

**Clinical trial results:****Randomized, Placebo-controlled, Clinical Trial to Evaluate the Efficacy of Probiotic Bacillus Clausii in the Treatment of Pediatric Patients With Irritable Bowel Syndrome****Summary**

EudraCT number	2018-004519-31
Trial protocol	Outside EU/EEA
Global end of trial date	25 November 2020

Results information

Result version number	v1 (current)
This version publication date	10 June 2021
First version publication date	10 June 2021

Trial information**Trial identification**

Sponsor protocol code	ENTERL08784
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Study name: BaclauSII

Notes:

Sponsors

Sponsor organisation name	Sanofi Aventis de México SA de CV
Sponsor organisation address	Av. Universidad 1738 Coyoacán Centro CDMX, Z.P., Mexico, 04000
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	15 February 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	25 November 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the proportion of subjects with clinical improvement of symptoms (assessed with Global Assessment Questions) between Bacillus clausii versus placebo groups, both added to conventional treatment, at Week 8, in 6 to less than (<) 18-year-old subjects with irritable bowel syndrome (IBS).

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency. Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 March 2019
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	Mexico: 259
Worldwide total number of subjects	259
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)	0
Children (2-11 years)	154
Adolescents (12-17 years)	105
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 multiple sites in Mexico. A total of 311 subjects were screened from 11-Mar-2019 to 10-Jul-2020, of which 52 subjects were non-randomised.

Pre-assignment

Screening details:

A total of 259 subjects were randomised and treated in this study.

Period 1

Period 1 title	Overall (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Bacillus clausii

Arm description:

Subjects received Bacillus clausii spores once daily (QD) for 8 weeks.

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

Dosage and administration details:

Oral suspension of Bacillus clausii at total daily dose of 4 billion colony forming units (CFU) per day, divided in 5 millilitres (mL) per vial of 2 billion CFU, QD every morning prior to meal.

Arm title	Placebo
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Arm description:

Subjects received placebo matched to Bacillus clausii QD for 8 weeks.

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

Dosage and administration details:

Oral suspension of match placebo to Bacillus clausii vials QD every morning prior to meal.

Number of subjects in period 1	Bacillus clausii	Placebo
Started	129	130
Completed	124	129
Not completed	5	1
Protocol violation	1	1
Other-misunderstood discontinuation criteria	1	-
Subject withdrawn informed consent form	3	-

Baseline characteristics

Reporting groups

Reporting group title	Bacillus clausii
Reporting group description: Subjects received Bacillus clausii spores once daily (QD) for 8 weeks.	
Reporting group title	Placebo
Reporting group description: Subjects received placebo matched to Bacillus clausii QD for 8 weeks.	

Reporting group values	Bacillus clausii	Placebo	Total
Number of subjects	129	130	259
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	10.93 ± 3.30	11.19 ± 3.12	-
Gender categorical Units: Subjects			
Female	76	81	157
Male	53	49	102

End points

End points reporting groups

Reporting group title	Bacillus clausii
Reporting group description:	
Subjects received Bacillus clausii spores once daily (QD) for 8 weeks.	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo matched to Bacillus clausii QD for 8 weeks.	

Primary: Percentage of Subjects With Clinical Improvement of Symptoms at Week 8 (Global Assessment): Intention-to-treat (ITT) Population

End point title	Percentage of Subjects With Clinical Improvement of Symptoms at Week 8 (Global Assessment): Intention-to-treat (ITT) Population
End point description:	
Response rates was defined as subjects with clinical improvement of symptoms in the global assessment questions: a) 'How well did the medication relieve your symptoms?', where satisfaction with treatment was rated as 'Excellent' or 'Good'; and b) 'Overall how do you feel your problem is?', where symptom relief was rated as 'Better'. Treatment responders was defined as subjects having satisfaction with treatment and symptoms relief at Week 8. Analysis was performed on ITT population that included all randomised subjects, analyzed according to the treatment group allocated by randomization.	
End point type	Primary
End point timeframe:	
Week 8	

End point values	Bacillus clausii	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	130		
Units: percentage of subjects				
number (not applicable)	73.6	78.5		

Statistical analyses

Statistical analysis title	Bacillus clausii versus Placebo
Comparison groups	Bacillus clausii v Placebo
Number of subjects included in analysis	259
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8182
Method	Chi-square test
Parameter estimate	Difference in percentage
Point estimate	-4.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.5
upper limit	3.9

Primary: Percentage of Subjects With Clinical Improvement of Symptoms at Week 8 (Global Assessment): Per-protocol (PP) Population

End point title	Percentage of Subjects With Clinical Improvement of Symptoms at Week 8 (Global Assessment): Per-protocol (PP) Population
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End point description:

Response rates was defined as subjects with clinical improvement of symptoms in the global assessment questions: a) 'How well did the medication relieve your symptoms?', where satisfaction with treatment was rated as 'Excellent' or 'Good' ; and b) 'Overall how do you feel your problem is?', where symptom relief was rated as 'Better'. Treatment responders was defined as subjects having satisfaction with treatment and symptoms relief at Week 8. Analysis was performed on PP population that included all subjects who completed the study without major protocol deviations (may include errors in the allocation of the Investigational Medicinal Product (IMP), the use of treatments not allowed by protocol, poor adherence to treatment (compliance <20%), or lost to follow-up).

End point type	Primary
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End point timeframe:

Week 8

End point values	Bacillus clausii	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	71		
Units: percentage of subjects				
number (not applicable)	80.0	78.9		

Statistical analyses

Statistical analysis title	Bacillus clausii versus Placebo
Comparison groups	Bacillus clausii v Placebo
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4332
Method	Chi-square test
Parameter estimate	Difference in percentage
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.9
upper limit	12.1

Secondary: Percentage of Subjects With Clinical Improvement of Symptoms at Week 4 (Global Assessment)

End point title	Percentage of Subjects With Clinical Improvement of Symptoms at Week 4 (Global Assessment)
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End point description:

Subjects with clinical improvement of symptoms was assessed using global assessment questions: a) 'How well did the medication relieve your symptoms?', where satisfaction with treatment was rated as 'Excellent' or 'Good' ; and b) 'Overall how do you feel your problem is?', where symptom relief was rated as 'Better'. Treatment responders was defined as subjects having satisfaction with treatment and symptoms relief at Week 4. Analysis was performed on ITT population.

End point type	Secondary
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End point timeframe:

Week 4

End point values	Bacillus clausii	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	130		
Units: percentage of subjects				
number (not applicable)	72.4	76.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Clinical Improvement of Symptoms at Week 4 and Week 8: Assessed by Subject's Global Assessment of Relief in Children (SGARC)

End point title	Percentage of Subjects With Clinical Improvement of Symptoms at Week 4 and Week 8: Assessed by Subject's Global Assessment of Relief in Children (SGARC)
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End point description:

Clinical Improvement of symptoms by SGARC was assessed by asking a question from subject/caregiver: "Consider how your child felt this past week in regard to his or her IBS; especially the overall well-being, symptoms of stomach discomfort, pain, and altered bowel habits. Compared with the way he or she usually felt before entering the study, how do you rate the relief of symptoms during the last week?" Subject/Caregiver responded on a scale ranging from 0-4, where: 0=Complete relief; 1=Considerable relief; 2=Somewhat relieved; 3=Unchanged and 4=Worse, where higher scores indicated worse outcomes. Responders to the treatment were defined as subjects with a complete relief or a considerable relief. Analysis was performed on ITT population. Here, "number of subjects analysed" signifies number of subjects evaluable for this endpoint and "n" signifies number of subjects with available data for specified category for each arm, respectively.

End point type	Secondary
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End point timeframe:

Weeks 4 and 8

End point values	Bacillus clausii	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	130		
Units: percentage of subjects				
number (not applicable)				
Week 4 (n=127,129)	61.4	70.3		
Week 8 (n=126,129)	76.0	85.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Days With Bloating Episodes

End point title	Percentage of Days With Bloating Episodes
End point description:	
<p>Abdominal distention/bloating was assessed by 3-point likert scale that consisted of single question, i.e., "Compared to the way you felt before entering the study, have your abdominal distention/bloating symptoms over past 4 weeks been". Subject/Caregiver responded on scale that ranged from 1 to 3, where 1=Better; 2=Same; and 3=Worse, where higher scores indicated worst outcomes. Percentage of days with bloating episodes was calculated as: percentage of days with bloating at Visit i = total number of days with bloating episodes (between Visit i and Visit i-1)/total number of days between Visit i and Visit i-1 *100; where number of visit: i = 2 (Week 4), 3 (Week 8), 4 (Week 16); expressed in terms of mean and standard deviation in this endpoint. Analysis was performed on ITT population. Here, "number of subjects analysed" signifies number of subjects evaluable for this endpoint and "n" signifies number of subjects with available data for specified category for each arm, respectively.</p>	
End point type	Secondary
End point timeframe:	
Weeks 4, 8 and 16	

End point values	Bacillus clausii	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	130		
Units: percentage of days				
arithmetic mean (standard deviation)				
Week 4 (n=127,128)	22.25 (± 26.17)	22.15 (± 21.07)		
Week 8 (n=123,129)	18.41 (± 28.42)	15.91 (± 23.21)		
Week 16 (n=109,117)	12.71 (± 19.85)	15.46 (± 23.18)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Number of Abdominal Pain Episodes Per Day

End point title	Mean Number of Abdominal Pain Episodes Per Day
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End point description:

Mean number of abdominal pain episodes (according to the subject diary information) by day was calculated using formula: mean number of abdominal pain per day at Visit i = sum of all number of abdominal pain episodes (between Visit i and Visit i-1)/total number of days (between Visit i and Visit i-1), where number of Visit i = 2 (Week 4), 3 (Week 8), 4 (Week 16). Analysis was performed on ITT population. Here, "number of subjects analysed" signifies number of subjects evaluable for this endpoint and "n" signifies number of subjects with available data for specified category for each arm, respectively.

End point type	Secondary
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End point timeframe:

Weeks 4, 8 and 16

End point values	Bacillus clausii	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	130		
Units: abdominal pain episodes per day				
arithmetic mean (standard deviation)				
Week 4 (n=123,121)	0.47 (± 0.74)	0.55 (± 0.66)		
Week 8 (n=113,115)	0.29 (± 0.45)	0.29 (± 0.58)		
Week 16 (n=99,107)	0.33 (± 0.75)	0.31 (± 0.50)		

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 time from the IMP administration up to 1 day after last IMP administration regardless of seriousness or relationship to IMP.

Adverse event reporting additional description:

Reported adverse events (AE) were treatment-emergent AE that developed or worsened during treatment-emergent period (time from the IMP administration up to 1 day after last IMP administration). Analysis was performed on safety population that included subjects who had actually received at least 1 dose or part of a dose of IMP.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.1
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Reporting groups

Reporting group title	Bacillus clausii
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Reporting group description:

Subjects received Bacillus clausii spores QD for 8 weeks.

Reporting group title	Placebo
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Reporting group description:

Subjects received placebo matched to Bacillus clausii QD for 8 weeks.

Serious adverse events	Bacillus clausii	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 129 (0.00%)	0 / 130 (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 %

Non-serious adverse events	Bacillus clausii	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 129 (13.18%)	20 / 130 (15.38%)	
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 129 (8.53%)	14 / 130 (10.77%)	
occurrences (all)	14	16	
Infections and infestations			
Influenza			

subjects affected / exposed	7 / 129 (5.43%)	7 / 130 (5.38%)	
occurrences (all)	7	7	

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