



Clinical trial results:

Trial Consisting of an 8-week Double-blind Placebo-controlled Part to Evaluate Efficacy, Safety, Tolerability and Pharmacokinetics of Prucalopride in Paediatric Subjects With Functional Constipation, Aged 6 Months to <18 Years, Followed by a 16-week Open-label Comparator (PEG) Controlled Part, to Document Safety and Tolerability up to 24 Weeks

Summary

| | |
|--------------------------|-------------------------|
| EudraCT number | 2010-022402-40 |
| Trial protocol | BE NL FR GB DE HU PL IT |
| Global end of trial date | 01 March 2013 |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v1 (current) |
| This version publication date | 04 September 2018 |
| First version publication date | 25 January 2015 |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | SPD555-303 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|--------------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01330381 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Study number: M0001-C303 |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Shire Development LLC |
| Sponsor organisation address | 725 Chesterbrook Boulevard, Wayne, Pennsylvania, United States, 19087 |
| Public contact | Study Physician, Shire, 1866 8425335, |
| Scientific contact | Study Physician, Shire, 1866 8425335, |

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-000459-PIP01-08 |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes |

Notes:

Results analysis stage

| | |
|--|---------------|
| Analysis stage | Final |
| Date of interim/final analysis | 01 March 2013 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 01 March 2013 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of prucalopride compared to placebo for the treatment of functional constipation in a paediatric population, aged greater than or equal to (\geq) 6 months to less than ($<$) 18 years.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation-Good Clinical Practice, the principles of the Declaration of Helsinki, as well as other applicable local ethical and legal requirements.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 28 April 2011 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Germany: 7 |
| Country: Number of subjects enrolled | Belgium: 8 |
| Country: Number of subjects enrolled | France: 4 |
| Country: Number of subjects enrolled | Italy: 3 |
| Country: Number of subjects enrolled | Netherlands: 51 |
| Country: Number of subjects enrolled | United Kingdom: 20 |
| Country: Number of subjects enrolled | Poland: 48 |
| Country: Number of subjects enrolled | Hungary: 74 |
| Worldwide total number of subjects | 215 |
| EEA total number of subjects | 215 |

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) | 3 |
| Children (2-11 years) | 158 |
| Adolescents (12-17 years) | 54 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects who completed the 8-week double-blind treatment period and wished to continue were re-randomized after the double-blind treatment period to the 16-week open-label treatment period. Out of 215 subjects randomized in the study, 213 subjects received treatment and 2 subjects withdrew consent before treatment.

Pre-assignment period milestones

| | |
|--|--------------|
| Number of subjects started | 215 |
| Intermediate milestone: Number of subjects | Treated: 213 |
| Number of subjects completed | 213 |

Pre-assignment subject non-completion reasons

| | |
|----------------------------|---------------------------------|
| Reason: Number of subjects | Consent withdrawn by subject: 2 |
|----------------------------|---------------------------------|

Period 1

| | |
|------------------------------|---|
| Period 1 title | Double-blind Treatment Period (8 Weeks) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Investigator, Carer, Assessor, Subject |

Arms

| | |
|------------------------------|--------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Prucalopride |

Arm description:

Subjects with weight less than or equal to (\leq) 50 kilogram (kg) received 0.04 milligram per kilogram (mg/kg) prucalopride once daily as oral solution of 0.4 mg/millilitre (mg/mL).

Subjects with weight greater than ($>$) 50 kg received prucalopride 2 mg oral tablet once daily.

| | |
|--|---------------|
| Arm type | Experimental |
| Investigational medicinal product name | Prucalopride |
| Investigational medicinal product code | SPD555 |
| Other name | Resolor |
| Pharmaceutical forms | Oral solution |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects with weight \leq 50 kg received 0.04 mg/kg prucalopride once daily as oral solution of 0.4 mg/mL.

| | |
|--|--------------------|
| Investigational medicinal product name | Prucalopride |
| Investigational medicinal product code | SPD555 |
| Other name | Resolor |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects with weight $>$ 50 kg received prucalopride 2 mg oral tablet once daily.

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Subjects with weight ≤ 50 kg received placebo matching to prucalopride oral solution.
 Subjects with weight >50 kg received placebo matching prucalopride oral tablet.

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

Dosage and administration details:

Subjects with weight ≤ 50 kg received placebo matching to prucalopride oral solution.

| | |
|--|--------------------|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects with weight >50 kg received placebo matching prucalopride oral tablet.

| Number of subjects in period 1^[1] | Prucalopride | Placebo |
|---|--------------|---------|
| Started | 106 | 107 |
| Completed | 96 | 101 |
| Not completed | 10 | 6 |
| Consent withdrawn by subject | 4 | 3 |
| Non-compliance | 2 | 1 |
| Did not fulfill inclusion/exclusion | 1 | - |
| Adverse event | 1 | 1 |
| Lost to follow-up | 1 | - |
| Lack of efficacy | 1 | 1 |

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: Not all enrolled subjects were treated with study drugs. Since baseline included treated subjects only, the worldwide number enrolled in the trial differs with the number of subjects reported in the baseline period.

Period 2

| | |
|------------------------------|--|
| Period 2 title | Open-label Treatment Period (16 Weeks) |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|---|--------------------|
| Arm title | Prucalopride |
| Arm description: Subjects with weight ≤ 50 kg received 0.04 mg/kg prucalopride once daily as oral solution of 0.4 mg/mL. Subjects with weight > 50 kg received prucalopride 2 mg oral tablet once daily. | |
| Arm type | Experimental |
| Investigational medicinal product name | Prucalopride |
| Investigational medicinal product code | SPD555 |
| Other name | Resolor |
| Pharmaceutical forms | Oral solution |
| Routes of administration | Oral use |
| Dosage and administration details: Subjects with weight ≤ 50 kg received 0.04 mg/kg prucalopride once daily as oral solution of 0.4 mg/mL. | |
| Investigational medicinal product name | Prucalopride |
| Investigational medicinal product code | SPD555 |
| Other name | Resolor |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:
Subjects with weight > 50 kg received prucalopride 2 mg oral tablet once daily.

| | |
|---|------------------------------------|
| Arm title | PEG 4000 (Polyethylene Glycol) |
| Arm description: Subjects received PEG 4000 oral solution at a dose of 4 gram to 20 gram once daily. | |
| Arm type | Active comparator |
| Investigational medicinal product name | Polyethylene glycol 4000 |
| Investigational medicinal product code | PEG 4000 |
| Other name | Forlax Junior, Forlax |
| Pharmaceutical forms | Powder for oral solution in sachet |
| Routes of administration | Oral use |

Dosage and administration details:
Subjects with age ≥6 months to <1 year, received PEG 4000 oral solution at a dose of 4 gram once daily.
Subjects with age ≥1 year to <4 years, received PEG 4000 oral solution at a dose of 8 gram once daily.
Subjects with age ≥4 years to <8 years, received PEG 4000 oral solution at a dose of 12 gram once daily.
Subjects with age ≥8 year to <18 years, received PEG 4000 oral solution at a dose of 20 gram once daily.

| Number of subjects in period 2 | Prucalopride | PEG 4000 (Polyethylene Glycol) |
|--------------------------------|--------------|--------------------------------|
| | | |
| Started | 98 | 99 |
| Completed | 88 | 81 |
| Not completed | 10 | 18 |
| Sponsor's decision | 1 | 1 |
| Consent withdrawn by subject | 7 | 16 |
| Adverse event | 2 | - |
| Non-compliance | - | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | Prucalopride |
|-----------------------|--------------|

Reporting group description:

Subjects with weight less than or equal to (\leq) 50 kilogram (kg) received 0.04 milligram per kilogram (mg/kg) prucalopride once daily as oral solution of 0.4 mg/millilitre (mg/mL).

Subjects with weight greater than ($>$) 50 kg received prucalopride 2 mg oral tablet once daily.

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Subjects with weight \leq 50 kg received placebo matching to prucalopride oral solution.

Subjects with weight $>$ 50 kg received placebo matching prucalopride oral tablet.

| Reporting group values | Prucalopride | Placebo | Total |
|--|--------------|------------|-------|
| Number of subjects | 106 | 107 | 213 |
| Age categorical | | | |
| Safety Set was defined as all subjects who were randomized and used the investigational product at least once. | | | |
| Units: Subjects | | | |
| \leq 18 years | 106 | 107 | 213 |
| Between 18 and 65 years | 0 | 0 | 0 |
| \geq 65 years | 0 | 0 | 0 |
| Age continuous | | | |
| Safety Set was defined as all subjects who were randomized and used the investigational product at least once. | | | |
| Units: years | | | |
| arithmetic mean | 8.3 | 8.2 | |
| standard deviation | \pm 4.54 | \pm 4.69 | - |
| Gender categorical | | | |
| Safety Set was defined as all subjects who were randomized and used the investigational product at least once. | | | |
| Units: Subjects | | | |
| Female | 60 | 58 | 118 |
| Male | 46 | 49 | 95 |

End points

End points reporting groups

| | |
|--|--------------------------------|
| Reporting group title | Prucalopride |
| Reporting group description: Subjects with weight less than or equal to (\leq) 50 kilogram (kg) received 0.04 milligram per kilogram (mg/kg) prucalopride once daily as oral solution of 0.4 mg/millilitre (mg/mL). Subjects with weight greater than ($>$) 50 kg received prucalopride 2 mg oral tablet once daily. | |
| Reporting group title | Placebo |
| Reporting group description: Subjects with weight \leq 50 kg received placebo matching to prucalopride oral solution. Subjects with weight $>$ 50 kg received placebo matching prucalopride oral tablet. | |
| Reporting group title | Prucalopride |
| Reporting group description: Subjects with weight \leq 50 kg received 0.04 mg/kg prucalopride once daily as oral solution of 0.4 mg/mL. Subjects with weight $>$ 50 kg received prucalopride 2 mg oral tablet once daily. | |
| Reporting group title | PEG 4000 (Polyethylene Glycol) |
| Reporting group description: Subjects received PEG 4000 oral solution at a dose of 4 gram to 20 gram once daily. | |

Primary: Percent of Responders in the Last Four Weeks of the Double-Blind Treatment Period

| | |
|--|---|
| End point title | Percent of Responders in the Last Four Weeks of the Double-Blind Treatment Period |
| End point description: Responders are defined as subjects with an average spontaneous defecation frequency is ≥ 3 times per week AND the average number of fecal incontinence episodes per 2 weeks is ≤ 1 episode (only for subjects after acquisition of toileting skills). Full Analysis Set includes all subjects who were randomized and received at least 1 dose of investigational product. | |
| End point type | Primary |
| End point timeframe: Last 4 weeks of double-blind treatment period | |

| End point values | Prucalopride | Placebo | | |
|-------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 106 | 107 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 17 | 17.8 | | |

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | Prucalopride v Placebo |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 213 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9002 |
| Method | Cochran-Mantel-Haenszel |

Secondary: Percent of Subjects With Bowel Frequency of 3 or More Spontaneous Bowel Movements (SBM) Per Week in the Last Four Weeks of the Double-Blind Treatment Period

| | |
|-----------------|--|
| End point title | Percent of Subjects With Bowel Frequency of 3 or More Spontaneous Bowel Movements (SBM) Per Week in the Last Four Weeks of the Double-Blind Treatment Period |
|-----------------|--|

End point description:

Spontaneous Bowel Movements defined as a bowel movement that is not preceded within a period of 24 hours by the intake of a laxative agent or by the use of an enema. Full Analysis Set includes all subjects who were randomized and received at least 1 dose of investigational product.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Last 4 weeks of double-blind treatment period

| | | | | |
|-------------------------------|-----------------|-----------------|--|--|
| End point values | Prucalopride | Placebo | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 106 | 107 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 29.2 | 35.5 | | |

Statistical analyses

| | |
|---|-------------------------|
| Statistical analysis title | Statistical analysis 1 |
| Comparison groups | Prucalopride v Placebo |
| Number of subjects included in analysis | 213 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.352 |
| Method | Cochran-Mantel-Haenszel |

Secondary: Percent of Subjects With Fecal Incontinence Episodes of 1 or Less Per 2 Weeks in the Last Four Weeks of the Double-Blind Treatment Period

| | |
|-----------------|---|
| End point title | Percent of Subjects With Fecal Incontinence Episodes of 1 or Less Per 2 Weeks in the Last Four Weeks of the Double-Blind Treatment Period |
|-----------------|---|

End point description:

Fecal incontinence is a lack of control over defecation, leading to involuntary loss of bowel contents

(only for subjects after acquisition of toileting skills). Full Analysis Set includes all subjects who were randomized and received at least 1 dose of investigational product.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Last 4 weeks of double-blind treatment period | |

| End point values | Prucalopride | Placebo | | |
|-------------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 93 ^[1] | 93 ^[2] | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 43 | 43 | | |

Notes:

[1] - Not all subjects in the Full Analysis Set had data for this outcome.

[2] - Not all subjects in the Full Analysis Set had data for this outcome.

Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|---|-------------------------|
| Comparison groups | Prucalopride v Placebo |
| Number of subjects included in analysis | 186 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5228 |
| Method | Cochran-Mantel-Haenszel |

Secondary: Number of Retentive Posturing or Excessive Volitional Stool Retention in the Double-Blind Treatment Period

| | |
|-----------------|--|
| End point title | Number of Retentive Posturing or Excessive Volitional Stool Retention in the Double-Blind Treatment Period |
|-----------------|--|

End point description:

Purposefully avoiding defecation. Full Analysis Set includes all subjects who were randomized and received at least 1 dose of investigational product.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Over the 8 week double blind treatment period | |

| End point values | Prucalopride | Placebo | | |
|--------------------------------------|--------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 105 ^[3] | 107 | | |
| Units: retentions/week | | | | |
| arithmetic mean (standard deviation) | 1.1 (± 1.82) | 1.2 (± 1.71) | | |

Notes:

[3] - Not all subjects in the Full Analysis Set had data for this outcome.

Statistical analyses

No statistical analyses for this end point

Secondary: Painful Bowel Movements Score in the Double-Blind Treatment Period

| | |
|-----------------|--|
| End point title | Painful Bowel Movements Score in the Double-Blind Treatment Period |
|-----------------|--|

End point description:

Pain was rated on a 6-point scale (0=no hurt, 1=hurts little bit, 2=hurts little more, 3=hurts even more, 4=hurts whole lot, 5=hurts worst) in subjects of 3 years and older. Lower scores represent less pain. Full Analysis Set includes all subjects who were randomized and received at least 1 dose of investigational product.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Over the 8 week double blind treatment period

| End point values | Prucalopride | Placebo | | |
|--------------------------------------|-------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 98 ^[4] | 100 ^[5] | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | 1.3 (\pm 1.25) | 1.7 (\pm 1.34) | | |

Notes:

[4] - Not all subjects in the Full Analysis Set had data for this outcome.

[5] - Not all subjects in the Full Analysis Set had data for this outcome.

Statistical analyses

No statistical analyses for this end point

Secondary: Stool Consistency Per SBM Score in Children Without Diapers in the Double-Blind Treatment Period

| | |
|-----------------|--|
| End point title | Stool Consistency Per SBM Score in Children Without Diapers in the Double-Blind Treatment Period |
|-----------------|--|

End point description:

Measured using the 7-point Bristol scale where 1-2 indicate constipation, 3-4 are ideal stools, and 5-7 tending toward diarrhea. Full Analysis Set includes all subjects who were randomized and received at least 1 dose of investigational product.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Over the 8 week double blind treatment period

| End point values | Prucalopride | Placebo | | |
|--------------------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 92 ^[6] | 93 ^[7] | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | 3.8 (\pm 0.96) | 3.6 (\pm 1.17) | | |

Notes:

[6] - Not all subjects in the Full Analysis Set had data for this outcome.

[7] - Not all subjects in the Full Analysis Set had data for this outcome.

Statistical analyses

No statistical analyses for this end point

Secondary: Stool Consistency Per SBM Score in Children With Diapers in the Double-Blind Treatment Period

| | |
|-----------------|---|
| End point title | Stool Consistency Per SBM Score in Children With Diapers in the Double-Blind Treatment Period |
|-----------------|---|

End point description:

Measured on a 4-point scale where 1 is constipation, 2-3 is ideal, and 4 is diarrhea. Full Analysis Set includes all subjects who were randomized and received at least 1 dose of investigational product.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Over the 8 week double blind treatment period

| End point values | Prucalopride | Placebo | | |
|--------------------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 13 ^[8] | 14 ^[9] | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | 2.1 (\pm 0.47) | 2 (\pm 0.59) | | |

Notes:

[8] - Not all subjects in the Full Analysis Set had data for this outcome.

[9] - Not all subjects in the Full Analysis Set had data for this outcome.

Statistical analyses

No statistical analyses for this end point

Secondary: Large Diameter Stools in the Double-Blind Treatment Period

| | |
|-----------------|--|
| End point title | Large Diameter Stools in the Double-Blind Treatment Period |
|-----------------|--|

End point description:

Large diameter stools make defecation more difficult. Small diameter stools are better. Full Analysis Set includes all subjects who were randomized and received at least 1 dose of investigational product.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Over the 8 week double blind treatment period

| End point values | Prucalopride | Placebo | | |
|--------------------------------------|---------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 105 ^[10] | 107 | | |
| Units: large diameter stools/week | | | | |
| arithmetic mean (standard deviation) | 1.7 (± 1.67) | 1.7 (± 1.2) | | |

Notes:

[10] - Not all subjects in the Full Analysis Set had data for this outcome.

Statistical analyses

No statistical analyses for this end point

Secondary: Abdominal Pain Score in Double-Blind Treatment Period

| | |
|-----------------|---|
| End point title | Abdominal Pain Score in Double-Blind Treatment Period |
|-----------------|---|

End point description:

Pain was rated on a 6-point scale (0=no hurt, 1=hurts little bit, 2=hurts little more, 3=hurts even more, 4=hurts whole lot, 5=hurts worst) in subjects of 3 years and older. Lower scores represent less pain. Full Analysis Set includes all subjects who were randomized and received at least 1 dose of investigational product.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Over the 8 week double blind treatment period

| End point values | Prucalopride | Placebo | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 96 ^[11] | 95 ^[12] | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | 0.9 (± 1.18) | 1.1 (± 1.15) | | |

Notes:

[11] - Not all subjects in the Full Analysis Set had data for this outcome.

[12] - Not all subjects in the Full Analysis Set had data for this outcome.

Statistical analyses

No statistical analyses for this end point

Secondary: Frequency of Toilet Training in the Double-Blind Treatment Period

| | |
|-----------------|---|
| End point title | Frequency of Toilet Training in the Double-Blind Treatment Period |
|-----------------|---|

End point description:

Only for subjects after acquisition of toileting skills. Full Analysis Set includes all subjects who were randomized and received at least 1 dose of investigational product.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Over the 8 week double blind treatment period

| End point values | Prucalopride | Placebo | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 82 ^[13] | 75 ^[14] | | |
| Units: toilet trainings/week | | | | |
| arithmetic mean (standard deviation) | 4.9 (± 2.47) | 5.1 (± 2.47) | | |

Notes:

[13] - Not all subjects in the Full Analysis Set had data for this outcome.

[14] - Not all subjects in the Full Analysis Set had data for this outcome.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Rescue Medications Taken in the Double-Blind Treatment Period

| | |
|-----------------|---|
| End point title | Number of Rescue Medications Taken in the Double-Blind Treatment Period |
|-----------------|---|

End point description:

Full Analysis Set includes all subjects who were randomized and received at least 1 dose of investigational product.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Over the 8 week double blind treatment period

| End point values | Prucalopride | Placebo | | |
|--------------------------------------|---------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 105 ^[15] | 107 | | |
| Units: rescue medications/week | | | | |
| arithmetic mean (standard deviation) | 1.2 (± 1.25) | 1.3 (± 1.09) | | |

Notes:

[15] - Not all subjects in the Full Analysis Set had data for this outcome.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First SBM in the Double-Blind Treatment Period

| | |
|-----------------|--|
| End point title | Time to First SBM in the Double-Blind Treatment Period |
|-----------------|--|

End point description:

After intake of the trial medication on Day 1. Full Analysis Set includes all subjects who were randomized and received at least 1 dose of investigational product.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 1 onwards

| End point values | Prucalopride | Placebo | | |
|----------------------------------|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 106 | 107 | | |
| Units: hours | | | | |
| median (confidence interval 95%) | 67 (49.42 to 101.17) | 99.75 (73.75 to 204) | | |

Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|---|------------------------|
| Comparison groups | Prucalopride v Placebo |
| Number of subjects included in analysis | 213 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.377 |
| Method | Chi-squared |

Secondary: Number of SBM Per Week in the Double-Blind Treatment Period

| | |
|--|---|
| End point title | Number of SBM Per Week in the Double-Blind Treatment Period |
| End point description: Full Analysis Set includes all subjects who were randomized and received at least 1 dose of investigational product. | |
| End point type | Secondary |
| End point timeframe: Over the 8 week double blind treatment period | |

| End point values | Prucalopride | Placebo | | |
|--------------------------------------|---------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 105 ^[16] | 107 | | |
| Units: SBM/week | | | | |
| arithmetic mean (standard deviation) | 2.3 (± 2.35) | 2.1 (± 1.74) | | |

Notes:

[16] - Not all subjects in the Full Analysis Set had data for this outcome.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Number of SBM Per Week Over the 8 Week Double Blind Treatment Period

| | |
|-----------------|--|
| End point title | Change From Baseline in the Number of SBM Per Week Over the 8 Week Double Blind Treatment Period |
|-----------------|--|

End point description:

Full Analysis Set includes all subjects who were randomized and received at least 1 dose of

investigational product.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline and over the 8 week double blind treatment period | |

| End point values | Prucalopride | Placebo | | |
|--------------------------------------|---------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 105 ^[17] | 107 | | |
| Units: SBM/week | | | | |
| arithmetic mean (standard deviation) | 1.5 (± 2.35) | 1 (± 1.78) | | |

Notes:

[17] - Not all subjects in the Full Analysis Set had data for this outcome.

Statistical analyses

No statistical analyses for this end point

Secondary: Severity of Constipation Over the Past 2 Weeks for the Final On Treatment Assessment in the Double-Blind Treatment Period

| | |
|-----------------|---|
| End point title | Severity of Constipation Over the Past 2 Weeks for the Final On Treatment Assessment in the Double-Blind Treatment Period |
|-----------------|---|

End point description:

Full Analysis Set includes all subjects who were randomized and received at least 1 dose of investigational product.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| 2 weeks | |

| End point values | Prucalopride | Placebo | | |
|-------------------------------|---------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 103 ^[18] | 107 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| Absent | 15.5 | 5.6 | | |
| Mild | 21.4 | 18.7 | | |
| Moderate | 19.4 | 27.1 | | |
| Severe | 27.2 | 24.3 | | |
| Very severe | 16.5 | 24.3 | | |

Notes:

[18] - Not all subjects in the Full Analysis Set had data for this outcome.

Statistical analyses

| | |
|----------------------------|------------------------|
| Statistical analysis title | Statistical analysis 1 |
| Comparison groups | Prucalopride v Placebo |

| | |
|---|------------------|
| Number of subjects included in analysis | 210 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1599 |
| Method | Van Elteren test |

Secondary: Severity of Constipation Over the Past 2 Weeks for the Final On Treatment Assessment in the Open-Label Treatment Period

| | |
|------------------------|---|
| End point title | Severity of Constipation Over the Past 2 Weeks for the Final On Treatment Assessment in the Open-Label Treatment Period |
| End point description: | Full Analysis Set includes all subjects who were randomized and received at least 1 dose of investigational product. |
| End point type | Secondary |
| End point timeframe: | 2 weeks |

| End point values | Prucalopride | PEG 4000 (Polyethylene Glycol) | | |
|-------------------------------|--------------------|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 97 ^[19] | 93 ^[20] | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| Absent | 24.7 | 46.2 | | |
| Mild | 17.5 | 16.1 | | |
| Moderate | 17.5 | 9.7 | | |
| Severe | 15.5 | 15.1 | | |
| Very severe | 24.7 | 12.9 | | |

Notes:

[19] - Not all subjects in the Full Analysis Set had data for this outcome.

[20] - Not all subjects in the Full Analysis Set had data for this outcome.

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Statistical analysis 1 |
| Comparison groups | Prucalopride v PEG 4000 (Polyethylene Glycol) |
| Number of subjects included in analysis | 190 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0003 |
| Method | Van Elteren test |

Secondary: Efficacy of Treatment for Final On Treatment Assessment in Double-Blind Treatment Period

| | |
|-----------------|--|
| End point title | Efficacy of Treatment for Final On Treatment Assessment in |
|-----------------|--|

End point description:

Full Analysis Set includes all subjects who were randomized and received at least 1 dose of investigational product.

End point type Secondary

End point timeframe:

Over the 8 week double blind treatment period

| End point values | Prucalopride | Placebo | | |
|-------------------------------|---------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 103 ^[21] | 107 | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| Not at all effective | 33 | 32.7 | | |
| Little bit effective | 14.6 | 18.7 | | |
| Moderately effective | 15.5 | 25.2 | | |
| Quite a bit effective | 22.3 | 14 | | |
| Extremely effective | 14.6 | 9.3 | | |

Notes:

[21] - Not all subjects in the Full Analysis Set had data for this outcome.

Statistical analyses

| | |
|---|------------------------|
| Statistical analysis title | Statistical analysis 1 |
| Comparison groups | Placebo v Prucalopride |
| Number of subjects included in analysis | 210 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4647 |
| Method | Van Elteren test |

Secondary: Efficacy of Treatment for Final On Treatment Assessment in Open-Label Treatment Period

End point title Efficacy of Treatment for Final On Treatment Assessment in Open-Label Treatment Period

End point description:

Full Analysis Set includes all subjects who were randomized and received at least 1 dose of investigational product.

End point type Secondary

End point timeframe:

Over the 16 week open label treatment period

| End point values | Prucalopride | PEG 4000 (Polyethylene Glycol) | | |
|-------------------------------|--------------------|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 97 ^[22] | 93 ^[23] | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| Not at all effective | 29.9 | 15.1 | | |
| Little bit effective | 10.3 | 5.4 | | |
| Moderately effective | 20.6 | 11.8 | | |
| Quite a bit effective | 18.6 | 21.5 | | |
| Extremely effective | 20.6 | 46.2 | | |

Notes:

[22] - Not all subjects in the Full Analysis Set had data for this outcome.

[23] - Not all subjects in the Full Analysis Set had data for this outcome.

Statistical analyses

| Statistical analysis title | Statistical analysis 1 |
|---|---|
| Comparison groups | PEG 4000 (Polyethylene Glycol) v Prucalopride |
| Number of subjects included in analysis | 190 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 |
| Method | Van Elteren test |

Secondary: Convenience of Treatment for Final On Treatment Assessment in Open-Label Treatment Period

| | |
|-----------------|---|
| End point title | Convenience of Treatment for Final On Treatment Assessment in Open-Label Treatment Period |
|-----------------|---|

End point description:

Full Analysis Set includes all subjects who were randomized and received at least 1 dose of investigational product.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Over the 16 week open label treatment period

| End point values | Prucalopride | PEG 4000 (Polyethylene Glycol) | | |
|-------------------------------|--------------------|-----------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 97 ^[24] | 90 ^[25] | | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| Neutral | 16.5 | 15.6 | | |
| Very difficult | 1 | 2.2 | | |
| Quite difficult | 0 | 5.6 | | |
| Quite easy | 27.8 | 28.9 | | |
| Very easy | 54.6 | 47.8 | | |

Notes:

[24] - Not all subjects in the Full Analysis Set had data for this outcome.

[25] - Not all subjects in the Full Analysis Set had data for this outcome.

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Statistical analysis 1 |
| Comparison groups | Prucalopride v PEG 4000 (Polyethylene Glycol) |
| Number of subjects included in analysis | 187 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3044 |
| Method | Van Elteren test |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to Week 24

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 12.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|------------------------------------|
| Reporting group title | Prucalopride (Double-blind Period) |
|-----------------------|------------------------------------|

Reporting group description:

Subjects with weight ≤ 50 kg received 0.04 mg/kg prucalopride once daily as oral solution of 0.4 mg/mL.

Subjects with weight > 50 kg received prucalopride 2 mg oral tablet once daily.

| | |
|-----------------------|-------------------------------|
| Reporting group title | Placebo (Double-blind Period) |
|-----------------------|-------------------------------|

Reporting group description:

Subjects with weight ≤ 50 kg received placebo matching to prucalopride oral solution.

Subjects with weight > 50 kg received placebo matching prucalopride oral tablet.

| | |
|-----------------------|----------------------------------|
| Reporting group title | Prucalopride (Open-label Period) |
|-----------------------|----------------------------------|

Reporting group description:

Subjects with weight ≤ 50 kg received 0.04 mg/kg prucalopride once daily as oral solution of 0.4 mg/mL.

Subjects with weight > 50 kg received prucalopride 2 mg oral tablet once daily.

| | |
|-----------------------|------------------------------|
| Reporting group title | PEG 4000 (Open-label Period) |
|-----------------------|------------------------------|

Reporting group description:

Subjects received PEG 4000 oral solution at a dose of 4 gram to 20 gram once daily.

| Serious adverse events | Prucalopride (Double-blind Period) | Placebo (Double-blind Period) | Prucalopride (Open-label Period) |
|---|------------------------------------|-------------------------------|----------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 5 / 106 (4.72%) | 2 / 107 (1.87%) | 4 / 98 (4.08%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 107 (0.00%) | 1 / 98 (1.02%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Dizziness | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 107 (0.00%) | 0 / 98 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 107 (0.00%) | 0 / 98 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 1 / 107 (0.93%) | 0 / 98 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constipation | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 107 (0.93%) | 2 / 98 (2.04%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 107 (0.00%) | 1 / 98 (1.02%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhea | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 107 (0.00%) | 0 / 98 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 107 (0.00%) | 0 / 98 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Proctalgia | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 107 (0.00%) | 0 / 98 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anorectal discomfort | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 106 (0.00%) | 1 / 107 (0.93%) | 0 / 98 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 107 (0.00%) | 0 / 98 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 107 (0.00%) | 0 / 98 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 106 (0.94%) | 0 / 107 (0.00%) | 0 / 98 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral infection | | | |
| subjects affected / exposed | 0 / 106 (0.00%) | 0 / 107 (0.00%) | 1 / 98 (1.02%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|------------------------------|--|--|
| Serious adverse events | PEG 4000 (Open-label Period) | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 99 (1.01%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | | | |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 0 / 99 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Dizziness | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 99 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Syncope | | | |
| subjects affected / exposed | 0 / 99 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 99 (1.01%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Constipation | | | |
| subjects affected / exposed | 0 / 99 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 99 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diarrhea | | | |
| subjects affected / exposed | 0 / 99 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nausea | | | |
| subjects affected / exposed | 0 / 99 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Proctalgia | | | |
| subjects affected / exposed | 1 / 99 (1.01%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Anorectal discomfort | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 99 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 99 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 99 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 99 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Viral infection | | | |
| subjects affected / exposed | 0 / 99 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | Prucalopride (Double-blind Period) | Placebo (Double-blind Period) | Prucalopride (Open-label Period) |
|---|------------------------------------|-------------------------------|----------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 53 / 106 (50.00%) | 50 / 107 (46.73%) | 44 / 98 (44.90%) |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 17 / 106 (16.04%) | 9 / 107 (8.41%) | 3 / 98 (3.06%) |
| occurrences (all) | 24 | 11 | 3 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |

| | | | |
|--|-------------------------|----------------------|---------------------|
| subjects affected / exposed occurrences (all) | 15 / 106 (14.15%) 18 | 3 / 107 (2.80%) 4 | 5 / 98 (5.10%) 5 |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 2 / 106 (1.89%) | 2 / 107 (1.87%) | 6 / 98 (6.12%) |
| occurrences (all) | 3 | 2 | 8 |
| Vomiting | | | |
| subjects affected / exposed | 14 / 106 (13.21%) | 5 / 107 (4.67%) | 9 / 98 (9.18%) |
| occurrences (all) | 16 | 5 | 10 |
| Abdominal pain | | | |
| subjects affected / exposed | 13 / 106 (12.26%) | 12 / 107 (11.21%) | 9 / 98 (9.18%) |
| occurrences (all) | 17 | 21 | 9 |
| Diarrhea | | | |
| subjects affected / exposed | 5 / 106 (4.72%) | 6 / 107 (5.61%) | 3 / 98 (3.06%) |
| occurrences (all) | 5 | 6 | 5 |
| Nausea | | | |
| subjects affected / exposed | 9 / 106 (8.49%) | 6 / 107 (5.61%) | 4 / 98 (4.08%) |
| occurrences (all) | 11 | 6 | 4 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 6 / 106 (5.66%) | 2 / 107 (1.87%) | 4 / 98 (4.08%) |
| occurrences (all) | 6 | 2 | 4 |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 2 / 106 (1.89%) | 7 / 107 (6.54%) | 5 / 98 (5.10%) |
| occurrences (all) | 2 | 8 | 5 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 3 / 106 (2.83%) | 2 / 107 (1.87%) | 6 / 98 (6.12%) |
| occurrences (all) | 3 | 2 | 6 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 2 / 106 (1.89%) | 5 / 107 (4.67%) | 5 / 98 (5.10%) |
| occurrences (all) | 4 | 7 | 6 |
| Viral infection | | | |
| subjects affected / exposed | 6 / 106 (5.66%) | 5 / 107 (4.67%) | 3 / 98 (3.06%) |
| occurrences (all) | 6 | 5 | 4 |
| Pharyngitis | | | |

| | | | |
|-----------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed | 3 / 106 (2.83%) | 6 / 107 (5.61%) | 5 / 98 (5.10%) |
| occurrences (all) | 3 | 6 | 5 |

| | | | |
|---|------------------------------|--|--|
| Non-serious adverse events | PEG 4000 (Open-label Period) | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 44 / 99 (44.44%) | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 7 / 99 (7.07%) | | |
| occurrences (all) | 7 | | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 7 / 99 (7.07%) | | |
| occurrences (all) | 7 | | |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 2 / 99 (2.02%) | | |
| occurrences (all) | 2 | | |
| Vomiting | | | |
| subjects affected / exposed | 5 / 99 (5.05%) | | |
| occurrences (all) | 6 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 11 / 99 (11.11%) | | |
| occurrences (all) | 12 | | |
| Diarrhea | | | |
| subjects affected / exposed | 12 / 99 (12.12%) | | |
| occurrences (all) | 13 | | |
| Nausea | | | |
| subjects affected / exposed | 1 / 99 (1.01%) | | |
| occurrences (all) | 1 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 6 / 99 (6.06%) | | |
| occurrences (all) | 6 | | |
| Infections and infestations | | | |

| | | | |
|-----------------------------------|----------------|--|--|
| Bronchitis | | | |
| subjects affected / exposed | 3 / 99 (3.03%) | | |
| occurrences (all) | 3 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 5 / 99 (5.05%) | | |
| occurrences (all) | 6 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 5 / 99 (5.05%) | | |
| occurrences (all) | 7 | | |
| Viral infection | | | |
| subjects affected / exposed | 4 / 99 (4.04%) | | |
| occurrences (all) | 5 | | |
| Pharyngitis | | | |
| subjects affected / exposed | 4 / 99 (4.04%) | | |
| occurrences (all) | 4 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 13 December 2010 | The volumes of blood to be taken for biochemistry and hematology panels were corrected. |
| 27 January 2011 | Upon request of the Competent Authorities, the following changes were made: 1. Severe renal insufficiency was added to the exclusion criteria 2. "The rescue medication products have to be used in respect to the contraindications, warnings and precautions of use, and interactions of their Summary of Product Characteristics" was added as a warning for rescue medication 3. "Prucalopride should be used with caution in subjects receiving concomitant drugs known to cause QTc prolongation" was added as a warning for prucalopride |
| 18 April 2011 | 1. The sponsor's name was changed from Movetis to Shire-Movetis 2. SAE reporting procedures were changed from Movetis to Shire procedures 3. It was indicated that a paper medication intake form was to be used in the Open-label Treatment Period |
| 19 December 2011 | 1. The Shire study number (SPD555-303) was added to the front page of the protocol 2. Measurement of Tanner stages for sexual maturation was added 3. In response to scientific input of experienced clinicians at an investigator follow-up meeting, some sections in the protocol were slightly reworded and clarified to be in line with clinical practice Apart from the above, minor editorial changes were performed |
| 31 July 2012 | Reference to a proposed study for the follow-up of growth and sexual maturation was removed. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported