Clinical trial results:
Open label, randomized, prospective, controlled, multicenter clinical investigation on the performance and safety of Promelaxin® based micro-enemas versus Macrogol 4000 per os, in the treatment of chronic functional constipation in infants and young children aged 6-48 months

Summary

EudraCT number	2015-005111-32
Trial protocol	IT
Global end of trial date	17 March 2020

Results information

Result version number	v1 (current)
This version publication date	13 December 2021
First version publication date	13 December 2021

Trial information

Trial identification

Sponsor protocol code	ABO-MELI-15

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02751411
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Aboca SpA Società Agricola
Sponsor organisation address	Località Aboca 20, Sansepolcro Arezzo, Italy, 52037
Public contact	Dr. Andrea Cossu, Aboca SpA Società Agricola, +39 3668231464, acossu@aboca.it
Scientific contact	Dr. Andrea Cossu, Aboca SpA Società Agricola, +39 3668231464, acossu@aboca.it

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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 December 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 March 2020
Global end of trial reached?	Yes
Global end of trial date	17 March 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the performance, in terms of frequency of evacuations per week, of the administration of evacuative micro-enemas containing Promelaxin® compared to the oral intake of Macrogol 4000 in the treatment of chronic functional constipation in infants and children aged between 6 and ≤ 48 months.

Protection of trial subjects:

Treated in routine care

Background therapy:

None

Evidence for comparator:

The comparator used in the study was Paxabel 4g (Macrogol 4000), sachets for oral administration. The product is a known efficacious and safe product in the therapy of children with chronic functional constipation. It increases the evacuative frequency, improves the consistency of the stool and reduces the frequency of faecal incontinence.

Actual start date of recruitment	18 April 2016
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: 161
Worldwide total number of subjects	161
EEA total number of subjects	161

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)	83
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:

A total of 161 subjects signed the informed consent and no. 158 entered the active phase of the study and were randomized to treatment. Four clinical sites in Italy were involved. The first subject was enrolled on April 18th, 2016 and the last subject on December 31st, 2019. The last subject completed the study on March, 17th, 2020.

Pre-assignment

Screening details:

A 7 days screening phase was planned. Three patients withdrew before randomization: two of them for consent withdrawal and one for adverse event occurred in the screening phase.

Period 1

Period 1 title	Randomization and treatment start (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Melilax paediatric (Promelaxin) - class IIb medical device

Arm description:

Half a 5 g Promelaxin® micro-enema for infants aged between 6 and 12 months, one 5 g Promelaxin® micro-enema for children aged from 12 to ≤ 48 months, every evening for a week, then on alternate evenings for another week and then as needed in the following 6 weeks (see Administration Scheme). To children from 36 to ≤ 48 months, as per the instructions for use of the product, and based on the investigator's judgment, it was possible to administer 2 consecutive micro-enemas of 5 g Promelaxin®. In this case, the investigator established how long to treat children from 36 to ≤ 48 months with 2 consecutive micro-enemas of Promelaxin®, taken into account that the product under study was to be administered every evening for a week, then on alternate evenings for a another week and then as needed in the following 6 weeks.

Arm type	Experimental
Investigational medicinal product name	Melilax Paediatric
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Enema
Routes of administration	Rectal use

Dosage and administration details:

Half a 5 g Promelaxin® micro-enema for infants aged between 6 and 12 months, one 5 g Promelaxin® micro-enema for children aged from 12 to ≤ 48 months, every evening for a week, then on alternate evenings for another week and then as needed in the following 6 weeks (see Administration Scheme). To children from 36 to ≤ 48 months, as per the instructions for use of the product, and based on the investigator's judgment, it was possible to administer 2 consecutive micro-enemas of 5 g Promelaxin®. In this case, the investigator established how long to treat children from 36 to ≤ 48 months with 2 consecutive micro-enemas of Promelaxin®, taken into account that the product under study was to be administered every evening for a week, then on alternate evenings for a another week and then as needed in the following 6 weeks

Arm title	Paxabel 4g (Macrogol 4000)

Arm description:

The daily dose of Paxabel 4g was defined by the investigator, based on the child's body weight, according to the SmPC: one sachet of Paxabel 4g per day for infants aged between 6 and 12 months and one-two sachets per day for children from 12 to ≤ 48 months. Paxabel was taken every day for a week, then on alternate days for another week and then as needed in the following 6 weeks of study.

Arm type	Active comparator

Investigational medicinal product name	Paxabel 4g
Investigational medicinal product code	IMP1
Other name	
Pharmaceutical forms	Powder for oral solution in sachet
Routes of administration	Oral use

Dosage and administration details:

The daily dose of Paxabel 4g was defined by the investigator, based on the child's body weight, according to the SmPC: one sachet of Paxabel 4g per day for infants aged between 6 and 12 months and one-two sachets per day for children from 12 to ≤ 48 months. Paxabel was taken every day for a week, then on alternate days for another week and then as needed in the following 6 weeks of study.

Number of subjects in period 1[1]	Melilax paediatric (Promelaxin) - class IIb medical device	Paxabel 4g (Macrogol 4000)
Started	76	77
Visit 3 (14 days of treatment)	69	69
Visit 4 (21 days of treatment)	57	64
Visit 5 (56 days-End of Treatmen/Study)	49	57
Completed	49	57
Not completed	27	20
Consent withdrawn by subject	20	14
other	7	6

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Due to Amendment n. 5 dated 12/11/2018, the number of enrolled subjects was 160 instead of 120, as expected in the baseline period.

Baseline characteristics

Reporting groups

Reporting group title	Melilax paediatric (Promelaxin) - class IIb medical device

Reporting group description:

Half a 5 g Promelaxin® micro-enema for infants aged between 6 and 12 months, one 5 g Promelaxin® micro-enema for children aged from 12 to ≤ 48 months, every evening for a week, then on alternate evenings for another week and then as needed in the following 6 weeks (see Administration Scheme). To children from 36 to ≤ 48 months, as per the instructions for use of the product, and based on the investigator's judgment, it was possible to administer 2 consecutive micro-enemas of 5 g Promelaxin®. In this case, the investigator established how long to treat children from 36 to ≤ 48 months with 2 consecutive micro-enemas of Promelaxin®, taken into account that the product under study was to be administered every evening for a week, then on alternate evenings for a another week and then as needed in the following 6 weeks.

Reporting group title	Paxabel 4g (Macrogol 4000)

Reporting group description:

The daily dose of Paxabel 4g was defined by the investigator, based on the child's body weight, according to the SmPC: one sachet of Paxabel 4g per day for infants aged between 6 and 12 months and one-two sachets per day for children from 12 to ≤ 48 months. Paxabel was taken every day for a week, then on alternate days for another week and then as needed in the following 6 weeks of study.

Reporting group values	Melilax paediatric (Promelaxin) - class IIb medical device	Paxabel 4g (Macrogol 4000)	Total
Number of subjects	76	77	153
Age categorical			
Infants and children of both sexes aged between 6 and 48 months.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	40	39	79
Children (2-11 years)	36	38	74
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	37	45	82
Male	39	32	71

Subject analysis sets

Subject analysis set title	FAS
Subject analysis set type	Full analysis

Subject analysis set description:

Full Analysis Set (FAS) population included all the randomized subjects that received at least one dose of study treatment. This set coincides with Safety Set. No. 158 subjects were randomized but only 153 started the treatment (no. 5 did not receive at least one dose of study products).

Subject analysis set title	mFAS
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Modified FAS (mFAS) population included all the randomized subjects that received at least one dose of study treatment and had at least a compliance of 50%.

Subject analysis set title	PP
Subject analysis set type	Per protocol

Subject analysis set description:

Per-Protocol (PP) population included all the subjects in the primary FAS population who did not experience any major protocol deviation until Visit 3, and with the primary endpoint evaluable.

Subject analysis set title	Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety population included all the randomized subjects who received at least one dose of study treatment. This set conincides with FAS.
No. 158 subjects were randomized to treatment but only no. 153 received at least one dose (no. 5 subjects did not receive at least one dose).

Subject analysis set title	Microbiota population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The Microbiota population included the patients from Safety population where fecal samples were collected and microbiota analysis was performed.

Reporting group values	FAS	mFAS	PP
Number of subjects	153	130	101
Age categorical			
Infants and children of both sexes aged between 6 and 48 months.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	79	71	54
Children (2-11 years)	74	59	47
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical			
Units: Subjects			
Female	82	69	57
Male	71	61	44

Reporting group values	Safety	Microbiota population	
Number of subjects	153	105	
Age categorical			
Infants and children of both sexes aged between 6 and 48 months.			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	79	58	
Children (2-11 years)	74	47	

Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	82		
Male	71		

End points

End points reporting groups

Reporting group title	Melilax paediatric (Promelaxin) - class IIb medical device

Reporting group description:

Half a 5 g Promelaxin® micro-enema for infants aged between 6 and 12 months, one 5 g Promelaxin® micro-enema for children aged from 12 to ≤ 48 months, every evening for a week, then on alternate evenings for another week and then as needed in the following 6 weeks (see Administration Scheme). To children from 36 to ≤ 48 months, as per the instructions for use of the product, and based on the investigator's judgment, it was possible to administer 2 consecutive micro-enemas of 5 g Promelaxin®. In this case, the investigator established how long to treat children from 36 to ≤ 48 months with 2 consecutive micro-enemas of Promelaxin®, taken into account that the product under study was to be administered every evening for a week, then on alternate evenings for a another week and then as needed in the following 6 weeks.

Reporting group title	Paxabel 4g (Macrogol 4000)

Reporting group description:

The daily dose of Paxabel 4g was defined by the investigator, based on the child's body weight, according to the SmPC: one sachet of Paxabel 4g per day for infants aged between 6 and 12 months and one-two sachets per day for children from 12 to ≤ 48 months. Paxabel was taken every day for a week, then on alternate days for another week and then as needed in the following 6 weeks of study.

Subject analysis set title	FAS
Subject analysis set type	Full analysis

Subject analysis set description:

Full Analysis Set (FAS) population included all the randomized subjects that received at least one dose of study treatment. This set coincides with Safety Set. No. 158 subjects were randomized but only 153 started the treatment (no. 5 did not receive at least one dose of study products).

Subject analysis set title	mFAS
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Modified FAS (mFAS) population included all the randomized subjects that received at least one dose of study treatment and had at least a compliance of 50%.

Subject analysis set title	PP
Subject analysis set type	Per protocol

Subject analysis set description:

Per-Protocol (PP) population included all the subjects in the primary FAS population who did not experience any major protocol deviation until Visit 3, and with the primary endpoint evaluable.

Subject analysis set title	Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety population included all the randomized subjects who received at least one dose of study treatment. This set conincides with FAS.
No. 158 subjects were randomized to treatment but only no. 153 received at least one dose (no. 5 subjects did not receive at least one dose).

Subject analysis set title	Microbiota population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The Microbiota population included the patients from Safety population where fecal samples were collected and microbiota analysis was performed.

Primary: Change in the frequency of stool evacuations on day 14 - FAS population

End point title	Change in the frequency of stool evacuations on day 14 - FAS population

End point description:

The primary endpoint was the improvement of constipation assessed as an increase in the frequency of stool evacuations. The treatment was considered effective if the infant/child presented, on Visit 3, three or more evacuations per week in association with an average increase, compared to baseline, of at least 1 evacuation per week.

End point type	Primary

End point timeframe:

From Baseline (day 1 - Visit 2) to day 14 (Visit 3)

End point values	Melilax paediatric (Promelaxin) - class IIb medical device	Paxabel 4g (Macrogol 4000)	FAS	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	76	77	153	
Units: evacuations per week	76	77	153	

Statistical analyses

Statistical analysis title	Efficacy analysis - primary endpoint - FAS

Statistical analysis description:

The primary efficacy endpoint was the improvement of constipation assessed as an increase in the frequency of evacuations detected through the patient's diary. The treatment was considered effective if, at Visit 3 (day 14), the number of evacuations was greater than or equal to 3 during both weeks of treatment and if, at the same time, the difference between the mean number of evacuations per week of treatment and the number of evacuations at baseline was greater than 1.

Comparison groups	Paxabel 4g (Macrogol 4000) v Melilax paediatric (Promelaxin) - class IIb medical device
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	≤ 0.05
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.11
upper limit	4.53

Notes:

[1] - The frequency of subjects was compared between treatment groups with chi-square test. Logistic regression was used to estimate OR and to adjust for confounding factors. The Risk to be a Responder was estimated as the proportion of Responders. The Risk difference was estimated with its 95% CI.

Primary: Change in the frequency of stool evacuations on day 14 - mFAS population

End point title	Change in the frequency of stool evacuations on day 14 - mFAS population

End point description:

The primary endpoint was the improvement of constipation assessed as an increase in the frequency of stool evacuations. The treatment was considered effective if the infant/child presented, on Visit 3, three or more evacuations per week in association with an average increase, compared to baseline, of at least 1 evacuation per week.

End point type	Primary

End point timeframe:

From Baseline (day 1 - Visit 2) to day 14 (Visit 3)

End point values	Melilax paediatric (Promelaxin) - class IIb medical device	Paxabel 4g (Macrogol 4000)	mFAS	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	66	64	130	
Units: evacuations per week	66	64	130	

Statistical analyses

Statistical analysis title	Efficacy analysis - primary endpoint - mFAS

Statistical analysis description:

The primary efficacy endpoint was the improvement of constipation assessed as an increase in the frequency of evacuations detected through the patient's diary. The treatment was considered effective if, at Visit 3 (day 14), the number of evacuations was greater than or equal to 3 during both weeks of treatment and if, at the same time, the difference between the mean number of evacuations per week of treatment and the number of evacuations at baseline was greater than 1.

Comparison groups	Melilax paediatric (Promelaxin) - class IIb medical device v Paxabel 4g (Macrogol 4000)
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	≤ 0.05
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	4.78

Notes:

[2] - The frequency of subjects was compared between treatment groups with chi-square test. Logistic regression was used to estimate OR and to adjust for confounding factors. The Risk to be a Responder was estimated as the proportion of Responders. The Risk difference was estimated with its 95% CI.

Primary: Change in the frequency of stool evacuations on day 14 - PP population

End point title	Change in the frequency of stool evacuations on day 14 - PP population

End point description:

The primary endpoint was the improvement of constipation assessed as an increase in the frequency of stool evacuations. The treatment was considered effective if the infant/child presented, on Visit 3, three or more evacuations per week in association with an average increase, compared to baseline, of at least 1 evacuation per week.

End point type	Primary

End point timeframe:

From Baseline (day 1 - Visit 2) to day 14 (Visit 3)

End point values	Melilax paediatric (Promelaxin) - class IIb medical device	Paxabel 4g (Macrogol 4000)	PP	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	56	45	101	
Units: evacuations per week	56	45	101	

Statistical analyses

Statistical analysis title	Efficacy analysis - primary endpoint - PP

Statistical analysis description:

he primary efficacy endpoint was the improvement of constipation assessed as an increase in the frequency of evacuations detected through the patient's diary. The treatment was considered effective if, at Visit 3 (day 14), the number of evacuations was greater than or equal to 3 during both weeks of treatment and if, at the same time, the difference between the mean number of evacuations per week of treatment and the number of evacuations at baseline was greater than 1.

Comparison groups	Melilax paediatric (Promelaxin) - class IIb medical device v Paxabel 4g (Macrogol 4000)
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	≤ 0.05
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	5.42

Notes:

[3] - The frequency of subjects was compared between treatment groups with chi-square test. Logistic regression was used to estimate OR and to adjust for confounding factors. The Risk to be a Responder was estimated as the proportion of Responders. The Risk difference was estimated with its 95% CI.

Secondary: Parents' quality of life score calculated on days 21 and 56 - PP population

End point title	Parents' quality of life score calculated on days 21 and 56 - PP population

End point description:

Change in QoL measured through VAS score from Baseline (day 1 - Visit 2) to day 21 (Visit 4) and 56 (Visit 5) of treatment.

End point type	Secondary

End point timeframe:

From Baseline (day 1 - Visit 2) to day 21 (Visit 4) and day 56 (Visit 5) of treatment.

End point values	Melilax paediatric (Promelaxin) - class IIb medical device	Paxabel 4g (Macrogol 4000)	PP	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	56	45	101[4]	
Units: VAS score	56	45	101	

Notes:

[4] - Some patients excluded from analysis due to missing data

Statistical analyses

Statistical analysis title	Parents' quality of life score at V4 -Mother

Statistical analysis description:

Quality of life score for parents was assessed through a VAS scale ranging between 0mm (Very good) and 100mm (Very bad). A reduction from baseline of at least 1 point was considered as an improvement.

Comparison groups	Melilax paediatric (Promelaxin) - class IIb medical device v Paxabel 4g (Macrogol 4000)
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	≤ 0.05
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	1.49

Notes:

[5] - The number of subjects with an improvement in the QoL was compared between the two treatments groups using the chi-square test. A logistic regression model was used to estimate Odds Ratio (OR), adjusting for clinical site. Analyses were performed separately for mothers and fathers.

Statistical analysis title	Parents' quality of life score at V4 - Father

Statistical analysis description:

Quality of life score for parents was assessed through a VAS scale ranging between 0mm (Very good) and 100mm (Very bad). A reduction from baseline of at least 1 point was considered as an improvement.

Comparison groups	Paxabel 4g (Macrogol 4000) v Melilax paediatric (Promelaxin) - class IIb medical device
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	≤ 0.05
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.54

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.22
upper limit	1.35

Notes:

[6] - The number of subjects with an improvement in the QoL was compared between the two treatments groups using the chi-square test. A logistic regression model was used to estimate Odds Ratio (OR), adjusting for clinical site. Analyses were performed separately for mothers and fathers.

Statistical analysis title	Parents' quality of life score at V5 - Mother

Statistical analysis description:

Quality of life score for parents was assessed through a VAS scale ranging between 0mm (Very good) and 100mm (Very bad). A reduction from baseline of at least 1 point was considered as an improvement.

Comparison groups	Paxabel 4g (Macrogol 4000) v Melilax paediatric (Promelaxin) - class IIb medical device
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	≤ 0.05
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.22
upper limit	1.15

Notes:

[7] - The number of subjects with an improvement in the QoL was compared between the two treatments groups using the chi-square test. A logistic regression model was used to estimate Odds Ratio (OR), adjusting for clinical site. Analyses were performed separately for mothers and fathers.

Statistical analysis title	Parents' quality of life score at V5 - Father

Statistical analysis description:

Quality of life score for parents was assessed through a VAS scale ranging between 0mm (Very good) and 100mm (Very bad). A reduction from baseline of at least 1 point was considered as an improvement.

Comparison groups	Paxabel 4g (Macrogol 4000) v Melilax paediatric (Promelaxin) - class IIb medical device
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	≤ 0.05
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.26
upper limit	1.62

Notes:

[8] - The number of subjects with an improvement in the QoL was compared between the two treatments groups using the chi-square test. A logistic regression model was used to estimate Odds Ratio (OR), adjusting for clinical site. Analyses were performed separately for mothers and fathers.

Secondary: Quality of life score for children calculated on days 21 and 56 - PP population

End point title	Quality of life score for children calculated on days 21 and 56 - PP population

End point description:

Change in QoL measured through PedSQL from Baseline (day 1 - Visit 2) to day 21 (Visit 4) and 56 (Visit 5) of treatment.

End point type	Secondary

End point timeframe:

From Baseline (day 1 - Visit 2) to day 21 (Visit 4) and day 56 (Visit 5).

End point values	Melilax paediatric (Promelaxin) - class IIb medical device	Paxabel 4g (Macrogol 4000)	PP	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	56	45	101[9]	
Units: Questionnaire QoL (from PedsQL) score	56	45	101	

Notes:

[9] - Some patients excluded from analysis due to missing data

Statistical analyses

Statistical analysis title	Quality of life score for children at V4

Statistical analysis description:

Quality of life (QoL) score for children was assessed through 26 questions taken from the PedsQL™. For each question, a value of 0 was assigned to the answer "Sì" (Yes) and a value of 1 to the answer "No". The global score was calculated as the sum of the values given to the answers. Then, the questionnaire used in this study could range between 0 (worst QoL) to 26 (best QoL). An increase from baseline of at least 1 point was considered as an improvement.

Comparison groups	Paxabel 4g (Macrogol 4000) v Melilax paediatric (Promelaxin) - class IIb medical device
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	≤ 0.05
Method	Regression, Linear
Parameter estimate	Odds ratio (OR)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	2.18

Notes:

[10] - The number of patients with an improvement in the QoL was compared between the two treatments groups using the chi-square test. A logistic regression model was used to estimate Odds Ratio (OR), adjusting for clinical site.

Statistical analysis title	Quality of life score for children at V5

Statistical analysis description:

Quality of life (QoL) score for children was assessed through 26 questions taken from the PedsQL™. For each question, a value of 0 was assigned to the answer "Sì" (Yes) and a value of 1 to the answer "No". The global score was calculated as the sum of the values given to the answers. Then, the questionnaire used in this study could range between 0 (worst QoL) to 26 (best QoL). An increase from baseline of at least 1 point was considered as an improvement.

Comparison groups	Paxabel 4g (Macrogol 4000) v Melilax paediatric (Promelaxin) - class IIb medical device
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	≤ 0.05
Method	Regression, Linear
Parameter estimate	Odds ratio (OR)
Point estimate	1.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	3.59

Notes:

[11] - The number of patients with an improvement in the QoL was compared between the two treatments groups using the chi-square test. A logistic regression model was used to estimate Odds Ratio (OR), adjusting for clinical site.

Secondary: Gastrointestinal symptoms in children on days 14, 21 and 56 - FAS population

End point title	Gastrointestinal symptoms in children on days 14, 21 and 56 - FAS population

End point description:

The mean number of days with gastrointestinal symptoms (regurgitation, vomiting, flatulence, loss of appetite, diarrhea, none) on day 14 (Visit 3), day 21 (Visit 4) and day 56 (Visit 5).

End point type	Secondary

End point timeframe:

Day 14 (Visit 3).

End point values	Melilax paediatric (Promelaxin) - class IIb medical device	Paxabel 4g (Macrogol 4000)	FAS	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	76	77	153	
Units: days with gastrointestinal symptoms	76	77	153	

Statistical analyses

Statistical analysis title	Regurgitation at V3

Statistical analysis description:

Parents reported on the diary every day any patients' gastrointestinal symptoms observed (regurgitation, vomiting, flatulence, loss of appetite, diarrhea, none) during the clinical investigation.

Comparison groups	Paxabel 4g (Macrogol 4000) v Melilax paediatric (Promelaxin) - class IIb medical device
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	≤ 0.05
Method	Poisson regression

Notes:

[12] - The mean number of days with gastrointestinal symptoms (regurgitation, vomiting, flatulence, loss of appetite, diarrhea, none) was compared between treatment groups on day 14, 21, 56 using Poisson regression, adjusting for clinical site.

Statistical analysis title	Vomiting at V3

Statistical analysis description:

Parents reported on the diary every day any patients' gastrointestinal symptoms observed (regurgitation, vomiting, flatulence, loss of appetite, diarrhea, none) during the clinical investigation.

Comparison groups	Paxabel 4g (Macrogol 4000) v Melilax paediatric (Promelaxin) - class IIb medical device
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	≤ 0.05
Method	Poisson regression

Notes:

[13] - The mean number of days with gastrointestinal symptoms (regurgitation, vomiting, flatulence, loss of appetite, diarrhea, none) was compared between treatment groups on day 14, 21, 56 using Poisson regression, adjusting for clinical site.

Statistical analysis title	Flatulence at V3

Statistical analysis description:

Parents reported on the diary every day any patients' gastrointestinal symptoms observed (regurgitation, vomiting, flatulence, loss of appetite, diarrhea, none) during the clinical investigation.

Comparison groups	Melilax paediatric (Promelaxin) - class IIb medical device v Paxabel 4g (Macrogol 4000)
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	other[14]
P-value	≤ 0.05
Method	Poisson regression

Notes:

[14] - The mean number of days with gastrointestinal symptoms (regurgitation, vomiting, flatulence, loss of appetite, diarrhea, none) was compared between treatment groups on day 14, 21, 56 using Poisson regression, adjusting for clinical site.

Statistical analysis title	Loss of appetite at V3

Statistical analysis description:

Parents reported on the diary every day any patients' gastrointestinal symptoms observed (regurgitation, vomiting, flatulence, loss of appetite, diarrhea, none) during the clinical investigation.

Comparison groups	Paxabel 4g (Macrogol 4000) v Melilax paediatric (Promelaxin) - class IIb medical device
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	other[15]
P-value	≤ 0.05
Method	Poisson regression

Notes:

[15] - The mean number of days with gastrointestinal symptoms (regurgitation, vomiting, flatulence, loss of appetite, diarrhea, none) was compared between treatment groups on day 14, 21, 56 using Poisson regression, adjusting for clinical site.

Statistical analysis title	Diarrhea at V3

Statistical analysis description:

Parents reported on the diary every day any patients' gastrointestinal symptoms observed (regurgitation, vomiting, flatulence, loss of appetite, diarrhea, none) during the clinical investigation.

Comparison groups	Paxabel 4g (Macrogol 4000) v Melilax paediatric (Promelaxin) - class IIb medical device
Number of subjects included in analysis	153
Analysis specification	Pre-specified
Analysis type	other[16]
P-value	≤ 0.05
Method	Poisson regression

Notes:

[16] - The mean number of days with gastrointestinal symptoms (regurgitation, vomiting, flatulence, loss of appetite, diarrhea, none) was compared between treatment groups on day 14, 21, 56 using Poisson regression, adjusting for clinical site.

Secondary: Gastrointestinal symptoms in children on days 14, 21 and 56 - PP population

End point title	Gastrointestinal symptoms in children on days 14, 21 and 56 - PP population

End point description:

The mean number of days with gastrointestinal symptoms (regurgitation, vomiting, flatulence, loss of appetite, diarrhea, none) on day 14 (Visit 3), day 21 (Visit 4) and day 56 (Visit 5).

End point type	Secondary

End point timeframe:

Day 14 (Visit 3), day 21 (Visit 4) and day 56 (Visit 5).

End point values	Melilax paediatric (Promelaxin) - class IIb medical device	Paxabel 4g (Macrogol 4000)	PP	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	56	45	101[17]	
Units: days with gastrointestinal symptoms	56	45	101	

Notes:

[17] - Some patients excluded from analysis due to missing data

Statistical analyses

Statistical analysis title	Regurgitation at V3

Statistical analysis description:

Parents reported on the diary every day any patients' gastrointestinal symptoms observed (regurgitation, vomiting, flatulence, loss of appetite, diarrhea, none) during the clinical investigation.

Comparison groups	Paxabel 4g (Macrogol 4000) v Melilax paediatric (Promelaxin) - class IIb medical device
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	other[18]
P-value	≤ 0.05
Method	Poisson regression

Notes:

[18] - The mean number of days with gastrointestinal symptoms (regurgitation, vomiting, flatulence, loss of appetite, diarrhea, none) was compared between treatment groups on day 14, 21, 56 using Poisson regression, adjusting for clinical site.

Statistical analysis title	Vomiting at V3

Statistical analysis description:

Parents reported on the diary every day any patients' gastrointestinal symptoms observed (regurgitation, vomiting, flatulence, loss of appetite, diarrhea, none) during the clinical investigation.

Comparison groups	Paxabel 4g (Macrogol 4000) v Melilax paediatric (Promelaxin) - class IIb medical device
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	other[19]
P-value	≤ 0.05
Method	Poisson regression

Notes:

[19] - The mean number of days with gastrointestinal symptoms (regurgitation, vomiting, flatulence, loss of appetite, diarrhea, none) was compared between treatment groups on day 14, 21, 56 using Poisson regression, adjusting for clinical site.

Statistical analysis title	Flatulence at V3

Statistical analysis description:

Parents reported on the diary every day any patients' gastrointestinal symptoms observed (regurgitation, vomiting, flatulence, loss of appetite, diarrhea, none) during the clinical investigation.

Comparison groups	Paxabel 4g (Macrogol 4000) v Melilax paediatric (Promelaxin) - class IIb medical device
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	other[20]
P-value	≤ 0.05
Method	Poisson regression

Notes:

[20] - The mean number of days with gastrointestinal symptoms (regurgitation, vomiting, flatulence, loss of appetite, diarrhea, none) was compared between treatment groups on day 14, 21, 56 using Poisson regression, adjusting for clinical site.

Statistical analysis title	Loss of appetite at V3

Statistical analysis description:

Parents reported on the diary every day any patients' gastrointestinal symptoms observed (regurgitation, vomiting, flatulence, loss of appetite, diarrhea, none) during the clinical investigation.

Comparison groups	Paxabel 4g (Macrogol 4000) v Melilax paediatric (Promelaxin) - class IIb medical device
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	other[21]
P-value	≤ 0.05
Method	Poisson regression

Notes:

[21] - The mean number of days with gastrointestinal symptoms (regurgitation, vomiting, flatulence, loss of appetite, diarrhea, none) was compared between treatment groups on day 14, 21, 56 using Poisson regression, adjusting for clinical site.

Statistical analysis title	Diarrhea at V3

Statistical analysis description:

Parents reported on the diary every day any patients' gastrointestinal symptoms observed (regurgitation, vomiting, flatulence, loss of appetite, diarrhea, none) during the clinical investigation.

Comparison groups	Paxabel 4g (Macrogol 4000) v Melilax paediatric (Promelaxin) - class IIb medical device
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	other[22]
P-value	≤ 0.05
Method	Poisson regression

Notes:

[22] - The mean number of days with gastrointestinal symptoms (regurgitation, vomiting, flatulence, loss of appetite, diarrhea, none) was compared between treatment groups on day 14, 21, 56 using Poisson regression, adjusting for clinical site.

Statistical analysis title	Regurgitation at V4

Statistical analysis description:

Parents reported on the diary every day any patients' gastrointestinal symptoms observed (regurgitation, vomiting, flatulence, loss of appetite, diarrhea, none) during the clinical investigation.

Comparison groups	Melilax paediatric (Promelaxin) - class IIb medical device v Paxabel 4g (Macrogol 4000)
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	other[23]
P-value	≤ 0.05
Method	Poisson regression

Notes:

[23] - The mean number of days with gastrointestinal symptoms (regurgitation, vomiting, flatulence, loss of appetite, diarrhea, none) was compared between treatment groups on day 14, 21, 56 using Poisson regression, adjusting for clinical site.

Statistical analysis title	Vomiting at V4

Statistical analysis description:

Parents reported on the diary every day any patients' gastrointestinal symptoms observed (regurgitation, vomiting, flatulence, loss of appetite, diarrhea, none) during the clinical investigation.

Comparison groups	Paxabel 4g (Macrogol 4000) v Melilax paediatric (Promelaxin) - class IIb medical device

Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	other[24]
P-value	≤ 0.05
Method	Poisson regression

Notes:

[24] - The mean number of days with gastrointestinal symptoms (regurgitation, vomiting, flatulence, loss of appetite, diarrhea, none) was compared between treatment groups on day 14, 21, 56 using Poisson regression, adjusting for clinical site.

Statistical analysis title	Flatulence at V4

Statistical analysis description:

Parents reported on the diary every day any patients' gastrointestinal symptoms observed (regurgitation, vomiting, flatulence, loss of appetite, diarrhea, none) during the clinical investigation.

Comparison groups	Paxabel 4g (Macrogol 4000) v Melilax paediatric (Promelaxin) - class IIb medical device
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	other[25]
P-value	≤ 0.05
Method	Poisson regression

Notes:

[25] - The mean number of days with gastrointestinal symptoms (regurgitation, vomiting, flatulence, loss of appetite, diarrhea, none) was compared between treatment groups on day 14, 21, 56 using Poisson regression, adjusting for clinical site.

Statistical analysis title	Loss of appetite at V4

Statistical analysis description:

Parents reported on the diary every day any patients' gastrointestinal symptoms observed (regurgitation, vomiting, flatulence, loss of appetite, diarrhea, none) during the clinical investigation.

Comparison groups	Paxabel 4g (Macrogol 4000) v Melilax paediatric (Promelaxin) - class IIb medical device
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	other[26]
P-value	≤ 0.05
Method	Poisson regression

Notes:

[26] - The mean number of days with gastrointestinal symptoms (regurgitation, vomiting, flatulence, loss of appetite, diarrhea, none) was compared between treatment groups on day 14, 21, 56 using Poisson regression, adjusting for clinical site.

Statistical analysis title	Diarrhea at V4

Statistical analysis description:

Parents reported on the diary every day any patients' gastrointestinal symptoms observed (regurgitation, vomiting, flatulence, loss of appetite, diarrhea, none) during the clinical investigation.

Comparison groups	Paxabel 4g (Macrogol 4000) v Melilax paediatric (Promelaxin) - class IIb medical device
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	other[27]
P-value	≤ 0.05
Method	Poisson regression

Notes:

[27] - The mean number of days with gastrointestinal symptoms (regurgitation, vomiting, flatulence, loss of appetite, diarrhea, none) was compared between treatment groups on day 14, 21, 56 using Poisson regression, adjusting for clinical site.

Statistical analysis title	Regurgitation at V5

Statistical analysis description:

Parents reported on the diary every day any patients' gastrointestinal symptoms observed (regurgitation, vomiting, flatulence, loss of appetite, diarrhea, none) during the clinical investigation.

Comparison groups	Melilax paediatric (Promelaxin) - class IIb medical device v Paxabel 4g (Macrogol 4000)
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	other[28]
P-value	≤ 0.05
Method	Poisson regression

Notes:

[28] - The mean number of days with gastrointestinal symptoms (regurgitation, vomiting, flatulence, loss of appetite, diarrhea, none) was compared between treatment groups on day 14, 21, 56 using Poisson regression, adjusting for clinical site.

Statistical analysis title	Vomiting at V5

Statistical analysis description:

Parents reported on the diary every day any patients' gastrointestinal symptoms observed (regurgitation, vomiting, flatulence, loss of appetite, diarrhea, none) during the clinical investigation.

Comparison groups	Paxabel 4g (Macrogol 4000) v Melilax paediatric (Promelaxin) - class IIb medical device
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	other[29]
P-value	≤ 0.05
Method	Poisson regression

Notes:

[29] - The mean number of days with gastrointestinal symptoms (regurgitation, vomiting, flatulence, loss of appetite, diarrhea, none) was compared between treatment groups on day 14, 21, 56 using Poisson regression, adjusting for clinical site.

Statistical analysis title	Flatulence at V5

Statistical analysis description:

Parents reported on the diary every day any patients' gastrointestinal symptoms observed (regurgitation, vomiting, flatulence, loss of appetite, diarrhea, none) during the clinical investigation.

Comparison groups	Paxabel 4g (Macrogol 4000) v Melilax paediatric (Promelaxin) - class IIb medical device
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	other[30]
P-value	≤ 0.05
Method	Poisson regression

Notes:

[30] - The mean number of days with gastrointestinal symptoms (regurgitation, vomiting, flatulence, loss of appetite, diarrhea, none) was compared between treatment groups on day 14, 21, 56 using Poisson regression, adjusting for clinical site.

Statistical analysis title	Loss of appetite at V5

Statistical analysis description:

Parents reported on the diary every day any patients' gastrointestinal symptoms observed (regurgitation, vomiting, flatulence, loss of appetite, diarrhea, none) during the clinical investigation.

Comparison groups	Paxabel 4g (Macrogol 4000) v Melilax paediatric (Promelaxin) -

	class IIb medical device
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	other[31]
P-value	≤ 0.05
Method	Poisson regression

Notes:

[31] - The mean number of days with gastrointestinal symptoms (regurgitation, vomiting, flatulence, loss of appetite, diarrhea, none) was compared between treatment groups on day 14, 21, 56 using Poisson regression, adjusting for clinical site.

Statistical analysis title	Diarrhea at V5

Statistical analysis description:

Parents reported on the diary every day any patients' gastrointestinal symptoms observed (regurgitation, vomiting, flatulence, loss of appetite, diarrhea, none) during the clinical investigation.

Comparison groups	Paxabel 4g (Macrogol 4000) v Melilax paediatric (Promelaxin) - class IIb medical device
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	other[32]
P-value	≤ 0.05
Method	Poisson regression

Notes:

[32] - The mean number of days with gastrointestinal symptoms (regurgitation, vomiting, flatulence, loss of appetite, diarrhea, none) was compared between treatment groups on day 14, 21, 56 using Poisson regression, adjusting for clinical site.

Secondary: Stool frequency and consistency with respect to the use of the study product on days 21 and 56 - PP population

End point title	Stool frequency and consistency with respect to the use of the study product on days 21 and 56 - PP population

End point description:

Change in the stool frequency and consistency of the feces from day 14 (Visit 3) to day 21 (Visit 4) and 56 (Visit 5) of treatment.

End point type	Secondary

End point timeframe:

From day 14 (Visit 3) to day 21 (Visit 4) and day 56 (Visit 5) of treatment.

End point values	Melilax paediatric (Promelaxin) - class IIb medical device	Paxabel 4g (Macrogol 4000)	PP	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	56	45	101[33]	
Units: number of days	56	45	101	

Notes:

[33] - Some patients excluded from analysis due to missing data

Statistical analyses

Statistical analysis title	Number of days to reach improvement at V4

Statistical analysis description:

The number of days of treatment to reach the improvement in the stool frequency and consistency was described within each treatment group.

Comparison groups	Paxabel 4g (Macrogol 4000) v Melilax paediatric (Promelaxin) - class IIb medical device
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	other[34]
P-value	≤ 0.05
Method	Poisson regression

Notes:

[34] - The number of days of treatment on demand between Visit 3 and Visit 4 and between Visit 3 and Visit 5 was compared between treatment groups using Poisson regression.

Statistical analysis title	Number of days to reach improvement at V5

Statistical analysis description:

The number of days of treatment to reach the improvement in the stool frequency and consistency was described within each treatment group.

Comparison groups	Paxabel 4g (Macrogol 4000) v Melilax paediatric (Promelaxin) - class IIb medical device
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	other[35]
P-value	≤ 0.05
Method	Poisson regression

Notes:

[35] - The number of days of treatment on demand between Visit 3 and Visit 4 and between Visit 3 and Visit 5 was compared between treatment groups using Poisson regression.

Secondary: Assessment of changes in gut microbiota between treatment arms by Next Generation Sequencing (Illumina Miseq), Qiime2 analysis of 16S rRNA gene sequences

End point title	Assessment of changes in gut microbiota between treatment arms by Next Generation Sequencing (Illumina Miseq), Qiime2 analysis of 16S rRNA gene sequences

End point description:

Wilcoxon pairwise test between relative abundance of taxa at each timepoint.

End point type	Secondary

End point timeframe:

Visit 2, Visit 4 and Visit 5.

End point values	Melilax paediatric (Promelaxin) - class IIb medical device	Paxabel 4g (Macrogol 4000)	Microbiota population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	53	52	105	
Units: percentage				
arithmetic mean (standard deviation)	53 (± 0)	52 (± 0)	105 (± 0)	

Statistical analyses

Statistical analysis title	Percentage relative abundance
Statistical analysis description: Wilcoxon pairwise test between relative abundance of taxa at each timepoint	
Comparison groups	Paxabel 4g (Macrogol 4000) v Melilax paediatric (Promelaxin) - class IIb medical device
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other[36]
P-value	≤ 0.05 [37]
Method	Non parametric pairwise Wilcoxon test
Parameter estimate	Percentage relative abundance
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[36] - Pairwise comparison

[37] - FDR corrected p-value (Benjamini and Hochberg)

Secondary: Assessment of changes in gut microbiota between treatment arms by Next Generation Sequencing (Illumina Miseq), Qiime2 analysis of 16S rRNA gene sequences

End point title	Assessment of changes in gut microbiota between treatment arms by Next Generation Sequencing (Illumina Miseq), Qiime2 analysis of 16S rRNA gene sequences
End point description: Kruskal-Wallis test	
End point type	Secondary
End point timeframe: Visit 2, Visit 4 and Visit 5.	

End point values	Melilax paediatric (Promelaxin) - class IIb medical device	Paxabel 4g (Macrogol 4000)	Microbiota population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	53	52	105	
Units: units				
arithmetic mean (standard deviation)	53 (± 0)	52 (± 0)	105 (± 0)	

Statistical analyses

Statistical analysis title	Alpha diversity - Chao dissimilarity index
Statistical analysis description:	
Kruskal-Wallis test	
Comparison groups	Melilax paediatric (Promelaxin) - class IIb medical device v Paxabel 4g (Macrogol 4000)
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other[38]
P-value	≤ 0.05 [39]
Method	Non parametric Kruskal-Wallis test
Parameter estimate	Chao dissimilarity index
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[38] - Pairwise comparison

[39] - FDR corrected p-value (Benjamini and Hochberg)

Statistical analysis title	Alpha diversity - Shannon index
Statistical analysis description:	
Kruskal-Wallis test	
Comparison groups	Melilax paediatric (Promelaxin) - class IIb medical device v Paxabel 4g (Macrogol 4000)
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other[40]
P-value	≤ 0.05 [41]
Method	Non parametric Kruskal-Wallis test
Parameter estimate	Shannon index
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[40] - Pairwise comparison

[41] - FDR corrected p-value (Benjamini and Hochberg)

Statistical analysis title	Alpha diversity - Number of OTUs
Statistical analysis description:	
Kruskal-Wallis test	
Comparison groups	Melilax paediatric (Promelaxin) - class IIb medical device v Paxabel 4g (Macrogol 4000)

Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other[42]
P-value	≤ 0.05 [43]
Method	Non parametric Kruskal-Wallis test
Parameter estimate	Number of OTUs
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[42] - Pairwise comparison

[43] - FDR corrected p-value (Benjamini and Hochberg)

Secondary: Assessment of changes in gut microbiota between treatment arms by Next Generation Sequencing (Illumina Miseq), Qiime2 analysis of 16S rRNA gene sequences

End point title	Assessment of changes in gut microbiota between treatment arms by Next Generation Sequencing (Illumina Miseq), Qiime2 analysis of 16S rRNA gene sequences

End point description:

PERMANOVA

End point type	Secondary

End point timeframe:

Visit 2, Visit 4 and Visit 5.

End point values	Melilax paediatric (Promelaxin) - class IIb medical device	Paxabel 4g (Macrogol 4000)	Microbiota population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	53	52	105	
Units: units				
arithmetic mean (standard deviation)	53 (± 0)	52 (± 0)	105 (± 0)	

Statistical analyses

Statistical analysis title	Beta diversity

Statistical analysis description:

PERMANOVA

Comparison groups	Melilax paediatric (Promelaxin) - class IIb medical device v Paxabel 4g (Macrogol 4000)

Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	other[44]
P-value	≤ 0.05 [45]
Method	PERMANOVA
Parameter estimate	Bray curtis dissimilarity index
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Notes:

[44] - Pairwise comparison

[45] - FDR corrected p-value (Benjamini and Hochberg)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From treatment start (day 1-Visit 2) to end of study (day 56 - Visit 5).

Adverse event reporting additional description:

Product safety and tolerability in terms of adverse events were reported by the subject's parents / legal guardian at visits.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Melilax paediatric (Promelaxin) - class IIb medical device

Reporting group description:

Half a 5 g Promelaxin® micro-enema for infants aged between 6 and 12 months, one 5 g Promelaxin® micro-enema for children aged from 12 to ≤ 48 months, every evening for a week, then on alternate evenings for another week and then as needed in the following 6 weeks.
To children from 36 to ≤ 48 months, it was possible to administer 2 consecutive micro-enemas of 5 g Promelaxin®. In this case, the investigator established how long to treat children from 36 to ≤ 48 months with 2 consecutive micro-enemas of Promelaxin®, taken into account that the product under study was to be administered every evening for a week, then on alternate evenings for a another week and then as needed in the following 6 weeks.

Reporting group title	Paxabel 4g (Macrogol 4000)

Reporting group description:

The daily dose of Paxabel 4g was defined by the investigator, based on the child's body weight, according to the SmPC: one sachet of Paxabel 4g per day for infants aged between 6 and 12 months and one-two sachets per day for children from 12 to ≤ 48 months. Paxabel was taken every day for a week, then on alternate days for another week and then as needed in the following 6 weeks of study.

Serious adverse events	Melilax paediatric (Promelaxin) - class IIb medical device	Paxabel 4g (Macrogol 4000)	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 76 (1.32%)	1 / 77 (1.30%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Gastroenteritis	Additional description: The subjects was hospitalized for gastroenteritis, after having started the Paxabel 4g treatment few days before. The treatment was temporary suspended and re-started after hospital discharge. The event was evaluated as not related to the treatment.		
subjects affected / exposed	0 / 76 (0.00%)	1 / 77 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatosplenomegaly	Additional description: The event occurred about 1 month after Melilax paediatric start. Subj. was hospitalized and treatment definitey interrupted. No follow-up on the SAE was available to Investigators. The SAE was assessed as not related to study treatment.		

subjects affected / exposed	1 / 76 (1.32%)	0 / 77 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Melilax paediatric (Promelaxin) - class IIb medical device	Paxabel 4g (Macrogol 4000)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	37 / 76 (48.68%)	41 / 77 (53.25%)	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	14 / 76 (18.42%)	22 / 77 (28.57%)	
occurrences (all)	19	32	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	3 / 76 (3.95%)	5 / 77 (6.49%)	
occurrences (all)	3	5	
Vomiting			
subjects affected / exposed	1 / 76 (1.32%)	5 / 77 (6.49%)	
occurrences (all)	2	8	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 76 (9.21%)	6 / 77 (7.79%)	
occurrences (all)	9	6	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 76 (1.32%)	3 / 77 (3.90%)	
occurrences (all)	1	5	
Influenza			
subjects affected / exposed	5 / 76 (6.58%)	4 / 77 (5.19%)	
occurrences (all)	6	7	
Pharyngitis			
subjects affected / exposed	4 / 76 (5.26%)	0 / 77 (0.00%)	
occurrences (all)	4	0	
Upper respiratory tract infection			

subjects affected / exposed occurrences (all)	2 / 76 (2.63%) 2	3 / 77 (3.90%) 8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 December 2016	Amendment no. 2, date 06-Dec-2016: this Amendment modified two inclusion criteria. Initially the clinical investigation inclusion criterion no. 1 was intended to include only infants/children aged 6 to 24 months. With this amendment the age was modified up to 48 months (6-48 months, included). In addition, the inclusion criterion no. 3 was better explained: the use of faecal softeners in the 7 days before the study start was not allowed. With this amendment it was specified that the prohibition was only for the 7 days before the study treatment start.
12 November 2018	Amendment no. 5, date 12-Nov-2018: the amendment was issued to update the primary objective and the statistical analysis setup. In particular, the amendment was submitted to request the possibility to demonstrate also the non-inferiority of Medical Device, setting the non-inferiority margin in the study protocol. Furthermore, a modification of the primary endpoint was requested, maintaining only the stool frequency and setting the stool consistency as a secondary endpoint.

Notes:

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.

None

Notes: