Clinical trial results:
A Randomized, Double-blind, Placebo-Controlled, Parallel Group, Multicenter, Comparative Study to Assess the Efficacy and Safety of Spores of Enterogermina in Combination with Oral Rehydration Therapy (ORT) and Zinc Versus Placebo in Combination with ORT and Zinc Administered for 5 Days in the Treatment of Acute Diarrhea in Children.

Summary

EudraCT number	2016-005165-31
Trial protocol	Outside EU/EEA
Global end of trial date	24 March 2020

Results information

Result version number	v1 (current)
This version publication date	07 October 2020
First version publication date	07 October 2020

Trial information

Trial identification

Sponsor protocol code	LPS14914

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	U1111-1189-8467
Other trial identifiers	Study name: KIDDIE

Notes:

Sponsors

Sponsor organisation name	Sanofi-aventis Recherche & Développement
Sponsor organisation address	1, Avenue Pierre Brossolette, Chilly Mazarin, France, 91385
Public contact	Trial Transparency Team, Sanofi-aventis recherche & développement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi-aventis recherche & développement, 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	11 June 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 March 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the efficacy of Bacillus clausii probiotic strain (Enterogermina) in combination with oral rehydration therapy (ORT) and Zinc compared to placebo in combination with ORT and Zinc, for a period of 5 days in Indian children with acute diarrhea.

Protection of trial subjects:

The study was conducted by investigators experienced in the treatment of paediatric subjects. The parent(s) or guardian(s) were fully informed and consented of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time. The consent form for the parent(s)/guardian(s) was provided. Repeated invasive procedures were minimised. 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 minimise distress and discomfort.

Background therapy:

ORT and Zinc were administered as non-investigational medicinal products.

Evidence for comparator: -

Actual start date of recruitment	08 December 2018
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: 457
Worldwide total number of subjects	457
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)	234
Children (2-11 years)	223
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 9 active centers in India between 08 December 2018 and 19 March 2020.

Pre-assignment

Screening details:

A total of 464 subjects were screened in this study, of which 7 subjects were screening failure. Screening failure was mainly due to inclusion criteria not met. A total of 457 subjects were randomised to receive either placebo and Enterogermina in a 1:1 ratio, of which 454 subjects were treated in the 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, Subject, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects received placebo matched to Enterogermina 2 times in a day: one in the morning and one in the evening for a period of 5 days (Days 1 to 5) along with ORT for 5 days and zinc 20 milligrams (mg) once a day for up to 14 days.

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

Dosage and administration details:

Placebo was administered as 2 mini bottles per day, one in the morning, one in the evening for a period of 5 days in combination with ORT and zinc. If the first dose was administered in the morning of Day 1, the last dose (i.e., tenth dose) was administered in the evening of Day 5. If the first dose was administered in the evening of Day 1, the tenth dose was administered in the morning of Day 6. Placebo could be taken with or without food or drink.

Arm title	Enterogermina

Arm description:

Subjects received Enterogermina 2 times in a day: one in the morning and one in the evening for a period of 5 days (Days 1 to 5) along with ORT for 5 days and zinc 20 mg once a day for up to 14 days.

Arm type	Experimental
Investigational medicinal product name	Enterogermina
Investigational medicinal product code	SSR29263
Other name	Bacillus clausii
Pharmaceutical forms	Suspension for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Enterogermina (4 billion spores of polyantibiotic-resistant B. clausii per day) was administered as 2 mini bottles per day, one in the morning, one in the evening for a period of 5 days in combination with ORT and zinc. If the first dose was administered in the morning of Day 1, the last dose (ie, tenth dose) was administered in the evening of Day 5. If the first dose was administered in the evening of Day 1, the tenth dose was administered in the morning of Day 6. Enterogermina could be taken with or without food or drink.

Number of subjects in period 1	Placebo	Enterogermina
Started	228	229
Treated	227	227
Completed	222	223
Not completed	6	6
Randomised and not treated	1	2
Subject’s parent or legal guardian decision	1	2
Adverse event	4	2

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo matched to Enterogermina 2 times in a day: one in the morning and one in the evening for a period of 5 days (Days 1 to 5) along with ORT for 5 days and zinc 20 milligrams (mg) once a day for up to 14 days.	
Reporting group title	Enterogermina
Reporting group description:	
Subjects received Enterogermina 2 times in a day: one in the morning and one in the evening for a period of 5 days (Days 1 to 5) along with ORT for 5 days and zinc 20 mg once a day for up to 14 days.	

Reporting group values	Placebo	Enterogermina	Total
Number of subjects	228	229	457
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	2.0	2.0	
standard deviation	± 1.1	± 1.1	-
Gender categorical			
Units: Subjects			
Female	116	116	232
Male	112	113	225
Duration of current diarrhea episode			
Units: hours			
arithmetic mean	29.3	31.1	
standard deviation	± 8.7	± 9.3	-

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects received placebo matched to Enterogermina 2 times in a day: one in the morning and one in the evening for a period of 5 days (Days 1 to 5) along with ORT for 5 days and zinc 20 milligrams (mg) once a day for up to 14 days.

Reporting group title	Enterogermina

Reporting group description:

Subjects received Enterogermina 2 times in a day: one in the morning and one in the evening for a period of 5 days (Days 1 to 5) along with ORT for 5 days and zinc 20 mg once a day for up to 14 days.

Primary: Duration of Diarrhea in Children With Acute Diarrhea

End point title	Duration of Diarrhea in Children With Acute Diarrhea

End point description:

The duration of acute diarrhea (in hours), was counted from the date/time of randomisation up to diarrhea recovery. Diarrhea recovery was defined as the first normal stool as recorded according to Bristol scores. A score <5 was described as normalisation of stool. Analysis was performed by Kaplan-Meier estimates. The 95% Confidence Interval (CI) was calculated using the log-log transformation. Analysis was performed on Intent-to-treat (ITT) population which included all randomised subjects analysed according to the treatment group allocated by randomisation.

End point type	Primary

End point timeframe:

From the time of randomisation up to recovery (maximum duration: 5 days)

End point values	Placebo	Enterogermina		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228	229		
Units: hours				
median (confidence interval 95%)	42.13 (39.80 to 43.87)	42.83 (40.90 to 44.90)		

Statistical analyses

Statistical analysis title	Enterogermina group versus Placebo group

Statistical analysis description:

The stratified log-rank test included the following factors: age (less than 2 years; greater than or equal to 2 years) viral status (viral; non-viral) and breast feeding status (Yes; No; Mixed). Hazard ratio and corresponding 95% CI were provided using a Cox proportional hazard model which included the same factors as in the stratified log-rank test.

Comparison groups	Placebo v Enterogermina

Number of subjects included in analysis	457
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6968 [1]
Method	Stratified Log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	1.13

Notes:

[1] - Threshold for significance at 0.05 level.

Secondary: Frequency of Stools per Visit

End point title	Frequency of Stools per Visit

End point description:

Percentage frequency of stool per day: 0 times, 1 time, 2 times, 3 times, and more than 3 times was reported in the end-point. Analysis was performed on ITT population. Here "n"= subjects with available data for each specified categories.

End point type	Secondary

End point timeframe:

From Baseline (Day 1) up to Day 5

End point values	Placebo	Enterogermina		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228	229		
Units: percentage of stools				
number (not applicable)				
Day 1: 0 times (n=228,229)	0.9	0.4		
Day 1: 1 time (n=228,229)	0.9	0.9		
Day 1: 2 times (n=228,229)	12.3	16.2		
Day 1: 3 times (n=228,229)	15.4	16.2		
Day 1: More than 3 times (n=228,229)	70.6	66.4		
Day 2: 0 times (n=227,228)	0.4	0.9		
Day 2: 1 time (n=227,228)	10.6	8.3		
Day 2: 2 times (n=227,228)	20.3	21.5		
Day 2: 3 times (n=227,228)	25.1	29.8		
Day 2: More than 3 times (n=227,228)	43.6	39.5		
Day 3: 0 times (n=226,225)	1.8	1.3		
Day 3: 1 time (n=226,225)	33.2	35.1		
Day 3: 2 times (n=226,225)	27.4	31.1		
Day 3: 3 times (n=226,225)	19.5	13.8		
Day 3: More than 3 times (n=226,225)	18.1	18.7		
Day 4: 0 times (n=214, 211)	0.9	0.9		
Day 4: 1 time (n=214, 211)	51.9	53.1		
Day 4: 2 times (n=214, 211)	26.6	26.1		

Day 4: 3 times (n=214, 211)	11.2	10.0		
Day 4: More than 3 times (n=214, 211)	9.3	10.0		
Day 5: 0 times (n=201, 200)	1.0	1.0		
Day 5: 1 time (n=201, 200)	60.2	67.5		
Day 5: 2 times (n=201, 200)	25.4	20.5		
Day 5: 3 times (n=201, 200)	7.5	5.0		
Day 5: More than 3 times (n=201, 200)	6.0	6.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Dehydration Status Evaluated by Investigator Using World Health Organization (WHO) Classification

End point title	Dehydration Status Evaluated by Investigator Using World Health Organization (WHO) Classification

End point description:

Dehydration status evaluated as per WHO classification at each day was categorised as: no dehydration, some dehydration, and severe dehydration. Dehydration status was evaluated before each IMP intake during the hospitalisation. Analysis was performed on ITT population. Here "n"= subjects with available data for each specified categories.

End point type	Secondary

End point timeframe:

From Baseline (Day 1) up to Day 5

End point values	Placebo	Enterogermina		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228	229		
Units: subjects				
number (not applicable)				
Day 1: No dehydration (n=225,224)	0	0		
Day 1: Some dehydration (n=225,224)	225	224		
Day 1: Severe dehydration (n=225,224)	0	0		
Day 2: No dehydration (n=224,225)	65	57		
Day 2: Some dehydration (n=224,225)	158	168		
Day 2: Severe dehydration (n=224,225)	1	0		
Day 3: No dehydration (n=144,151)	77	89		
Day 3: Some dehydration (n=144,151)	67	62		
Day 3: Severe dehydration (n=144,151)	0	0		
Day 4: No dehydration (n=78,93)	58	66		
Day 4: Some dehydration (n=78,93)	20	27		
Day 4: Severe dehydration (n=78,93)	0	0		
Day 5: No dehydration (n=50,59)	43	44		
Day 5: Some dehydration (n=50,59)	7	15		
Day 5: Severe dehydration (n=50,59)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAE)

End point title	Number of Subjects With Treatment Emergent Adverse Events (TEAEs) and Serious Adverse Events (SAE)

End point description:

Adverse events (AEs) were any untoward medical occurrence in a patient or clinical study subject, administered a pharmaceutical product and which does not necessarily have to have a causal relationship with treatment. TEAEs were defined as AEs that developed, worsened or became serious during the TEAE period (defined as date/time from first dose of study drug to the date/time of the last dose of study drug taken + 24 hours). SAE were defined as any untoward medical occurrence that, at any dose: a) resulted in death; b) was life-threatening; c) required inpatient hospitalisation or prolongation of existing hospitalisation; d) resulted in persistent disability/incapacity e) was a congenital anomaly/birth defect. Analysis was performed on safety population which included all randomized subjects who received at least one dose or part of a dose of the double-blind Investigational Medicinal Product.

End point type	Secondary

End point timeframe:

From Baseline (Day 1) up to Day 6

End point values	Placebo	Enterogermina		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	227	227		
Units: subjects				
number (not applicable)				
Any TEAE	28	22		
Any treatment emergent SAE	0	0		
Any TEAE leading to death	0	0		
Any TEAE leading to treatment discontinuation	3	2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs were collected from the randomisation up to end of study (Day 6) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported AEs are TEAEs that developed/worsened during 'TEAE period'(defined as the date/time from the first dose of study drug to the date/time of the last dose of the study drug taken + 24 hours) i.e. up to Day 6. Analysis was performed on safety population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects received placebo matched to Enterogermina 2 times in a day: one in the morning and one in the evening for a period of 5 days (Days 1 to 5) along with ORT for 5 days and zinc 20 mg once a day for up to 14 days.

Reporting group title	Enterogermina

Reporting group description:

Subjects received Enterogermina 2 times in a day: one in the morning and one in the evening for a period of 5 days (Days 1 to 5) along with ORT for 5 days and zinc 20 mg once a day for up to 14 days.

Serious adverse events	Placebo	Enterogermina	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 227 (0.00%)	0 / 227 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

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

Non-serious adverse events	Placebo	Enterogermina	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 227 (12.33%)	22 / 227 (9.69%)	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 227 (0.00%)	1 / 227 (0.44%)	
occurrences (all)	0	1	
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed	6 / 227 (2.64%)	5 / 227 (2.20%)	
occurrences (all)	6	5	
Eye disorders			
Periorbital Swelling			
subjects affected / exposed	1 / 227 (0.44%)	0 / 227 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal Pain Upper			
subjects affected / exposed	1 / 227 (0.44%)	0 / 227 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	1 / 227 (0.44%)	0 / 227 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	6 / 227 (2.64%)	6 / 227 (2.64%)	
occurrences (all)	6	6	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 227 (0.88%)	0 / 227 (0.00%)	
occurrences (all)	2	0	
Rhinorrhoea			
subjects affected / exposed	2 / 227 (0.88%)	1 / 227 (0.44%)	
occurrences (all)	2	1	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 227 (0.00%)	1 / 227 (0.44%)	
occurrences (all)	0	1	
Rash Erythematous			
subjects affected / exposed	0 / 227 (0.00%)	1 / 227 (0.44%)	
occurrences (all)	0	1	
Infections and infestations			
Dysentery			
subjects affected / exposed	1 / 227 (0.44%)	0 / 227 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			

subjects affected / exposed	3 / 227 (1.32%)	5 / 227 (2.20%)	
occurrences (all)	3	5	
Upper Respiratory Tract Infection			
subjects affected / exposed	3 / 227 (1.32%)	1 / 227 (0.44%)	
occurrences (all)	3	1	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 227 (0.88%)	2 / 227 (0.88%)	
occurrences (all)	2	2	
Hypokalaemia			
subjects affected / exposed	0 / 227 (0.00%)	2 / 227 (0.88%)	
occurrences (all)	0	2	
Lactose Intolerance			
subjects affected / exposed	1 / 227 (0.44%)	0 / 227 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 January 2018	Following changes were made: this study was considered as a phase III instead of a phase IV study; removed the provision of the interim analysis; included objective parameters of efficacy.
19 June 2018	Following changes were made: changed the indication from acute diarrhea to acute moderate diarrhea.
02 July 2019	Following changes were made: Due to the RIDA QUICK rotavirus/adenovirus combi test no longer being available in India, it was replaced by another test kit for determination of rotavirus and/or adenovirus in stool samples. The instructions for the new test were added to the study manual; deleted from Appendix D the instructions for rotavirus/adenovirus test kit and add the test kit instructions to the study manual, so to avoid a protocol amendment in case of further virus test kit change.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported