



## 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, <a href="mailto:acossu@aboca.it">acossu@aboca.it</a> |
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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  |
| <b>Arm title</b>             | 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  $\leq 48$  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  $\leq 48$  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  $\leq 48$  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  $\leq 48$  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  $\leq 48$  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  $\leq 48$  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

|                  |                            |
|------------------|----------------------------|
| <b>Arm title</b> | 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  $\leq 48$  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  $\leq$  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.

| <b>Number of subjects in period 1<sup>[1]</sup></b> | 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 Treatment/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 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 coincides 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  $\leq 48$  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  $\leq 48$  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  $\leq 48$  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  $\leq 48$  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 coincides 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

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | 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 <sup>[1]</sup>  |
| 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 <sup>[2]</sup>  |
| 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)

| <b>End point values</b>     | 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

| <b>Statistical analysis title</b>   | Efficacy analysis - primary endpoint - PP   |
|---|---|
| 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   | 101   |
| Analysis specification  | Pre-specified   |
| Analysis type   | other <sup>[3]</sup>  |
| 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.                                      |   |

| <b>End point values</b>     | 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 <sup>[4]</sup>   |  |
| Units: VAS score            | 56   | 45                         | 101                  |  |

Notes:

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

## Statistical analyses

| <b>Statistical analysis title</b> | 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 <sup>[5]</sup>  |
| 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.

| <b>Statistical analysis title</b> | 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 <sup>[6]</sup>  |
| 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.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | 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 <sup>[7]</sup>  |
| 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.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | 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 <sup>[8]</sup>  |
| 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:<br>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:<br>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 <sup>[9]</sup>   |  |
| 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:<br>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 "Si" (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 <sup>[10]</sup>   |
| 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.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | 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 "Si" (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 <sup>[11]</sup>   |
| 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).

| <b>End point values</b>                    | 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

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Regurgitation at V3   |
| Statistical analysis description:<br>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 <sup>[12]</sup>   |
| 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.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Vomiting at V3  |
| Statistical analysis description:<br>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 <sup>[13]</sup>   |
| 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.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Flatulence at V3  |
| Statistical analysis description:<br>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 <sup>[14]</sup>   |
| 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.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Loss of appetite at V3  |
| Statistical analysis description:<br>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 <sup>[15]</sup>   |
| 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.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Diarrhea at V3  |
| Statistical analysis description:<br>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 <sup>[16]</sup>   |
| 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:<br>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:<br>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 <sup>[17]</sup>  |  |
| Units: days with gastrointestinal symptoms | 56   | 45                         | 101                  |  |

Notes:

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

## Statistical analyses

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Regurgitation at V3   |
| Statistical analysis description:<br>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 <sup>[18]</sup>   |
| 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.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Vomiting at V3  |
| Statistical analysis description:<br>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 <sup>[19]</sup>   |
| 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.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Flatulence at V3  |
| Statistical analysis description:<br>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 <sup>[20]</sup>   |
| 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.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Loss of appetite at V3  |
| Statistical analysis description:<br>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 <sup>[21]</sup>   |
| 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.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Diarrhea at V3  |
| Statistical analysis description:<br>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 <sup>[22]</sup>   |
| 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.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Regurgitation at V4   |
| Statistical analysis description:<br>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 <sup>[23]</sup>   |
| 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.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Vomiting at V4  |
| Statistical analysis description:<br>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 <sup>[24]</sup> |
| 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.

|                                   |                  |
|-----------------------------------|------------------|
| <b>Statistical analysis title</b> | 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 <sup>[25]</sup>   |
| 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.

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | 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 <sup>[26]</sup>   |
| 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.

|                                   |                |
|-----------------------------------|----------------|
| <b>Statistical analysis title</b> | 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 <sup>[27]</sup>   |
| 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.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Regurgitation at V5   |
| Statistical analysis description:<br>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 <sup>[28]</sup>   |
| 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.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Vomiting at V5  |
| Statistical analysis description:<br>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 <sup>[29]</sup>   |
| 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.

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Flatulence at V5  |
| Statistical analysis description:<br>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 <sup>[30]</sup>   |
| 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.

|  |  |
|--|--|
| <b>Statistical analysis title</b>  | Loss of appetite at V5   |
| Statistical analysis description:<br>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 <sup>[31]</sup>    |
| 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.

|                                   |                |
|-----------------------------------|----------------|
| <b>Statistical analysis title</b> | 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 <sup>[32]</sup>   |
| 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.

| <b>End point values</b>     | 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 <sup>[33]</sup>  |  |
| Units: number of days       | 56   | 45                         | 101                  |  |

Notes:

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

### **Statistical analyses**

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Number of days to reach improvement at V4   |
| Statistical analysis description:<br>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 <sup>[34]</sup>   |
| 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.

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Number of days to reach improvement at V5   |
| Statistical analysis description:<br>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 <sup>[35]</sup>   |
| 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.

| <b>End point values</b>              | 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

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Percentage relative abundance   |
| Statistical analysis description:<br>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 <sup>[36]</sup>   |
| P-value  | ≤ 0.05 <sup>[37]</sup>  |
| 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:<br>Kruskal-Wallis test         |   |
| End point type  | Secondary   |
| End point timeframe:<br>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

|  |   |
|--|---|
| <b>Statistical analysis title</b>                        | Alpha diversity - Chao dissimilarity index  |
| Statistical analysis description:<br>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 <sup>[38]</sup>   |
| P-value  | $\leq 0.05$ <sup>[39]</sup>   |
| 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)    |   |

|  |   |
|--|---|
| <b>Statistical analysis title</b>                        | Alpha diversity - Shannon index   |
| Statistical analysis description:<br>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 <sup>[40]</sup>   |
| P-value  | $\leq 0.05$ <sup>[41]</sup>   |
| 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)    |   |

|  |   |
|--|---|
| <b>Statistical analysis title</b>                        | Alpha diversity - Number of OTUs  |
| Statistical analysis description:<br>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 <sup>[42]</sup>              |
| P-value                                 | ≤ 0.05 <sup>[43]</sup>             |
| 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 <sup>[44]</sup>           |
| P-value                                 | $\leq 0.05$ <sup>[45]</sup>     |
| 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 definitely 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 %

| <b>Non-serious adverse events</b>                     | 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 | 2 / 76 (2.63%) | 3 / 77 (3.90%) |  |
| occurrences (all)           | 2              | 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:

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### 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: