



## Clinical trial results:

### **A Phase III, Controlled, Open-Label, Randomized, Parallel Group, Multicentric, Comparative Study to Assess the Efficacy and Safety of Oral Rehydration Therapy (ORT) in Combination With Spores of *Bacillus clausii* (Enterogermina™) Versus ORT Alone, Administered For 5 Days in the Treatment of Acute Diarrhea in Children**

#### **Summary**

EudraCT number	2014-004636-19
Trial protocol	Outside EU/EEA
Global end of trial date	26 December 2007

#### **Results information**

Result version number	v1 (current)
This version publication date	27 April 2016
First version publication date	25 July 2015

#### **Trial information**

##### **Trial identification**

Sponsor protocol code	ENTER_L_01486
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##### **Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00457353
WHO universal trial number (UTN)	-

Notes:

##### **Sponsors**

Sponsor organisation name	Sanofi India Limited
Sponsor organisation address	Sanofi House, CTS No.117-B, L&T Business Park, Saki Vihar Road, Powai, Mumbai, India, 400072
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	29 February 2008
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	26 December 2007
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To demonstrate the efficacy of treatment with oral rehydration therapy (ORT) in combination with *Bacillus clausii* probiotic strain (Enterogermina™) as compared to treatment with ORT alone, for a period of 5 days, in reducing the duration of acute diarrhea in Indian children.

Protection of trial subjects:

The study was conducted by investigators experienced in the treatment of pediatric 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 minimized. The number of blood samples as well as the amount of blood drawn were adjusted according to age and weight. A topical anesthesia may have been used to minimize distress and discomfort.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 March 2007
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	India: 264
Worldwide total number of subjects	264
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)	1
Infants and toddlers (28 days-23 months)	185
Children (2-11 years)	78
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 6 centers in India. A total of 487 subjects were screened between 02 March 2007 and 18 December 2007.

### Pre-assignment

Screening details:

Of 487 screened subjects, 264 subjects were randomized.

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	ORT + Bacillus clausii

Arm description:

Oral Rehydration Therapy (ORT) along with Bacillus clausii for 5 days.

Arm type	Experimental
Investigational medicinal product name	Bacillus clausii
Investigational medicinal product code	
Other name	Enterogermina™
Pharmaceutical forms	Suspension and effervescent granules for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Vial containing 2 billion spores twice daily.

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

Dosage and administration details:

ORS (based on World Health Organization formula) according to the Investigator's recommendation.

<b>Arm title</b>	Oral Rehydration Therapy
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Arm description:

ORS alone for 5 days.

Arm type	Active comparator
Investigational medicinal product name	ORS
Investigational medicinal product code	
Other name	ELECTRAL®
Pharmaceutical forms	Powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

ORS preparations administered according to the Investigator's recommendation.

<b>Number of subjects in period 1</b>	ORT + Bacillus clausii	Oral Rehydration Therapy
Started	132	132
Completed	130	127
Not completed	2	5
Adverse event	-	1
Subject moved	1	-
Lost to follow-up	1	4

## Baseline characteristics

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### Reporting groups

Reporting group title	ORT + Bacillus clausii
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Reporting group description:

Oral Rehydration Therapy (ORT) along with Bacillus clausii for 5 days.

Reporting group title	Oral Rehydration Therapy
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Reporting group description:

ORS alone for 5 days.

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Reporting group values	ORT + Bacillus clausii	Oral Rehydration Therapy	Total
Number of subjects	132	132	264
Age categorical Units: Subjects			
Newborns (0-27 days)	1	0	1
Infants and toddlers (28 days-23 months)	95	90	185
Children (2-11 years)	36	42	78
Gender categorical Units: Subjects			
Female	57	60	117
Male	75	72	147

## End points

### End points reporting groups

Reporting group title	ORT + Bacillus clausii
Reporting group description: Oral Rehydration Therapy (ORT) along with Bacillus clausii for 5 days.	
Reporting group title	Oral Rehydration Therapy
Reporting group description: ORS alone for 5 days.	

### Primary: Duration of Diarrhea

End point title	Duration of Diarrhea
End point description: Duration of diarrhea, as counted from the first intake of the investigational product up to the first appearance of a loose stool followed by two consecutive normal stools. Analysis was performed on safety population included all randomized and treated subjects.	
End point type	Primary
End point timeframe: From D1 to end of treatment visit (Day 6)	

End point values	ORT + Bacillus clausii	Oral Rehydration Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	126		
Units: hours				
arithmetic mean (standard deviation)	48.6 (± 38.2)	56.1 (± 40)		

### Statistical analyses

Statistical analysis title	ORT + Bacillus clausii vs ORT
Statistical analysis description: Analysis was performed by a log-rank test (Kaplan-Meier survival analysis).	
Comparison groups	Oral Rehydration Therapy v ORT + Bacillus clausii
Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.13
Method	Logrank

## Secondary: Number of Stools Per Day

End point title	Number of Stools Per Day
End point description: Analysis was performed on safety population. Number of subjects analysed = subjects with data available at each day.	
End point type	Secondary
End point timeframe: On each day (D1 to D6)	

End point values	ORT + Bacillus clausii	Oral Rehydration Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	111	101		
Units: stool episodes				
arithmetic mean (standard deviation)	7.4 ( $\pm$ 6.5)	8.6 ( $\pm$ 6.5)		

## 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 safety population.	
End point type	Secondary
End point timeframe: On each day (D1 to D6)	

End point values	ORT + Bacillus clausii	Oral Rehydration Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	126		
Units: subjects				
Day 1: Watery	57	52		
Day 1: Loose	61	64		
Day 2: Watery	31	34		
Day 2: Loose	66	62		
Day 3: Watery	14	18		
Day 3: Loose	53	63		
Day 4: Watery	4	6		
Day 4: Loose	35	44		
Day 5: Watery	3	5		
Day 5: Loose	25	26		

Day 6: Watery	3	2		
Day 6: Loose	14	18		

### 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 safety population. Here, "n" signifies the subjects with data available at specified time point.	
End point type	Secondary
End point timeframe: On each day (D1 to D6)	

End point values	ORT + Bacillus clausii	Oral Rehydration Therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	126		
Units: vomiting episodes				
arithmetic mean (standard deviation)				
Day 1 (n=129, 126)	0.4 (± 0.9)	0.4 (± 1)		
Day 2 (n=129, 126)	0.3 (± 0.8)	0.3 (± 0.8)		
Day 3 (n=129, 126)	0.2 (± 0.7)	0.2 (± 0.8)		
Day 4 (n=129, 126)	0.1 (± 0.6)	0.2 (± 0.6)		
Day 5 (n=129, 126)	0.1 (± 0.4)	0.1 (± 0.7)		
Day 6 (n=107, 100)	0.1 (± 0.4)	0.1 (± 0.6)		

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AE) were collected from signature of the informed consent form up to the final visit (visit 2) regardless of seriousness or relationship to investigational product. Analysis was performed on safety population.

Adverse event reporting additional description:

Reported adverse events are treatment-emergent adverse events that is AEs that developed/worsened during the 'on treatment period' (from first dose up to 12 days after last dose).

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.0
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### Reporting groups

Reporting group title	ORT + Bacillus clausii
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Reporting group description:

ORT along with Bacillus clausii for 5 days.

Reporting group title	Oral Rehydration Therapy
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Reporting group description:

ORS alone for 5 days.

<b>Serious adverse events</b>	ORT + Bacillus clausii	Oral Rehydration Therapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 129 (0.00%)	0 / 126 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

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

<b>Non-serious adverse events</b>	ORT + Bacillus clausii	Oral Rehydration Therapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 129 (23.26%)	27 / 126 (21.43%)	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	7 / 129 (5.43%)	6 / 126 (4.76%)	
occurrences (all)	7	6	
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	4 / 129 (3.10%)	7 / 126 (5.56%)	
occurrences (all)	4	8	
Vomiting			
subjects affected / exposed	20 / 129 (15.50%)	20 / 126 (15.87%)	
occurrences (all)	21	21	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 January 2007	1. Method of ORS preparation was changed. 2. As per part of the standard therapy in both the arms, Zinc supplements were given to all subjects in the dose of 20 mg/day for 14 days.
27 November 2007	The sample size was recalculated. The sample size with a drop out rate of 5% was determined to be 264 subjects.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported