Clinical trial results:
Evaluation of The Effects of Enterogermina, 2 Billion Bacillus clausii Spores, on The Intestinal Flora of Children Antibiotic-Treated for Bacterial Upper Respiratory Tract Infections: Open, Pilot Study

Summary

EudraCT number	2006-002482-39
Trial protocol	IT
Global end of trial date	28 December 2007

Results information

Result version number	v1 (current)
This version publication date	27 April 2016
First version publication date	19 March 2015

Trial information

Trial identification

Sponsor protocol code	PM_L_0199

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00424905
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sanofi S.pA
Sponsor organisation address	Viale Bodio 37/b, Milan, Italy, 20158
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	30 April 2008
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 December 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effects of Bacillus clausii (Enterogermina®) on fecal microbial flora (using polymerase chain reaction-denaturing gradient gel electrophoresis [PCR-DGGE] method) in antibiotic-treated children with complicated acute otitis media or beta-hemolytic streptococcal pharyngo-tonsillitis.

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.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 December 2006
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	Italy: 58
Worldwide total number of subjects	58
EEA total number of subjects	58

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)	9
Children (2-11 years)	49
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 1 centre in Italy between 15 December 2006 and 28 December 2007.

Pre-assignment

Screening details:

A total of 60 subjects were randomized of which no data was collected from 2 subjects due to informed consent issues and hence, overall 58 subjects were included in the analysis.

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
Arm title	Bacillus clausii + Amoxicillin

Arm description:

Bacillus clausii along with amoxicillin for 5-10 days, then alone for 7 additional days.

Arm type	Experimental
Investigational medicinal product name	Spores of polyantibiotic-resistant 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 of polyantibiotic resistant Bacillus clausii twice daily.

Investigational medicinal product name	Amoxicillin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Amoxicillin 50 milligram per kilogram per day (mg/kg/day) divided in 3 daily doses.

Arm title	Amoxicillin

Arm description:

Amoxicillin for 5-10 days.

Arm type	Untreated Control Arm
Investigational medicinal product name	Amoxicillin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Amoxicillin 50 mg/kg/day divided in 3 daily doses.

Number of subjects in period 1	Bacillus clausii + Amoxicillin	Amoxicillin
Started	30	28
Treated	29	26
Completed	22	21
Not completed	8	7
Randomized but not treated	1	2
Adverse event	1	2
Unspecified	2	2
Impossible to collect 1st faecal sample correctly	4	1

Baseline characteristics

Reporting groups	
Reporting group title	Bacillus clausii + Amoxicillin
Reporting group description:	
Bacillus clausii along with amoxicillin for 5-10 days, then alone for 7 additional days.	
Reporting group title	Amoxicillin
Reporting group description:	
Amoxicillin for 5-10 days.	

Reporting group values	Bacillus clausii + Amoxicillin	Amoxicillin	Total
Number of subjects	30	28	58
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	5	4	9
Children (2-11 years)	25	24	49
Age continuous Units: months			
arithmetic mean	40	42.1	
standard deviation	± 18.88	± 18.94	-
Gender categorical Units: Subjects			
Female	11	18	29
Male	19	10	29
Race Units: Subjects			
Caucasian	29	23	52
Asian	0	1	1
Black	0	1	1
Hispanic	1	0	1
Other	0	3	3
Primary Diagnosis Units: Subjects			
Complicated Acute Otitis Media	19	19	38
Beta-Hemolytic Streptococcal Pharyngo-Tonsillitis	11	9	20

End points

End points reporting groups

Reporting group title	Bacillus clausii + Amoxicillin
Reporting group description:	
Bacillus clausii along with amoxicillin for 5-10 days, then alone for 7 additional days.	
Reporting group title	Amoxicillin
Reporting group description:	
Amoxicillin for 5-10 days.	

Primary: Change of Microbial Composition of Fecal Bacterial Flora: Number of Responders

End point title	Change of Microbial Composition of Fecal Bacterial Flora: Number of Responders
End point description:	
Analysis of bacterial flora was performed by Polymerase Chain Reaction Denaturing Gradient Gel Electrophoresis (PCR-DGGE). Statistical analysis was performed on similarity coefficient on the basis of Dice algorithm. A subject was classified as responder if the similarity coefficient (similarity of bacterial groups between samples obtained at baseline and Day 13 to 18) was greater than or equal to (>=) 80%. Analysis was carried out on intent-to-treat (ITT) population which included all randomized and treated subjects with a baseline and post-baseline sample.	
End point type	Primary
End point timeframe:	
Baseline, Day 13 to 18	

End point values	Bacillus clausii + Amoxicillin	Amoxicillin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	21		
Units: subjects	6	6		

Statistical analyses

Statistical analysis title	Bacillus clausii + Amoxicillin vs Amoxicillin
Statistical analysis description:	
The proportion of responders was compared between the two treatment arms.	
Comparison groups	Bacillus clausii + Amoxicillin v Amoxicillin
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.836
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	1.15

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	4.47

Primary: Changes of Microbial Composition of Fecal Bacterial Flora: Mean Similarity Coefficient

End point title	Changes of Microbial Composition of Fecal Bacterial Flora: Mean Similarity Coefficient
End point description:	
Analysis was carried out on ITT population.	
End point type	Primary
End point timeframe:	
Baseline, Day 13 to 18	

End point values	Bacillus clausii + Amoxicillin	Amoxicillin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	21		
Units: percentage of similarity				
arithmetic mean (standard error)	74.4 (± 2.6)	72.4 (± 2.5)		

Statistical analyses

Statistical analysis title	Bacillus clausii + Amoxicillin vs Amoxicillin
Statistical analysis description:	
Similarity coefficient was analysed as continuous variable by means of Analysis of Variance (ANOVA).	
Comparison groups	Bacillus clausii + Amoxicillin v Amoxicillin
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.578
Method	ANOVA
Parameter estimate	Mean difference
Point estimate	2.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.31
upper limit	9.38

Secondary: Change From Baseline in Body Weight

End point title	Change From Baseline in Body Weight

End point description:

Analysis was carried out on ITT population.

End point type	Secondary

End point timeframe:

Baseline, Day 13 to 18

End point values	Bacillus clausii + Amoxicillin	Amoxicillin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	19		
Units: kilogram(s)				
arithmetic mean (standard error)	0.22 (± 0.16)	-0.09 (± 0.15)		

Statistical analyses

No statistical analyses for this end point

Secondary: Abdominal Symptoms

End point title	Abdominal Symptoms

End point description:

Abdominal symptoms such as discomfort, bloating, straining, stool frequency and consistency, reported daily on subject's diary in terms of a point rating scale or presence/absence. Analysis was carried out on ITT population.

End point type	Secondary

End point timeframe:

Baseline, Day 13 to 18

End point values	Bacillus clausii + Amoxicillin	Amoxicillin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	21		
Units: subjects				
Abdominal Discomfort – Day 1	5	3		
Abdominal Discomfort – Last measure	1	0		
Abdominal Bloating – Day 1	5	4		
Abdominal Bloating – Last Measure	1	0		
Abdominal Staining – Day 1	1	0		
Abdominal Staining – Last Measure	1	2		
Stool Episodes > 1 Per Day – Day 1	3	7		
Stool Episodes > 1 Per Day – Last Measure	3	3		
Abnormal Stool Consistency – Day 1	9	6		

Abnormal Stool Consistency – Last Measure	2	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Bacillus clausii Spores Count

End point title	Number of Subjects With Bacillus clausii Spores Count
End point description:	
Analysis was carried out on ITT population.	
End point type	Secondary
End point timeframe:	
Baseline, Day 13 to 18	

End point values	Bacillus clausii + Amoxicillin	Amoxicillin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	21		
Units: subjects				
Day 1	4	1		
Last Measure	17	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Gastrointestinal Intestinal (GI) Symptoms

End point title	Number of Subjects with Gastrointestinal Intestinal (GI) Symptoms
End point description:	
Analysis was carried out on ITT population.	
End point type	Secondary
End point timeframe:	
Baseline, Day 13 to 18	

End point values	Bacillus clausii + Amoxicillin	Amoxicillin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	21		
Units: subjects	0	0		

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 (13 - 18 days) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported adverse events are treatment-emergent adverse events that is AEs that developed/worsened during the 'on treatment period' (12 - 17 days). Analysis was carried out on safety population which included all randomized and treated subjects.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	11.0

Reporting groups

Reporting group title	Amoxicillin

Reporting group description:

Amoxicillin for 5 - 10 days.

Reporting group title	Bacillus clausii + Amoxicillin

Reporting group description:

Bacillus clausii along with amoxicillin for 5--10 days, then alone for 7 additional days.

Serious adverse events	Amoxicillin	Bacillus clausii + Amoxicillin	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 26 (0.00%)	1 / 29 (3.45%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Drug Toxicity			
subjects affected / exposed	0 / 26 (0.00%)	1 / 29 (3.45%)	
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: 5 %

Non-serious adverse events	Amoxicillin	Bacillus clausii + Amoxicillin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 26 (46.15%)	9 / 29 (31.03%)	
General disorders and administration site conditions			

Pyrexia subjects affected / exposed occurrences (all)	6 / 26 (23.08%) 6	7 / 29 (24.14%) 8	
Ear and labyrinth disorders Ear Pain subjects affected / exposed occurrences (all)	3 / 26 (11.54%) 3	0 / 29 (0.00%) 0	
Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all)	1 / 26 (3.85%) 1	3 / 29 (10.34%) 3	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	3 / 26 (11.54%) 3	0 / 29 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported