Clinical trial results:
A Double-Blind, Randomized, Multi-Center, Parallel-Group, Placebo-Controlled Study to Evaluate the Efficacy and Safety of a Single Dose of a 500-mg Chewable Tablet of Mebendazole in the Treatment of Soil-Transmitted Helminth Infestations (Ascaris lumbricoides and Trichuris trichiura) in Pediatric Subjects

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2016-000728-24
Trial protocol	Outside EU/EEA
Global end of trial date	03 September 2015

Results information

Result version number	v1 (current)
This version publication date	28 July 2016
First version publication date	28 July 2016

Trial information

Trial identification

Sponsor protocol code	MEBENDAZOLGAI3003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02034162
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Janssen Research & Development, LLC
Sponsor organisation address	920 US Route , Raritan, New Jersey, United States, 202
Public contact	Clinical Registry Group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.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	03 September 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 September 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to compare the efficacy and safety of a single dose of a 500 milligram (mg) chewable mebendazole tablet with placebo in treatment of Ascaris lumbricoides and Trichuris trichiura infestations in pediatric subjects.

Protection of trial subjects:

Safety evaluations included monitoring of adverse events (AEs), vital signs measurements, physical examinations including height and weight measurements, and body mass index (BMI) calculations. An Independent Data Monitoring Committee (IDMC) was established to ensure the safety of subjects.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 December 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	Ethiopia: 255
Country: Number of subjects enrolled	Rwanda: 40
Worldwide total number of subjects	295
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)	14
Children (2-11 years)	250
Adolescents (12-17 years)	31
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted from 8-Dec-2014 to 3-Sep-2015. A total of 295 subjects were enrolled and randomly assigned to study treatment; 278 subjects completed the study. Of the 295 subjects, 167 subjects were reported with Ascaris lumbricoides infestation and 243 subjects were reported with Trichuris trichiura infestation.

Pre-assignment

Screening details:

Of the 792 subjects screened, a total of 295 were randomly assigned to study treatments, of which 278 completed the study. 10 subjects had major protocol deviations. 9 subjects did not meet the inclusion/exclusion criteria and 1 subject was reported with wasting at Visits 3 and 5 (without any evidence of wasting at screening).

Period 1

Period 1 title	Double-blind Phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Mebendazole 500 mg

Arm description:

Subjects received a single 500-mg chewable tablet of Mebendazole in a double-blind manner at the baseline visit (Day 1) followed up to Visit 3 (Day 19+/-2).

Arm type	Experimental
Investigational medicinal product name	Mebendazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Chewable tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received a single 500-mg chewable tablet of Mebendazole in a double-blind manner at the baseline visit (Day 1) followed up to Visit 3 (Day 19+/-2).

Arm title	Placebo

Arm description:

Subjects received matching placebo as a single-dose chewable tablet in a double-blind manner at the baseline visit (Day 1) followed up to Visit 3 (Day 19+/-2).

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Chewable tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received matching placebo as a single-dose chewable tablet in a double-blind manner at the baseline visit (Day 1) followed up to Visit 3 (Day 19+/-2).

Number of subjects in period 1	Mebendazole 500 mg	Placebo
Started	149	146
Completed	141	137
Not completed	8	9
Physician decision	-	1
Lost to follow-up	-	3
Protocol deviation	1	-
Withdrawal by subject	7	5

Period 2

Period 2 title	Open-label Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Mebendazole 500 mg

Arm description:

Subjects received Mebendazole 500-mg chewable tablet in an open label manner at visit 3 (Day 19+/-2) followed up to Visit 5 (Day 7+/-1 from Visit 3).

Arm type	Experimental
Investigational medicinal product name	Mebendazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Chewable tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received Mebendazole 500-mg chewable tablet in an open label manner at visit 3 (Day 19+/-2) followed up to Visit 5 (Day 7+/-1 from Visit 3).

Number of subjects in period 2	Mebendazole 500 mg
Started	278
Completed	278

Baseline characteristics

Reporting groups	
Reporting group title	Mebendazole 500 mg
Reporting group description:	
Subjects received a single 500-mg chewable tablet of Mebendazole in a double-blind manner at the baseline visit (Day 1) followed up to Visit 3 (Day 19+/-2).	
Reporting group title	Placebo
Reporting group description:	
Subjects received matching placebo as a single-dose chewable tablet in a double-blind manner at the baseline visit (Day 1) followed up to Visit 3 (Day 19+/-2).	

Reporting group values	Mebendazole 500 mg	Placebo	Total
Number of subjects	149	146	295
Title for AgeCategorical			
Units: subjects			
infants and toddlers(28 days-23 months)	7	7	14
Children (2-11 years)	124	126	250
Adolescents (12-17 years)	18	13	31
Title for AgeContinuous			
Units: years			
arithmetic mean	7.9	7.7	
standard deviation	± 3.27	± 3.09	-
Title for Gender			
Units: subjects			
Female	78	74	152
Male	71	72	143

End points

End points reporting groups

Reporting group title	Mebendazole 500 mg
Reporting group description:	
Subjects received a single 500-mg chewable tablet of Mebendazole in a double-blind manner at the baseline visit (Day 1) followed up to Visit 3 (Day 19+/-2).	
Reporting group title	Placebo
Reporting group description:	
Subjects received matching placebo as a single-dose chewable tablet in a double-blind manner at the baseline visit (Day 1) followed up to Visit 3 (Day 19+/-2).	
Reporting group title	Mebendazole 500 mg
Reporting group description:	
Subjects received Mebendazole 500-mg chewable tablet in an open label manner at visit 3 (Day 19+/-2) followed up to Visit 5 (Day 7+/-1 from Visit 3).	
Subject analysis set title	Group 1 (1 to <3 years)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Group 1 represents pharmacokinetic analysis set which included subjects with age group 1 to less than (<) 3 years.	
Subject analysis set title	Group 2 (3 to 6 years)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Group 2 represents pharmacokinetic analysis set which included subjects with age group 3 to 6 years.	
Subject analysis set title	Group 3 (7 to 16 years)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Group 3 represents pharmacokinetic analysis set which included subjects with age group 7 to 16 years.	

Primary: Cure Rate for Ascaris lumbricoides at the End of Double-blind Treatment Period

End point title	Cure Rate for Ascaris lumbricoides at the End of Double-blind Treatment Period
End point description:	
Cure is defined as a post-treatment egg count of zero in subjects who had a positive egg count at baseline. The intent-to-treat (ITT) analysis set included all randomized subjects with a pretreatment stool sample positive for 1 or more worms of interest.	
End point type	Primary
End point timeframe:	
At Visit 3 (Day 19) of Double-blind treatment period	

End point values	Mebendazole 500 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86[1]	81[2]		
Units: percentage of participants				
number (confidence interval 95%)	83.7 (74.2 to 90.8)	11.1 (5.2 to 20.1)		

Notes:

[1] - Here 'N' signifies number of subjects analysed for this outcome measure.

[2] - Here 'N' signifies number of subjects analysed for this outcome measure.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Mebendazole 500 mg v Placebo
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel

Primary: Cure Rate for Trichuris trichiura at the End of Double-blind Treatment Period

End point title	Cure Rate for Trichuris trichiura at the End of Double-blind Treatment Period

End point description:

Cure is defined as a post-treatment egg count of zero in subjects who had a positive egg count at baseline. The ITT analysis set included all randomized subjects with a pretreatment stool sample positive for 1 or more worms of interest.

End point type	Primary

End point timeframe:

At Visit 3 (Day 19) of Double-blind treatment period

End point values	Mebendazole 500 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124[3]	119[4]		
Units: percentage of participants				
number (confidence interval 95%)	33.9 (25.6 to 42.9)	7.6 (3.5 to 13.9)		

Notes:

[3] - Here 'N' signifies number of subjects analysed for this outcome measure.

[4] - Here 'N' signifies number of subjects analysed for this outcome measure.

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Mebendazole 500 mg v Placebo

Number of subjects included in analysis	243
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cochran-Mantel-Haenszel

Primary: Number of Subjects Reporting Treatment Emergent Adverse Event (TEAE) in Double-Blind Treatment Period

End point title	Number of Subjects Reporting Treatment Emergent Adverse Event (TEAE) in Double-Blind Treatment Period[5]

End point description:

The safety analysis set consisted of all randomized subjects who received 1 dose of study agent (mebendazole or placebo) at baseline. An AE is any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. An serious adverse event (SAE) is 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/incapacity; congenital anomaly.

End point type	Primary

End point timeframe:

Up to Visit 3 (Day 19 +/-2)

Notes:

[5] - 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: Statistical analysis was not performed for this outcome measure.

End point values	Mebendazole 500 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144[6]	140[7]		
Units: subjects	9	8		

Notes:

[6] - Here 'N' signifies number of subjects analysed for this endpoint.

[7] - Here 'N' signifies number of subjects analysed for this endpoint.

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects Reporting Treatment Emergent Adverse Event (TEAE) in Open-Label Treatment Period

End point title	Number of Subjects Reporting Treatment Emergent Adverse Event (TEAE) in Open-Label Treatment Period[8]

End point description:

An AE is any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. A serious adverse event (SAE) is 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/incapacity; congenital anomaly. The open-label follow-up safety analysis set consisted of all randomized subjects who received a 500-mg chewable tablet of mebendazole at Visit 3.

End point type	Primary

End point timeframe:

At Visit 3 (Day 19+/-2) followed up to Visit 5 (Day 7+/-1 from Visit 3)

Notes:

[8] - 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: Statistical analysis was not performed for this outcome measure.

End point values	Mebendazole 500 mg			
Subject group type	Reporting group			
Number of subjects analysed	278			
Units: subjects	7			

Statistical analyses

No statistical analyses for this end point

Secondary: Egg Count Reduction Rate for Ascaris lumbricoides Infestation at the End of Double-blind Treatment Period

End point title	Egg Count Reduction Rate for Ascaris lumbricoides Infestation at the End of Double-blind Treatment Period

End point description:

Percent egg count reduction is defined as count of eggs at end of treatment period minus egg count at baseline divided by egg count at baseline. The ITT analysis set included all randomized subjects with a pretreatment stool sample positive for Ascaris lumbricoides.

End point type	Secondary

End point timeframe:

Baseline and Day 19 (Visit 3) at the End of Double-blind Treatment Period

End point values	Mebendazole 500 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86[9]	81[10]		
Units: percent change in egg count				
number (not applicable)	-97.9	-19.2		

Notes:

[9] - Here 'N' signifies number of subjects analysed for this outcome measure.

[10] - Here 'N' signifies number of subjects analysed for this outcome measure.

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Mebendazole 500 mg v Placebo
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA

Secondary: Egg Count Reduction Rate for Trichuris trichiura Infestation at the End of Double-blind Treatment Period

End point title	Egg Count Reduction Rate for Trichuris trichiura Infestation at the End of Double-blind Treatment Period

End point description:

Percent egg count reduction is defined as count of eggs at end of treatment period minus egg count at baseline divided by egg count at baseline. The ITT analysis set included all randomized subjects with a pretreatment stool sample positive for Trichuris trichiura.

End point type	Secondary

End point timeframe:

Baseline and Day 19 (Visit 3) at the End of Double-blind Treatment Period

End point values	Mebendazole 500 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124[11]	119[12]		
Units: percent change in egg count				
number (not applicable)	-59.7	-10.5		

Notes:

[11] - Here 'N' signifies number of subjects analysed for this outcome measure.

[12] - Here 'N' signifies number of subjects analysed for this outcome measure.

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Mebendazole 500 mg v Placebo
Number of subjects included in analysis	243
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA

Secondary: Maximum Plasma Concentration (Cmax) of Mebendazole

End point title	Maximum Plasma Concentration (Cmax) of Mebendazole

End point description:

The Cmax is the maximum plasma concentration. Pharmacokinetic (PK) population included all randomized subjects who received at least 1 dose of the study drug and had valid pharmacokinetic profile.

End point type	Secondary

End point timeframe:

Predose, 1, 2, 3, 5, 8 and 24 hours postdose at visit 4

End point values	Group 1 (1 to <3 years)	Group 2 (3 to 6 years)	Group 3 (7 to 16 years)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	22	12	10	
Units: nanogram per Milliliters (ng/mL)				
arithmetic mean (standard deviation)	210 (± 212)	49.9 (± 26.8)	34.2 (± 13.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Maximum Plasma Concentration (Tmax) of Mebendazole

End point title	Time to Reach Maximum Plasma Concentration (Tmax) of Mebendazole

End point description:

The Tmax is time to reach the maximum plasma concentration. PK population included all randomized subjects who received at least 1 dose of the study drug and had valid pharmacokinetic profile.

End point type	Secondary

End point timeframe:

Predose, 1, 2, 3, 5, 8 and 24 hours postdose at visit 4

End point values	Group 1 (1 to <3 years)	Group 2 (3 to 6 years)	Group 3 (7 to 16 years)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	22	12	10	
Units: hour (h)				
median (full range (min-max))	2.5 (1 to 8)	2 (0.98 to 3)	3 (1 to 8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration-time Curve From Time 0 to 8 Hours (AUC8h) of Medendazole

End point title	Area Under the Plasma Concentration-time Curve From Time 0 to 8 Hours (AUC8h) of Medendazole

End point description:

The (AUC8h) is the area under the plasma concentration-time curve from time 0 to 8 hours Post-dose. PK population included all randomized subjects who received at least 1 dose of the study drug and had valid pharmacokinetic profile.

End point type	Secondary

End point timeframe:

Predose, 1, 2, 3, 5, 8 and 24 hours postdose at visit 4

End point values	Group 1 (1 to <3 years)	Group 2 (3 to 6 years)	Group 3 (7 to 16 years)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	21[13]	9[14]	10	
Units: nanogram hour per Milliliters(ng*h/mL)				
arithmetic mean (standard deviation)	697 (± 367)	242 (± 139)	182 (± 66.3)	

Notes:

[13] - Here "N" signifies number of subjects analysed for this endpoint.

[14] - Here "N" signifies number of subjects analysed for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration-Time Curve From Time Zero to Time of the Last Quantifiable Concentration AUC(0-last) of Mebendazole

End point title	Area Under the Plasma Concentration-Time Curve From Time Zero to Time of the Last Quantifiable Concentration AUC(0-last) of Mebendazole

End point description:

The (AUC [0-last]) is the area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration. PK population included all randomized subjects who received at least 1 dose of the study drug and had valid pharmacokinetic profile.

End point type	Secondary

End point timeframe:

Predose, 1, 2, 3, 5, 8 and 24 hours postdose at visit 4

End point values	Group 1 (1 to <3 years)	Group 2 (3 to 6 years)	Group 3 (7 to 16 years)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	22	12	10	
Units: ng*h/mL				
arithmetic mean (standard deviation)	1320 (± 844)	416 (± 215)	387 (± 190)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Up to visit 5 (Day 26, 7+/-1 days after Visit 3)	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups	
Reporting group title	Double-blind/Mebendazole 500 mg
Reporting group description: Subjects received a single 500-mg chewable tablet of Mebendazole in a double-blind manner at the baseline visit (Day 1) followed up to Visit 3 (Day 19+/-2).	
Reporting group title	Open-label/Mebendazole 500 mg
Reporting group description: Subjects received Mebendazole 500-mg chewable tablet in an open label manner at visit 3 (Day 19+/-2) followed up to Visit 5 (Day 7+/-1 from Visit 3).	
Reporting group title	Double-blind/Placebo
Reporting group description: Subjects received matching placebo as a single-dose chewable tablet in a double-blind manner at the baseline visit (Day 1) followed up to Visit 3 (Day 19+/-2).	

Serious adverse events	Double-blind/Mebendazole 500 mg	Open-label/Mebendazole 500 mg	Double-blind/Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 144 (0.00%)	0 / 278 (0.00%)	0 / 140 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

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

Non-serious adverse events	Double-blind/Mebendazole 500 mg	Open-label/Mebendazole 500 mg	Double-blind/Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 144 (6.25%)	7 / 278 (2.52%)	8 / 140 (5.71%)
Injury, poisoning and procedural complications			
Soft Tissue Injury			
subjects affected / exposed	0 / 144 (0.00%)	1 / 278 (0.36%)	0 / 140 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			

Headache			
subjects affected / exposed	0 / 144 (0.00%)	1 / 278 (0.36%)	0 / 140 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Night Blindness			
subjects affected / exposed	0 / 144 (0.00%)	0 / 278 (0.00%)	1 / 140 (0.71%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal Distension			
subjects affected / exposed	2 / 144 (1.39%)	0 / 278 (0.00%)	1 / 140 (0.71%)
occurrences (all)	2	0	1
Abdominal Pain			
subjects affected / exposed	1 / 144 (0.69%)	1 / 278 (0.36%)	1 / 140 (0.71%)
occurrences (all)	1	2	1
Diarrhoea			
subjects affected / exposed	0 / 144 (0.00%)	2 / 278 (0.72%)	0 / 140 (0.00%)
occurrences (all)	0	2	0
Vomiting			
subjects affected / exposed	0 / 144 (0.00%)	1 / 278 (0.36%)	0 / 140 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 144 (0.69%)	0 / 278 (0.00%)	2 / 140 (1.43%)
occurrences (all)	1	0	2
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 144 (0.00%)	1 / 278 (0.36%)	0 / 140 (0.00%)
occurrences (all)	0	1	0
Rash Pruritic			
subjects affected / exposed	1 / 144 (0.69%)	0 / 278 (0.00%)	0 / 140 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	0 / 144 (0.00%)	0 / 278 (0.00%)	1 / 140 (0.71%)
occurrences (all)	0	0	1
Conjunctivitis Bacterial			

subjects affected / exposed	0 / 144 (0.00%)	0 / 278 (0.00%)	1 / 140 (0.71%)
occurrences (all)	0	0	1
Gastroenteritis			
subjects affected / exposed	1 / 144 (0.69%)	0 / 278 (0.00%)	0 / 140 (0.00%)
occurrences (all)	1	0	0
Malaria			
subjects affected / exposed	0 / 144 (0.00%)	1 / 278 (0.36%)	0 / 140 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	1 / 144 (0.69%)	0 / 278 (0.00%)	2 / 140 (1.43%)
occurrences (all)	1	0	2
Pneumonia			
subjects affected / exposed	0 / 144 (0.00%)	1 / 278 (0.36%)	0 / 140 (0.00%)
occurrences (all)	0	1	0
Tinea Infection			
subjects affected / exposed	1 / 144 (0.69%)	0 / 278 (0.00%)	0 / 140 (0.00%)
occurrences (all)	1	0	0
Tonsillitis			
subjects affected / exposed	0 / 144 (0.00%)	0 / 278 (0.00%)	1 / 140 (0.71%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Vitamin A Deficiency			
subjects affected / exposed	1 / 144 (0.69%)	0 / 278 (0.00%)	0 / 140 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 December 2014	This Amendment 4 included addition of information on additional collection of 2 venous blood samples (2.0 milliliters [mL] each) at 3- and 24-hour timepoints post-treatment for pharmacokinetic (PK) sampling (PK substudy) of 10 subjects in 7 to 16 years age group and collection of a back-up capillary PK sample at each timepoint (total of 14 samples) from each subject in the PK substudy.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported