Clinical trial results:
Bacillus Clausii in the Treatment of Acute Community-acquired Diarrhea Among Latin American Children (cadiLAc)

Summary

EudraCT number	2016-003444-37
Trial protocol	Outside EU/EEA
Global end of trial date	07 January 2016

Results information

Result version number	v1 (current)
This version publication date	19 November 2016
First version publication date	19 November 2016

Trial information

Trial identification

Sponsor protocol code	ENTERR06929

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02169817
WHO universal trial number (UTN)	U1111-1149-1704

Notes:

Sponsors

Sponsor organisation name	Sanofi aventis recherche & développement
Sponsor organisation address	1 avenue Pierre Brossolette, Chilly, Mazarin, France, 91380
Public contact	Trial Transparency Team, Sanofi Aventis Recherche & Developpement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi Aventis Recherche & Developpement, Contact-US@sanofi.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	14 March 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 January 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the effectiveness of treatment with Bacillus clausii probiotic strain (Enterogermina) in combination with oral rehydration therapy (ORT) for a period of 5 days, in the duration of acute community-acquired diarrhea in Latin American children.

Protection of trial subjects:

The study was conducted by investigators experienced in the treatment of paediatric subjects. The parent(s) or guardian(s) as well as the children were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time. In addition to the consent form for the parent(s)/guardian(s), an assent form in child appropriate language was provided and explained to the child. Repeated invasive procedures were minimised.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 July 2014
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	Guatemala: 71
Country: Number of subjects enrolled	Argentina: 50
Country: Number of subjects enrolled	Peru: 50
Country: Number of subjects enrolled	Brazil: 188
Country: Number of subjects enrolled	Colombia: 110
Country: Number of subjects enrolled	Mexico: 158
Worldwide total number of subjects	627
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)	338

Children (2-11 years)	289
Adolescents (12-17 years)	0
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 at 30 centers in 6 countries. A total of 642 subjects were screened between 18 July 2014 and 30 December 2015.

Pre-assignment

Screening details:

A total 642 subjects were screened, and 627 subjects were treated.

Period 1

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

Arms

Arm title	Bacillus clausii + ORT

Arm description:

Bacillus clausii along with oral rehydration therapy (ORT) was given for 5 days.

Arm type	Experimental
Investigational medicinal product name	Bacillus clausii
Investigational medicinal product code	
Other name	Enterogermina™
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Vial containing 2 billion spores twice daily.

Investigational medicinal product name	ORT
Investigational medicinal product code	
Other name	Enterolyte®
Pharmaceutical forms	Powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

ORT (low osmolarity formulation) according to the Investigator's recommendation.

Number of subjects in period 1	Bacillus clausii + ORT
Started	627
Completed	605
Not completed	22
Consent withdrawn by subject	2
Missed doses due to personal reasons	9
Adverse events	2
Overdosing	1
Lost to follow-up	8

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study
Reporting group description:	
Bacillus clausii along with ORT was given for 5 days.	

Reporting group values	Overall Study	Total	
Number of subjects	627	627	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	2.2		
standard deviation	± 1.3	-	
Gender categorical Units: Subjects			
Female	259	259	
Male	368	368	

End points

End points reporting groups

Reporting group title	Bacillus clausii + ORT

Reporting group description:

Bacillus clausii along with oral rehydration therapy (ORT) was given for 5 days.

Primary: Duration of Diarrhea

End point title	Duration of Diarrhea[1]

End point description:

Duration of diarrhea, as counted from the first intake of the investigation product up to the first appearance of a loose stool followed by two consecutive normal stools. Analysis was performed on per-protocol (PP) population included all eligible subjects (not screen failure subjects) with no major protocol deviations.

End point type	Primary

End point timeframe:

From Day 1 to Day 5

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: This was not a comparative study (no inference was planned). Primary endpoint was provided only in terms of descriptive statistics.

End point values	Bacillus clausii + ORT			
Subject group type	Reporting group			
Number of subjects analysed	598			
Units: hours				
arithmetic mean (standard deviation)	82.9 (± 40.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Number of Stools per Day

End point title	Mean Number of Stools per Day

End point description:

Analysis was performed on PP population.

End point type	Secondary

End point timeframe:

From Day 1 to Day 5

End point values	Bacillus clausii + ORT			
Subject group type	Reporting group			
Number of subjects analysed	600			
Units: stool episodes				
arithmetic mean (standard deviation)				
Baseline	5.6 (± 2.1)			
Day 1	3.5 (± 2.1)			
Day 2	3.4 (± 2)			
Day 3	2.6 (± 1.8)			
Day 4	2.2 (± 1.6)			
Day 5	1.8 (± 1.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Consistency of Stools

End point title	Consistency of Stools
End point description:	
Analysis was performed on PP population.	
End point type	Secondary
End point timeframe:	
From Day 1 to Day 5	

End point values	Bacillus clausii + ORT			
Subject group type	Reporting group			
Number of subjects analysed	600			
Units: stool episodes				
arithmetic mean (standard deviation)				
Day 1: Normal	0.1 (± 0.4)			
Day 1: Loose	1 (± 1.5)			
Day 1: Watery	2.4 (± 2.4)			
Day 2: Normal	0.2 (± 0.6)			
Day 2: Loose	1.4 (± 1.5)			
Day 2: Watery	1.8 (± 2.2)			
Day 3: Normal	0.4 (± 0.8)			
Day 3: Loose	1.4 (± 1.4)			
Day 3: Watery	0.8 (± 1.6)			
Day 4: Normal	0.7 (± 1)			
Day 4: Loose	1 (± 1.3)			
Day 4: Watery	0.4 (± 1.3)			
Day 5: Normal	0.9 (± 1)			
Day 5: Loose	0.6 (± 1.1)			
Day 5: Watery	0.2 (± 1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Vomiting Episodes per Day

End point title	Number of Vomiting Episodes per Day

End point description:

Analysis was performed on PP population. Here, "n" signifies the subjects with data available at specified time point.

End point type	Secondary

End point timeframe:

From Day 1 to Day 5

End point values	Bacillus clausii + ORT			
Subject group type	Reporting group			
Number of subjects analysed	600			
Units: vomiting episodes				
arithmetic mean (standard deviation)				
Baseline (n=599)	0.9 (± 1.7)			
Day 1 (n=600)	0.3 (± 0.7)			
Day 2 (n=600)	0.2 (± 0.5)			
Day 3 (n=600)	0.1 (± 0.4)			
Day 4 (n=600)	0 (± 0.3)			
Day 5 (n=599)	0 (± 0.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Parent / Legal Guardian's Assessment of Children's Overall Acceptance of Enterogermina

End point title	Parent / Legal Guardian's Assessment of Children's Overall Acceptance of Enterogermina

End point description:

Children’s acceptance of enterogermina was recorded by their parents/legal guardian on a diary as: Excellent, good, fair, poor. Acceptance was assessed separately after both Dose 1 and Dose 2. Total percentage of subjects (assessed after dose 1 and dose 2) were reported. Analysis was performed on PP population.

End point type	Secondary

End point timeframe:

From Day 1 to Day 5

End point values	Bacillus clausii + ORT			
Subject group type	Reporting group			
Number of subjects analysed	600			
Units: percentage of subjects				
number (not applicable)				
Excellent	73			
Good	20.4			
Fair	5.1			
Poor	1.5			

Statistical analyses

No statistical analyses for this end point

Secondary: Parent / Legal Guardian's Assessment of Children's Overall General State

End point title	Parent / Legal Guardian's Assessment of Children's Overall General State

End point description:

Children’s general state was recorded by their parents/legal guardian on a diary as: Good, fair and poor. Analysis was performed on PP population.

End point type	Secondary

End point timeframe:

From Day 1 to Day 5

End point values	Bacillus clausii + ORT			
Subject group type	Reporting group			
Number of subjects analysed	600			
Units: percentage of subjects				
number (not applicable)				
Day 1: Good	34			
Day 1: Fair	51.8			
Day 1: Poor	14.2			
Day 2: Good	49.7			
Day 2: Fair	43.3			
Day 2: Poor	7			
Day 3: Good	69.5			
Day 3: Fair	28.3			
Day 3: Poor	2.2			
Day 4: Good	82.8			
Day 4: Fair	15.5			
Day 4: Poor	1.7			

Day 5: Good	91.7			
Day 5: Fair	7.8			
Day 5: Poor	0.5			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from signature of informed consent form up to final visit (between Day 6 and Day 10) regardless of seriousness or relationship to investigational product. Analysis was done on safety population.

Adverse event reporting additional description:

Reported AE are treatment-emergent adverse events that is AEs that developed/worsened during the 'on treatment period' (first day of initial dose of study drug, up to the last visit).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Bacillus clausii + ORT

Reporting group description:

Bacillus clausii along with ORT was given for 5 days.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: No non-serious adverse events (equal or greater than threshold of 5%) were observed in any subjects during the study.

Serious adverse events	Bacillus clausii + ORT		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 627 (0.16%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Nervous system disorders			
Seizure			
subjects affected / exposed	1 / 627 (0.16%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Bacillus clausii + ORT		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 627 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 January 2014	Change in exclusion criteria to clarify the permission of probiotics and prebiotics in dairy food (such as yoghurt, cheese, milk) prior to study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported