Clinical trial results:
Bacillus clausii in Preventing Antibiotic-associated Diarrhea among Filipino Infants and Children: A Multi-center, Randomized, Open-label Clinical Trial of Efficacy and Safety

Summary

EudraCT number	2014-004629-42
Trial protocol	Outside EU/EEA
Global end of trial date	05 October 2007

Results information

Result version number	v1 (current)
This version publication date	23 May 2016
First version publication date	27 June 2015

Trial information

Trial identification

Sponsor protocol code	ENTER_L_01125

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00447161
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sanofi-aventis Philippines Inc.
Sponsor organisation address	3rd Floor, Feliza Building, 108 V.A. Rufino Street, Legaspi Village , Makati City, Philippines, 1229
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	06 February 2008
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 October 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy and safety of the probiotic Bacillus clausii in preventing antibiotic-associated diarrhea among hospitalized immunocompetent Filipino infant and 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	17 July 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	Philippines: 323
Worldwide total number of subjects	323
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)	103
Children (2-11 years)	210
Adolescents (12-17 years)	10
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 2 sites in the Philippines. A total of 323 subjects were screened between 17 July 2006 and 15 August 2007.

Pre-assignment

Screening details:

All 323 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
Arm title	Bacillus clausii

Arm description:

Bacillus clausii for 7 to 21 days along with antibiotic therapy.

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

Dosage and administration details:

Vial containing 2 billion spores twice daily.

Arm title	No intervention-control

Arm description:

Subjects received antibiotic therapy only.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Bacillus clausii	No intervention-control
Started	162	161
Completed	161	161
Not completed	1	0
Consent withdrawn by subject	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Bacillus clausii
Reporting group description: Bacillus clausii for 7 to 21 days along with antibiotic therapy.	
Reporting group title	No intervention-control
Reporting group description: Subjects received antibiotic therapy only.	

Reporting group values	Bacillus clausii	No intervention-control	Total
Number of subjects	162	161	323
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months)	48	55	103
Children (2-11 years)	109	100	209
Adolescents (12-17 years)	4	6	10
Not available	1	0	1
Gender categorical Units: Subjects			
Female	66	67	133
Male	96	94	190
Source of infection Units: Subjects			
Respiratory	120	119	239
Genito-urinary	15	11	26
Skin & soft tissue	26	31	57
Not available	1	0	1
Antibiotic exposure Units: Subjects			
Penicillins	69	82	151
Cephalosporin	60	52	112
Coamoxyclav/Ampicillin-Sulbactam	12	13	25
Combination/Sequential	21	14	35

End points

End points reporting groups

Reporting group title	Bacillus clausii
Reporting group description:	
Bacillus clausii for 7 to 21 days along with antibiotic therapy.	
Reporting group title	No intervention-control
Reporting group description:	
Subjects received antibiotic therapy only.	

Primary: Number of Antibiotic-Associated Diarrhea Events

End point title	Number of Antibiotic-Associated Diarrhea Events
End point description:	
Antibiotic-associated diarrhea is defined as diarrhea that occurs in association with the administration of antibiotics. Analysis was performed on all randomized and treated subjects.	
End point type	Primary
End point timeframe:	
Day 0 to 6 weeks post treatment (maximum 9 weeks)	

End point values	Bacillus clausii	No intervention-control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	162	161		
Units: events	3	7		

Statistical analyses

Statistical analysis title	Bacillus clausii vs No intervention-control
Statistical analysis description:	
Relative risk was calculated from cumulative incidence ratios, and two-tailed 95% test-based confidence intervals.	
Comparison groups	Bacillus clausii v No intervention-control
Number of subjects included in analysis	323
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.22
Method	Chi-squared
Parameter estimate	Relative risk
Point estimate	0.43

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.11
upper limit	1.62

Secondary: Number of Antibiotic Associated Diarrhea Events Per Day

End point title	Number of Antibiotic Associated Diarrhea Events Per Day

End point description:

End point type	Secondary

End point timeframe:

Day 0 to 6 weeks post treatment (maximum 9 weeks)

End point values	Bacillus clausii	No intervention-control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[1]	0[2]		
Units: events				

Notes:

[1] - Data was not analysed for this outcome measure.

[2] - Data was not analysed for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Gastrointestinal Related Symptoms

End point title	Number of Gastrointestinal Related Symptoms

End point description:

Gastrointestinal related symptoms included nausea, vomiting and abdominal pain. Analysis was performed on all randomized and treated subjects.

End point type	Secondary

End point timeframe:

Day 0 to 6 weeks post treatment (maximum 9 weeks)

End point values	Bacillus clausii	No intervention-control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	162	161		
Units: events				
Nausea	1	1		
Vomiting	7	4		
Abdominal pain	3	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Hospital Stay

End point title	Duration of Hospital Stay

End point description:

End point type	Secondary

End point timeframe:

Day 0 to 6 weeks post treatment (maximum 9 weeks)

End point values	Bacillus clausii	No intervention-control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[3]	0[4]		
Units: week				
arithmetic mean (standard deviation)	()	()		

Notes:

[3] - Data was not analysed for this outcome measure.

[4] - Data was not analysed for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Clostridium difficile Associated Diarrhea

End point title	Number of Subjects With Clostridium difficile Associated Diarrhea

End point description:

Analysis was performed on 10 subjects who developed diarrhea.

End point type	Secondary

End point timeframe:

Day 0 to 6 weeks post treatment (maximum 9 weeks)

End point values	Bacillus clausii	No intervention-control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	7		
Units: subjects	0	1		

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 the informed consent form up to the final visit (Week 9) regardless of seriousness or relationship to investigational product. Analysis was performed on all randomized and treated subjects.

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 of study medication up to 14 days after the last dose of study medication).

Assessment type	Systematic

Dictionary used

Dictionary name	Not applicable
Dictionary version	0.0

Reporting groups

Reporting group title	Bacillus clausii

Reporting group description:

Bacillus clausii for 7 to 21 days along with antibiotic therapy.

Reporting group title	No intervention-control

Reporting group description:

Subjects received antibiotic therapy only.

Serious adverse events	Bacillus clausii	No intervention-control	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 162 (0.00%)	0 / 161 (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	Bacillus clausii	No intervention-control	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 162 (0.00%)	0 / 161 (0.00%)	

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: Safety was very good and no adverse events related to Bacillus clausii were reported.

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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Age for 1 subject was missing and in subjects enrolled per age group field of Trial Information section this subject is reported under "Children (2-11 years)" to avoid validation error. Actual age distribution is provided in baseline characteristics.

Notes: