	--------------

Investigational medicinal product name	Canakinumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

4 mg/kg q8 wks followed by 4 mg/kg q12 wk and drug discontinuation if appropriate.

Number of subjects in period 2^[2]	Part II Dose Reduction	Part II Dose interval prolongation
Started	38	37
Completed	35	37
Not completed	3	0
Adverse event, non-fatal	1	-
Lost to follow-up	1	-
Lack of efficacy	1	-

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: 182 enrolled but 16 qualified immediately for Part II & were randomized while 166 continued in Part I & were treated with canakinumab 4 mg/kg every 4 weeks until study end unless they discontinued, or until they qualified for Part II. Of these, 40 discontinued. Most frequent reason was lack of efficacy

75 patients (Cohort 1: 56 and Cohort 2: 20) qualified for Study Part II and were randomized to receive canakinumab at either a reduced dose (n=38) or a prolonged dose interval (n=37)

Baseline characteristics

Reporting groups

Reporting group title	Part 1 Cohort 1
Reporting group description:	
Participants from study CACZ885G2301E1, aged ≥ 2 to < 20 years at the time of the patient's first dose of canakinumab, who at the time of evaluation for participation in CACZ885G2306 were being treated with canakinumab 4mg/kg and had inactive disease	
Reporting group title	PART 1: Cohort 2
Reporting group description:	
Participants who at screening were aged ≥ 2 to < 20 years, had active SJIA (as per protocol), and were canakinumab treatment-naïve	

Reporting group values	Part 1 Cohort 1	PART 1: Cohort 2	Total
Number of subjects	68	98	166
Age, Customized			
Units: Subjects			
2y - <12 y	31	73	104
12 y - <18 y	30	25	55
18 y - <65 y	7	0	7
65 y - <85 y	0	0	0
≥ 85 years	0	0	0
Age Continuous			
Units: Participants			
arithmetic mean	11.8	8.3	
standard deviation	± 4.53	± 4.20	-
Sex: Female, Male			
Units: Subjects			
Female	34	56	90
Male	34	42	76
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	1	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	1	2
White	66	81	147
More than one race	0	0	0
Unknown	0	1	1
Other	1	12	13
Asian	0	2	2

End points

End points reporting groups

Reporting group title	Part 1 Cohort 1
Reporting group description: Participants from study CACZ885G2301E1, aged ≥ 2 to < 20 years at the time of the patient's first dose of canakinumab, who at the time of evaluation for participation in CACZ885G2306 were being treated with canakinumab 4mg/kg and had inactive disease	
Reporting group title	PART 1: Cohort 2
Reporting group description: Participants who at screening were aged ≥ 2 to < 20 years, had active SJIA (as per protocol), and were canakinumab treatment-naïve	
Reporting group title	Part II Dose Reduction
Reporting group description: canakinumab 4 mg/kg every 4 weeks until study end unless discontinuation occurred, or until they qualified & entered Part II	
Reporting group title	Part II Dose interval prolongation
Reporting group description: canakinumab 4 mg/kg every 4 weeks until study end unless discontinuation occurred, or until they qualified & entered Part II	

Primary: Number of participants in clinical remission on canakinumab who are able to remain at an initial reduced canakinumab dose or prolonged canakinumab dose interval.

End point title	Number of participants in clinical remission on canakinumab who are able to remain at an initial reduced canakinumab dose or prolonged canakinumab dose interval.
End point description:	
End point type	Primary
End point timeframe: baseline to 24 weeks	

End point values	Part II Dose Reduction	Part II Dose interval prolongation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	37		
Units: participants				
Able to remain on dose	27	31		
Not able to remain on dose	11	6		

Statistical analyses

Statistical analysis title	Clinical Remission
Comparison groups	Part II Dose Reduction v Part II Dose interval prolongation

Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0001
Method	exact binomial test

Secondary: Number and percentage of patients with adverse events as a measure of long-term safety and tolerability of canakinumab - PART 1

End point title	Number and percentage of patients with adverse events as a measure of long-term safety and tolerability of canakinumab - PART 1
End point description:	AEs, Deaths, other serious adverse events or discontinuations due to AE, Part I (Safety set)
End point type	Secondary
End point timeframe:	During study parts I and II. The estimated study duration is not more than 216 weeks (with an average expected duration of 108 weeks).

End point values	Part 1 Cohort 1	PART 1: Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	98		
Units: number of participants				
Number of patients with at least one AE	57	91		
Number of patients with death	0	0		
Number of patients with at least one SAE	10	23		

Statistical analyses

No statistical analyses for this end point

Secondary: Number and percentage of patients with adverse events as a measure of long-term safety and tolerability of canakinumab - PART 2

End point title	Number and percentage of patients with adverse events as a measure of long-term safety and tolerability of canakinumab - PART 2
End point description:	AEs, Deaths, other serious adverse events or discontinuations due to AE, Part II (Safety set)
End point type	Secondary
End point timeframe:	During study parts I and II, estimated study duration was not more than 216 weeks (with an average duration of 108 weeks).

End point values	Part II Dose Reduction	Part II Dose interval prolongation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	37		
Units: number of participants				
Number of patients with at least one AE	38	34		
Number of patients with death	0	0		
Number of patients with at least one SAE	4	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	21.0
--------------------	------

Reporting groups

Reporting group title	Any ACZ Treatment Group
-----------------------	-------------------------

Reporting group description:

Any ACZ Treatment Group

Serious adverse events	Any ACZ Treatment Group		
Total subjects affected by serious adverse events			
subjects affected / exposed	37 / 182 (20.33%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Limb injury			
subjects affected / exposed	1 / 182 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thoracic vertebral fracture			
subjects affected / exposed	1 / 182 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Pericarditis			
subjects affected / exposed	2 / 182 (1.10%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Idiopathic intracranial hypertension			

subjects affected / exposed	1 / 182 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Histiocytosis haematophagic			
subjects affected / exposed	5 / 182 (2.75%)		
occurrences causally related to treatment / all	1 / 5		
deaths causally related to treatment / all	0 / 0		
Leukopenia			
subjects affected / exposed	1 / 182 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lymphadenitis			
subjects affected / exposed	1 / 182 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lymphadenopathy			
subjects affected / exposed	1 / 182 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 182 (0.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Eye swelling			
subjects affected / exposed	1 / 182 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	1 / 182 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain upper			
subjects affected / exposed	1 / 182 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 182 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Enteritis			
subjects affected / exposed	1 / 182 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Alveolar proteinosis			
subjects affected / exposed	1 / 182 (0.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Interstitial lung disease			
subjects affected / exposed	1 / 182 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Dermatitis atopic			
subjects affected / exposed	1 / 182 (0.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lichen planus			
subjects affected / exposed	1 / 182 (0.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Rash pruritic			
subjects affected / exposed	1 / 182 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rash scarlatiniform			
subjects affected / exposed	1 / 182 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 182 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 182 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Juvenile idiopathic arthritis			
subjects affected / exposed	8 / 182 (4.40%)		
occurrences causally related to treatment / all	1 / 8		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	1 / 182 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteonecrosis			
subjects affected / exposed	1 / 182 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	1 / 182 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Still's disease			
subjects affected / exposed	2 / 182 (1.10%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 182 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atypical pneumonia			
subjects affected / exposed	1 / 182 (0.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchitis			
subjects affected / exposed	1 / 182 (0.55%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	2 / 182 (1.10%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Infectious mononucleosis			
subjects affected / exposed	1 / 182 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	1 / 182 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Otitis media			
subjects affected / exposed	2 / 182 (1.10%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Otitis media acute			

subjects affected / exposed	1 / 182 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	2 / 182 (1.10%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	1 / 182 (0.55%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral infection			
subjects affected / exposed	2 / 182 (1.10%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Any ACZ Treatment Group		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	164 / 182 (90.11%)		
Nervous system disorders			
Headache			
subjects affected / exposed	36 / 182 (19.78%)		
occurrences (all)	81		
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	13 / 182 (7.14%)		
occurrences (all)	15		
General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	13 / 182 (7.14%)		
occurrences (all)	27		
Pyrexia			

subjects affected / exposed	51 / 182 (28.02%)		
occurrences (all)	101		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	24 / 182 (13.19%)		
occurrences (all)	34		
Abdominal pain upper			
subjects affected / exposed	16 / 182 (8.79%)		
occurrences (all)	25		
Diarrhoea			
subjects affected / exposed	23 / 182 (12.64%)		
occurrences (all)	49		
Nausea			
subjects affected / exposed	17 / 182 (9.34%)		
occurrences (all)	25		
Vomiting			
subjects affected / exposed	20 / 182 (10.99%)		
occurrences (all)	26		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	34 / 182 (18.68%)		
occurrences (all)	53		
Oropharyngeal pain			
subjects affected / exposed	24 / 182 (13.19%)		
occurrences (all)	48		
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	18 / 182 (9.89%)		
occurrences (all)	31		
Pruritus			
subjects affected / exposed	12 / 182 (6.59%)		
occurrences (all)	15		
Rash			
subjects affected / exposed	23 / 182 (12.64%)		
occurrences (all)	41		
Urticaria			

subjects affected / exposed	10 / 182 (5.49%)		
occurrences (all)	17		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	38 / 182 (20.88%)		
occurrences (all)	73		
Back pain			
subjects affected / exposed	15 / 182 (8.24%)		
occurrences (all)	22		
Juvenile idiopathic arthritis			
subjects affected / exposed	33 / 182 (18.13%)		
occurrences (all)	39		
Pain in extremity			
subjects affected / exposed	18 / 182 (9.89%)		
occurrences (all)	33		
Infections and infestations			
Bronchitis			
subjects affected / exposed	16 / 182 (8.79%)		
occurrences (all)	18		
Gastroenteritis			
subjects affected / exposed	20 / 182 (10.99%)		
occurrences (all)	26		
Influenza			
subjects affected / exposed	24 / 182 (13.19%)		
occurrences (all)	34		
Nasopharyngitis			
subjects affected / exposed	48 / 182 (26.37%)		
occurrences (all)	105		
Pharyngitis			
subjects affected / exposed	25 / 182 (13.74%)		
occurrences (all)	35		
Respiratory tract infection			
subjects affected / exposed	20 / 182 (10.99%)		
occurrences (all)	28		
Rhinitis			

subjects affected / exposed	29 / 182 (15.93%)		
occurrences (all)	45		
Tonsillitis			
subjects affected / exposed	15 / 182 (8.24%)		
occurrences (all)	25		
Upper respiratory tract infection			
subjects affected / exposed	34 / 182 (18.68%)		
occurrences (all)	62		
Viral infection			
subjects affected / exposed	17 / 182 (9.34%)		
occurrences (all)	26		
Metabolism and nutrition disorders			
Iron deficiency			
subjects affected / exposed	14 / 182 (7.69%)		
occurrences (all)	19		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported