Clinical trial results:
Efficacy of diosmectite (Smecta®) in the symptomatic treatment of acute diarrhoea in adults. A multicentre, randomised, double-blind, placebo-controlled, parallel groups study

Summary

EudraCT number	2015-001138-10
Trial protocol	PL CZ RO
Global end of trial date	08 April 2019

Results information

Result version number	v1 (current)
This version publication date	24 April 2020
First version publication date	24 April 2020

Trial information

Trial identification

Sponsor protocol code	F-FR-00250-105

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02704091
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ipsen Pharma SAS
Sponsor organisation address	65 quai Georges Gorse, Boulogne-Billancourt, France, 92100
Public contact	Medical Director, Ipsen Pharma SAS, clinical.trials@ipsen.com
Scientific contact	Medical Director, Ipsen Pharma SAS, clinical.trials@ipsen.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	08 April 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 April 2019
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 demonstrate that diosmectite efficacy (administered as 2 sachets three times a day [TID]) is superior to placebo regarding the time to recovery of an acute diarrhoea episode presumed of infectious origin in adult participants.

Protection of trial subjects:

The study was conducted under the provisions of the Declaration of Helsinki, in accordance with the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, Consolidated Guideline on Good Clinical Practice, in compliance with Independent Ethics Committees/Institutional Review Boards and informed consent regulations, and adhered to all local regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 March 2016
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	Tunisia: 188
Country: Number of subjects enrolled	Czech Republic: 187
Country: Number of subjects enrolled	Poland: 179
Country: Number of subjects enrolled	Egypt: 126
Country: Number of subjects enrolled	Algeria: 121
Country: Number of subjects enrolled	Lebanon: 52
Worldwide total number of subjects	853
EEA total number of subjects	366

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0

Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	804
From 65 to 84 years	45
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

The study enrolled adult participants with a recent episode of acute diarrhoea presumed of infectious origin, defined as the passage of 3 or more unformed (loose or watery) stools per day without alarm symptoms within the first 48 hours. Participants were randomised at 62 study centres in Algeria, Czech Republic, Egypt, Lebanon, Poland and Tunisia.

Pre-assignment

Screening details:

858 participants were randomised, of which 853 were included in the analysis and 5 were excluded due to invalid consent. Only participants included in the analysis are presented in the subject disposition. Participants received a diary evaluation booklet (DEB) to record each stool plus consistency on a daily basis from inclusion until end of study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Assessor, Carer, Data analyst, Subject, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	Diosmectite

Arm description:

Participants received diosmectite as 2 sachets, TID (2 sachets in the morning, 2 sachets at mid-day, and 2 sachets in the evening). Each sachet was taken in half a glass of water.
The mandatory treatment period was from Day 1 to Day 4 or Day 5 (with a minimum of 24 sachets taken within 4 or 5 days). Treatment could continue from Day 5 up to Day 8 or 9 (with a maximum of 48 sachets taken within 8 or 9 days).

Arm type	Experimental
Investigational medicinal product name	Diosmectite
Investigational medicinal product code	
Other name	Smecta®
Pharmaceutical forms	Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Diosmectite consisted of powder for suspension for oral use. Each sachet contained 3 grams diosmectite as active substance.

Arm title	Placebo

Arm description:

Participants received matching placebo as 2 sachets, TID (2 sachets in the morning, 2 sachets at mid-day, and 2 sachets in the evening). Each sachet was taken in half a glass of water.
The mandatory treatment period was from Day 1 to Day 4 or Day 5 (with a minimum of 24 sachets taken within 4 or 5 days). Treatment could continue from Day 5 up to Day 8 or 9 (with a maximum of 48 sachets taken within 8 or 9 days).

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

The placebo consisted of powder for suspension for oral use similar to the investigational product

without the active substance. The placebo was presented in sachets.

Number of subjects in period 1	Diosmectite	Placebo
Started	430	423
Completed	402	400
Not completed	28	23
Adverse event, non-fatal	4	3
Unspecified	2	8
Lost to follow-up	13	5
Consent withdrawn	4	4
Protocol deviation	5	3

Baseline characteristics

Reporting groups	
Reporting group title	Diosmectite
Reporting group description:	
Participants received diosmectite as 2 sachets, TID (2 sachets in the morning, 2 sachets at mid-day, and 2 sachets in the evening). Each sachet was taken in half a glass of water. The mandatory treatment period was from Day 1 to Day 4 or Day 5 (with a minimum of 24 sachets taken within 4 or 5 days). Treatment could continue from Day 5 up to Day 8 or 9 (with a maximum of 48 sachets taken within 8 or 9 days).	
Reporting group title	Placebo
Reporting group description:	
Participants received matching placebo as 2 sachets, TID (2 sachets in the morning, 2 sachets at mid-day, and 2 sachets in the evening). Each sachet was taken in half a glass of water. The mandatory treatment period was from Day 1 to Day 4 or Day 5 (with a minimum of 24 sachets taken within 4 or 5 days). Treatment could continue from Day 5 up to Day 8 or 9 (with a maximum of 48 sachets taken within 8 or 9 days).	

Reporting group values	Diosmectite	Placebo	Total
Number of subjects	430	423	853
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	39.7	38.6	
standard deviation	± 14.5	± 14.2	-
Gender categorical Units: Subjects			
Female	232	241	473
Male	198	182	380

End points

End points reporting groups

Reporting group title	Diosmectite

Reporting group description:

Participants received diosmectite as 2 sachets, TID (2 sachets in the morning, 2 sachets at mid-day, and 2 sachets in the evening). Each sachet was taken in half a glass of water.
The mandatory treatment period was from Day 1 to Day 4 or Day 5 (with a minimum of 24 sachets taken within 4 or 5 days). Treatment could continue from Day 5 up to Day 8 or 9 (with a maximum of 48 sachets taken within 8 or 9 days).

Reporting group title	Placebo

Reporting group description:

Participants received matching placebo as 2 sachets, TID (2 sachets in the morning, 2 sachets at mid-day, and 2 sachets in the evening). Each sachet was taken in half a glass of water.
The mandatory treatment period was from Day 1 to Day 4 or Day 5 (with a minimum of 24 sachets taken within 4 or 5 days). Treatment could continue from Day 5 up to Day 8 or 9 (with a maximum of 48 sachets taken within 8 or 9 days).

Primary: Time to Recovery

End point title	Time to Recovery

End point description:

Time to recovery was defined as the time from the first study treatment intake recorded in the electronic case report form (eCRF) to the first formed stool followed by a non-watery stool, recorded in the DEB. Results are presented as median time to recovery, calculated using the Kaplan-Meier technique. The Intention-To-Treat (ITT) population included all randomised participants (with the exception of those excluded from the analysis), analysed according to the arm to which they were randomised. Participants prematurely withdrawn without recovery or ending the study without recovery were censored (not responders) at the date/time of their last stool as recorded in the DEB. Participants who had not filled in the DEB (i.e. no post-baseline evaluation of stools) were censored at the date/time of their first study treatment intake (or the randomisation date/time if not administered).

End point type	Primary

End point timeframe:

From randomisation (Day 1) up to Day 9

End point values	Diosmectite	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	430	423		
Units: Hours				
median (confidence interval 95%)	66.0 (53.7 to 71.0)	68.6 (57.5 to 77.8)		

Statistical analyses

Statistical analysis title	Difference Between Treatment Groups

Statistical analysis description:

The primary analysis tested the equality of time to recovery between the 2 treatment groups, applying the 2-sided Gehan-Wilcoxon test (α=5%).

Comparison groups	Diosmectite v Placebo

Number of subjects included in analysis	853
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.2524
Method	Wilcoxon-Gehan test

Notes:

[1] - The following Null-hypothesis was tested:
H0: λA(t) = λB (t) versus H1: λA(t) ≠ λB (t),
where λ(t) represents the hazard at time t, A=diosmectite and B=placebo.

Secondary: Time From Diarrhoea Onset to Recovery

End point title	Time From Diarrhoea Onset to Recovery

End point description:

The event of diarrhoea onset (i.e. loose or watery stool) was recorded in the eCRF and the event of recovery (i.e. first formed stool followed by a non-watery stool) was recorded in the DEB. Results are presented as median time from diarrhoea onset to recovery, calculated using the Kaplan-Meier technique. The ITT population included all randomised participants (with the exception of those excluded from the analysis), analysed according to the arm to which they were randomised. Participants prematurely withdrawn without recovery or ending the study without recovery were censored (not responders) at the date/time of their last stool as recorded in the DEB. Participants who had not filled in the DEB (i.e. no post-baseline evaluation of stools) were censored at the date/time of their first study treatment intake (or the randomisation date/time if not administered).

End point type	Secondary

End point timeframe:

From randomisation (Day 1) up to Day 9

End point values	Diosmectite	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	429	423		
Units: Hours				
median (confidence interval 95%)	91.0 (82.5 to 107.0)	92.2 (84.2 to 102.8)		

Statistical analyses

Statistical analysis title	Difference Between Treatment Groups

Statistical analysis description:

Comparison between the 2 treatment groups for time from diarrhoea onset to recovery, analysed using the Gehan-Wilcoxon test.

Comparison groups	Diosmectite v Placebo
Number of subjects included in analysis	852
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3511
Method	Gehan-Wilcoxon test

Secondary: Time From Diarrhoea Onset to First Formed Stool

End point title	Time From Diarrhoea Onset to First Formed Stool

End point description:

The event of diarrhoea onset (i.e. loose or watery stool) was recorded in the eCRF and the event of first formed stool was recorded in the DEB. Results are presented as median time from diarrhoea onset to first formed stool, calculated using the Kaplan-Meier technique. The ITT population included all randomised participants (with the exception of those excluded from the analysis), analysed according to the arm to which they were randomised. Participants prematurely withdrawn with no formed stool or ending the study with no formed stool were censored at the date/time of their last stool as recorded in the DEB. Participants who had not filled in the DEB (i.e. no post-baseline evaluation of stools) were censored at the date/time of their first study treatment intake (or the randomisation date/time if not administered).

End point type	Secondary

End point timeframe:

From randomisation (Day 1) up to Day 9

End point values	Diosmectite	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	429	423		
Units: Hours				
median (full range (min-max))	84.3 (77.5 to 94.2)	84.6 (79.8 to 91.0)		

Statistical analyses

Statistical analysis title	Difference Between Treatment Groups

Statistical analysis description:

Comparison between the 2 treatment groups for time from diarrhoea onset to first formed stool, analysed using the Gehan-Wilcoxon test.

Comparison groups	Diosmectite v Placebo
Number of subjects included in analysis	852
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7285
Method	Gehan-Wilcoxon test

Secondary: Time From the First Study Treatment Intake to the Last Watery Stool

End point title	Time From the First Study Treatment Intake to the Last Watery Stool

End point description:

The event of first study treatment intake was recorded in the eCRF and the event of last watery stool was recorded in the DEB. Results are presented as median time from first study treatment intake to last watery stool, calculated using the Kaplan-Meier technique. The ITT population included all randomised participants (with the exception of those excluded from the analysis), analysed according to the arm to which they were randomised. Participants prematurely withdrawn with no watery stool or ending the study with no watery stool were censored at the date/time of their last stool as recorded in the DEB. Participants who had not filled in the DEB (i.e. no post-baseline evaluation of stools) were censored at the date/time of their first study treatment intake (or the randomisation date/time if not administered).

End point type	Secondary

End point timeframe:

From randomisation (Day 1) up to Day 9

End point values	Diosmectite	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	430	423		
Units: Hours				
median (confidence interval 95%)	56.2 (44.6 to 66.2)	60.0 (52.8 to 68.8)		

Statistical analyses

Statistical analysis title	Difference between Treatment Groups

Statistical analysis description:

Comparison between the 2 treatment groups for time from first study treatment intake to last watery stool, analysed using the Gehan-Wilcoxon test.

Comparison groups	Diosmectite v Placebo
Number of subjects included in analysis	853
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1807
Method	Gehan-Wilcoxon test

Secondary: Number of Stools, Per 12-Hour Period

End point title	Number of Stools, Per 12-Hour Period

End point description:

Number of stools, per 12-hour period, was recorded in the DEB. The ITT population included all randomised participants (with the exception of those excluded from the analysis), analysed according to the arm to which they were randomised. n = number of participants with data available for analysis for each specified time point. Note: median number of stools in the diosmectite arm at time point 204-216 hours was not calculated since zero participants were available for analysis (denoted by 999999).

End point type	Secondary

End point timeframe:

From randomisation (Day 1) up to Day 9

End point values	Diosmectite	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	413	412		
Units: Stools				
median (full range (min-max))				
0 - 12 hours (n=413, 412)	3.0 (0 to 11)	3.0 (0 to 14)		
12 - 24 hours (n=407, 411)	2.0 (0 to 7)	2.0 (0 to 7)		

24 - 36 hours (n=402, 407)	1.0 (0 to 8)	2.0 (0 to 19)		
36 - 48 hours (n=396, 400)	1.0 (0 to 7)	1.0 (0 to 6)		
48 - 60 hours (n=386, 391)	1.0 (0 to 7)	1.0 (0 to 9)		
60 - 72 hours (n=373, 383)	1.0 (0 to 6)	1.0 (0 to 7)		
72 - 84 hours (n=320, 329)	1.0 (0 to 12)	1.0 (0 to 7)		
84 - 96 hours (n=269, 264)	1.0 (0 to 6)	1.0 (0 to 7)		
96 - 108 hours (n=191, 174)	1.0 (0 to 5)	1.0 (0 to 7)		
108 - 120 hours (n=151, 143)	1.0 (0 to 5)	1.0 (0 to 6)		
120 - 132 hours (n=109, 120)	1.0 (0 to 4)	1.0 (0 to 6)		
132 - 144 hours (n=95, 109)	1.0 (0 to 6)	1.0 (0 to 4)		
144 - 156 hours (n=75, 100)	1.0 (0 to 4)	1.0 (0 to 6)		
156 - 168 hours (n=57, 80)	1.0 (0 to 4)	1.0 (0 to 5)		
168 - 180 hours (n=42, 60)	1.0 (0 to 5)	1.0 (0 to 4)		
180 - 192 hours (n=32, 44)	1.0 (0 to 5)	1.0 (0 to 5)		
192 - 204 hours (n=17, 16)	1.0 (1 to 4)	1.0 (0 to 4)		
204 - 216 hours (n=0, 1)	999999 (999999 to 999999)	1.0 (1 to 1)		

Statistical analyses

Statistical analysis title	Difference Between Treatment Groups Overall

Statistical analysis description:

Comparison between the 2 treatment groups for number of stools for the overall time period, based on an analysis of covariance (ANCOVA) method for repeated measurements. The model included the number of stools 24 hours before randomisation (baseline) as covariate, treatment, time point (12-hour period), the treatment by time point interaction as fixed effects and participant as random effect.

Comparison groups	Diosmectite v Placebo
Number of subjects included in analysis	825
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4294
Method	ANCOVA
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.15
upper limit	0.07

Secondary: Number of Watery Stools, Per 12-Hour Period

End point title	Number of Watery Stools, Per 12-Hour Period

End point description:

Number of watery stools, per 12-hour period, was recorded in the DEB. The ITT population included all randomised participants (with the exception of those excluded from the analysis), analysed according to the arm to which they were randomised. n = number of participants with data available for analysis for each specified time point. Note: median number of watery stools in the diosmectite arm at time point 204-216 hours was not calculated since zero participants were available for analysis (denoted by

999999).

End point type	Secondary

End point timeframe:

From randomisation (Day 1) up to Day 9

End point values	Diosmectite	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	413	412		
Units: Stools				
median (full range (min-max))				
0 - 12 hours (n=413, 412)	3.0 (0 to 11)	3.0 (0 to 14)		
12 - 24 hours (n=407, 411)	1.0 (0 to 7)	1.0 (0 to 7)		
24 - 36 hours (n=402, 407)	0.0 (0 to 8)	1.0 (0 to 19)		
36 - 48 hours (n=396, 400)	0.0 (0 to 7)	0.0 (0 to 6)		
48 - 60 hours (n=386, 391)	0.0 (0 to 7)	0.0 (0 to 9)		
60 - 72 hours (n=373, 383)	0.0 (0 to 6)	0.0 (0 to 7)		
72 - 84 hours (n=320, 329)	0.0 (0 to 10)	0.0 (0 to 7)		
84 - 96 hours (n=269, 264)	0.0 (0 to 6)	0.0 (0 to 7)		
96 - 108 hours (n=191, 174)	0.0 (0 to 5)	0.0 (0 to 7)		
108 - 120 hours (n=151,143)	0.0 (0 to 5)	0.0 (0 to 6)		
120 - 132 hours (n=109, 120)	0.0 (0 to 4)	0.0 (0 to 5)		
132 - 144 hours (n=95, 109)	0.0 (0 to 6)	0.0 (0 to 4)		
144 - 156 hours (n=75, 100)	0.0 (0 to 3)	0.0 (0 to 5)		
156 - 168 hours (n=57, 80)	0.0 (0 to 4)	0.0 (0 to 5)		
168 - 180 hours (n=42, 60)	0.0 (0 to 5)	0.0 (0 to 4)		
180 - 192 hours (n=32, 44)	0.0 (0 to 5)	0.0 (0 to 5)		
192 - 204 hours (n=17, 16)	0.0 (0 to 4)	0.0 (0 to 3)		
204 - 216 hours (n=0, 1)	999999 (999999 to 999999)	0.0 (0 to 0)		

Statistical analyses

Statistical analysis title	Difference Between Treatment Groups Overall

Statistical analysis description:

Comparison between the 2 treatment groups for number of watery stools for the overall time period, based on an ANCOVA method for repeated measurements. The model included the number of watery stools 24 hours before randomisation (baseline) as covariate, treatment, time point (12-hour period), the treatment by time point interaction as fixed effects and participant as random effect.

Comparison groups	Diosmectite v Placebo
Number of subjects included in analysis	825
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0465
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.12

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.24
upper limit	0

Secondary: Percentage of Participants With Associated Symptoms, Per 12-Hour Period

End point title	Percentage of Participants With Associated Symptoms, Per 12-Hour Period

End point description:

Percentage of participants with associated symptoms (at least 1 symptom of nausea, vomiting, abdominal pain or anal irritation) per 12-hour period is presented. Nausea, vomiting, abdominal pain and anal irritation were recorded in the DEB. The ITT population included all randomised participants (with the exception of those excluded from the analysis), analysed according to the arm to which they were randomised. n = number of participants with data available for analysis for each specified time point.

End point type	Secondary

End point timeframe:

From randomisation (Day 1) up to Day 9

End point values	Diosmectite	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	430	423		
Units: Percentage of participants				
number (not applicable)				
0 - 12 hours (n=400, 390)	76.3	76.4		
12 - 24 hours (n=395, 395)	67.1	64.6		
24 - 36 hours (n=402, 397)	56.2	54.2		
36 - 48 hours (n=395, 395)	44.8	45.6		
48 - 60 hours (n=392, 395)	34.9	35.4		
60 - 72 hours (n=376, 379)	28.7	28.8		
72 - 84 hours (n=370, 381)	24.3	22.0		
84 - 96 hours (n=329, 345)	21.6	20.6		
96 - 108 hours (n=228, 242)	20.6	24.0		
108 - 120 hours (n=177, 173)	18.6	24.9		
120 - 132 hours (n=136, 136)	18.4	27.9		
132 - 144 hours (n=103, 117)	12.6	21.4		
144 - 156 hours (n=86, 104)	10.5	19.2		
156 - 168 hours (n=71, 87)	8.5	16.1		
168 - 180 hours (n=58, 76)	8.6	11.8		
180 - 192 hours (n=49, 61)	8.2	9.8		
192 - 204 hours (n=31, 38)	9.7	10.5		
204 - 216 hours (n=17, 20)	5.9	0.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Abdominal Pain Intensity Scores, Per 12-Hour Period

End point title	Abdominal Pain Intensity Scores, Per 12-Hour Period

End point description:

Abdominal pain intensity per 12-hour period was recorded in the DEB. Abdominal pain intensity was rated with a 5-point ordinal scale: 0 = absent, 1= mild, 2 =moderate, 3 = severe, 4= very severe. Higher scores indicate a worse outcome. The median abdominal pain intensity score for each 12-hour period is presented. The ITT population included all randomised participants (with the exception of those excluded from the analysis), analysed according to the arm to which they were randomised. n = number of participants with data available for analysis for each specified time point.

End point type	Secondary

End point timeframe:

From randomisation (Day 1) up to Day 9

End point values	Diosmectite	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	430	423		
Units: Scores on a scale				
median (full range (min-max))				
0 - 12 hours (n=384, 377)	1.0 (0 to 4)	1.0 (0 to 4)		
12 - 24 hours (n=382, 379)	1.0 (0 to 4)	1.0 (0 to 4)		
24 - 36 hours (n=393, 386)	0.0 (0 to 4)	0.0 (0 to 4)		
36 - 48 hours (n=382, 380)	0.0 (0 to 4)	0.0 (0 to 4)		
48 - 60 hours (n=381, 380)	0.0 (0 to 4)	0.0 (0 to 4)		
60 - 72 hours (n=368, 366)	0.0 (0 to 4)	0.0 (0 to 4)		
72 - 84 hours (n=362, 369)	0.0 (0 to 4)	0.0 (0 to 4)		
84 - 96 hours (n=319, 336)	0.0 (0 to 4)	0.0 (0 to 4)		
96 - 108 hours (n=220, 233)	0.0 (0 to 3)	0.0 (0 to 4)		
108 - 120 hours (n=171, 171)	0.0 (0 to 3)	0.0 (0 to 4)		
120 - 132 hours (n=133, 133)	0.0 (0 to 4)	0.0 (0 to 4)		
132 - 144 hours (n=101, 113)	0.0 (0 to 2)	0.0 (0 to 4)		
144 - 156 hours (n=86, 104)	0.0 (0 to 3)	0.0 (0 to 4)		
156 - 168 hours (n=67, 86)	0.0 (0 to 3)	0.0 (0 to 4)		
168 - 180 hours (n=55, 75)	0.0 (0 to 3)	0.0 (0 to 4)		
180 - 192 hours (n=45, 60)	0.0 (0 to 2)	0.0 (0 to 4)		
192 - 204 hours (n=29, 38)	0.0 (0 to 4)	0.0 (0 to 4)		
204 - 216 hours (n=17, 20)	0.0 (0 to 1)	0.0 (0 to 0)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment emergent adverse events were collected from Day 1 until 7 days after the end of the study treatment, up to 16 days.

Adverse event reporting additional description:

The safety population included all randomised participants who received at least 1 dose of study treatment (except for those excluded from the analysis). Participants were analysed according to the actual treatment received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Diosmectite

Reporting group description:

Participants received diosmectite as 2 sachets, TID (2 sachets in the morning, 2 sachets at mid-day, and 2 sachets in the evening). Each sachet was taken in half a glass of water.
The mandatory treatment period was from Day 1 to Day 4 or Day 5 (with a minimum of 24 sachets taken within 4 or 5 days). Treatment could continue from Day 5 up to Day 8 or 9 (with a maximum of 48 sachets taken within 8 or 9 days).

Reporting group title	Placebo

Reporting group description:

Participants received matching placebo as 2 sachets, TID (2 sachets in the morning, 2 sachets at mid-day, and 2 sachets in the evening). Each sachet was taken in half a glass of water.
The mandatory treatment period was from Day 1 to Day 4 or Day 5 (with a minimum of 24 sachets taken within 4 or 5 days). Treatment could continue from Day 5 up to Day 8 or 9 (with a maximum of 48 sachets taken within 8 or 9 days).

Serious adverse events	Diosmectite	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 430 (0.23%)	1 / 421 (0.24%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 430 (0.23%)	0 / 421 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 430 (0.00%)	1 / 421 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			

subjects affected / exposed	1 / 430 (0.23%)	0 / 421 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 430 (0.23%)	0 / 421 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 430 (0.00%)	1 / 421 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Diosmectite	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 430 (6.74%)	32 / 421 (7.60%)	
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 430 (0.00%)	1 / 421 (0.24%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 430 (0.70%)	7 / 421 (1.66%)	
occurrences (all)	3	7	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 430 (0.23%)	0 / 421 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	9 / 430 (2.09%)	9 / 421 (2.14%)	
occurrences (all)	9	9	
Anorectal discomfort			

subjects affected / exposed	5 / 430 (1.16%)	3 / 421 (0.71%)	
occurrences (all)	5	3	
Constipation			
subjects affected / exposed	2 / 430 (0.47%)	3 / 421 (0.71%)	
occurrences (all)	2	3	
Nausea			
subjects affected / exposed	1 / 430 (0.23%)	3 / 421 (0.71%)	
occurrences (all)	1	4	
Proctalgia			
subjects affected / exposed	2 / 430 (0.47%)	0 / 421 (0.00%)	
occurrences (all)	2	0	
Anal pruritus			
subjects affected / exposed	1 / 430 (0.23%)	0 / 421 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	0 / 430 (0.00%)	1 / 421 (0.24%)	
occurrences (all)	0	1	
Flatulence			
subjects affected / exposed	0 / 430 (0.00%)	1 / 421 (0.24%)	
occurrences (all)	0	1	
Dyspepsia			
subjects affected / exposed	0 / 430 (0.00%)	1 / 421 (0.24%)	
occurrences (all)	0	1	
Gastrointestinal disorder			
subjects affected / exposed	1 / 430 (0.23%)	0 / 421 (0.00%)	
occurrences (all)	1	0	
Stomatitis			
subjects affected / exposed	1 / 430 (0.23%)	0 / 421 (0.00%)	
occurrences (all)	1	0	
Haemorrhoids			
subjects affected / exposed	0 / 430 (0.00%)	1 / 421 (0.24%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	1 / 430 (0.23%)	0 / 421 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal			

disorders			
Oropharyngeal pain			
subjects affected / exposed	1 / 430 (0.23%)	2 / 421 (0.48%)	
occurrences (all)	1	2	
Rhinorrhoea			
subjects affected / exposed	1 / 430 (0.23%)	1 / 421 (0.24%)	
occurrences (all)	1	1	
Cough			
subjects affected / exposed	1 / 430 (0.23%)	0 / 421 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Acrophobia			
subjects affected / exposed	0 / 430 (0.00%)	1 / 421 (0.24%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 430 (0.47%)	0 / 421 (0.00%)	
occurrences (all)	2	0	
Arthralgia			
subjects affected / exposed	1 / 430 (0.23%)	0 / 421 (0.00%)	
occurrences (all)	1	0	
Spinal pain			
subjects affected / exposed	0 / 430 (0.00%)	2 / 421 (0.48%)	
occurrences (all)	0	2	
Muscle spasms			
subjects affected / exposed	0 / 430 (0.00%)	1 / 421 (0.24%)	
occurrences (all)	0	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 430 (0.23%)	0 / 421 (0.00%)	
occurrences (all)	1	0	
Arthritis salmonella			
subjects affected / exposed	1 / 430 (0.23%)	0 / 421 (0.00%)	
occurrences (all)	1	0	
Rhinitis			

subjects affected / exposed	0 / 430 (0.00%)	1 / 421 (0.24%)	
occurrences (all)	0	1	
Urethritis			
subjects affected / exposed	0 / 430 (0.00%)	1 / 421 (0.24%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 430 (0.23%)	0 / 421 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 March 2016	- Rewording of an inclusion criteria to fit better with the clinical presentation of a recent acute diarrhoea episode; - At the request of Czech Republic Ethical Committee and Health Authorities: change or addition of some selection criteria and of criteria for withdrawal and poststudy follow up; standardisation of dietary measures.
07 January 2019	- Update of targeted countries for participant's recruitment; - Prolongation of study duration; - Update of exclusion criteria #21.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported