

**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
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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
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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
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Arm 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.

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 \leq 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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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 (± 0.47)	2 (± 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
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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
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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
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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
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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
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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
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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 (\pm 2.35)	1 (\pm 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
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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
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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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	12.1
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Reporting groups

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