



## Clinical trial results:

### An Open-label, Randomized, Crossover, Reader-blinded Study To Investigate the Effect of Prucalopride and Polyethylene Glycol 3350 on Colon Motility with Intraluminal Manometry in Subjects with Chronic Constipation

#### Summary

EudraCT number	2012-002495-13
Trial protocol	BE
Global end of trial date	27 November 2013

#### Results information

Result version number	v1 (current)
This version publication date	04 September 2018
First version publication date	13 March 2015

#### Trial information

##### Trial identification

Sponsor protocol code	SPD555-403
-----------------------	------------

##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01707667
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Shire Movetis NV
Sponsor organisation address	Veedijk 58(104), Turnhout, Belgium, 2300
Public contact	Medical Communications, Shire-Movetis, 0032 14404390, shire-movetis.clinicaltrials@shire.com
Scientific contact	Medical Communications, Shire-Movetis, 0032 14404390, shire-movetis.clinicaltrials@shire.com

Notes:

#### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 November 2013
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	27 November 2013
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To evaluate differences in pharmacodynamic effects of prucalopride and polyethylene glycol (PEG 3350) + electrolytes on the number of colonic high amplitude propagating contractions (HAPC) during a 12-hour intraluminal manometry in chronically constipated subjects.

Protection of trial subjects:

The subject's informed consent was a mandatory condition for taking part in the study. It was obtained in writing prior to the performance of any study-specific procedures. This study was conducted in accordance with International Conference on Harmonisation of 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	27 February 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	United States: 13
Worldwide total number of subjects	13
EEA total number of subjects	0

Notes:

### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	13
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted in 1 center (United States).

### Pre-assignment

Screening details:

Subjects were screened and entered a 10- to 19-day run in period, during which they recorded their bowel habits and rescue medication use in a daily diary and the existence of constipation was confirmed.

### Period 1

Period 1 title	Treatment Period 1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

To minimize bias, the study was reader-blinded: the tracings were read by an experienced gastroenterologist who received de-identified recordings that did not specify which treatment the subject had received.

### Arms

Are arms mutually exclusive?	Yes
Arm title	Prucalopride-Polyethylene glycol (PEG)

Arm description:

A single dose of prucalopride in the first period followed by 2 doses of PEG 3350 plus electrolytes in the second period.

Arm type	Experimental
Investigational medicinal product name	Prucalopride
Investigational medicinal product code	
Other name	Resolor
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One 2mg tablet administered with 125ml of water on Day 1

Arm title	Polyethylene glycol (PEG)-Prucalopride
-----------	--

Arm description:

Two doses of PEG 3350 plus electrolytes in the first period followed by a single dose of prucalopride in the second period.

Arm type	Experimental
Investigational medicinal product name	Polyethylene glycol (PEG) 3350
Investigational medicinal product code	
Other name	Movicol
Pharmaceutical forms	Powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

13.8g-sachets of PEG 3350 with sodium bicarbonate, sodium chloride, and potassium chloride as a solution in water (125ml). Administered twice on Day 1 (once in the morning and once prior to lunch).

Number of subjects in period 1	Prucalopride- Polyethylene glycol (PEG)	Polyethylene glycol (PEG)-Prucalopride
Started	7	6
Completed	6	6
Not completed	1	0
Expulsion of colonic sensor catheter	1	-

## Period 2

Period 2 title	Treatment Period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

To minimize bias, the study was reader-blinded: the tracings were read by an experienced gastroenterologist who received de-identified recordings that did not specify which treatment the subject had received.

## Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Prucalopride-Polyethylene glycol (PEG)

Arm description:

A single dose of prucalopride in the first period followed by 2 doses of PEG 3350 plus electrolytes in the second period.

Arm type	Experimental
Investigational medicinal product name	Polyethylene glycol (PEG) 3350
Investigational medicinal product code	
Other name	Movicol
Pharmaceutical forms	Powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

13.8g-sachets of PEG 3350 with sodium bicarbonate, sodium chloride, and potassium chloride as a solution in water (125ml). Administered twice on Day 1 (once in the morning and once prior to lunch).

<b>Arm title</b>	Polyethylene glycol (PEG)-Prucalopride
------------------	--

Arm description:

Two doses of PEG 3350 plus electrolytes in the first period followed by a single dose of prucalopride in the second period.

Arm type	Experimental
Investigational medicinal product name	Prucalopride
Investigational medicinal product code	
Other name	Resolor
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One 2mg tablet administered with 125ml of water on Day 1

Number of subjects in period 2	Prucalopride- Polyethylene glycol (PEG)	Polyethylene glycol (PEG)-Prucalopride
Started	6	6
Completed	6	6

## Baseline characteristics

### Reporting groups

Reporting group title	Prucalopride-Polyethylene glycol (PEG)
Reporting group description: A single dose of prucalopride in the first period followed by 2 doses of PEG 3350 plus electrolytes in the second period.	
Reporting group title	Polyethylene glycol (PEG)-Prucalopride
Reporting group description: Two doses of PEG 3350 plus electrolytes in the first period followed by a single dose of prucalopride in the second period.	

Reporting group values	Prucalopride- Polyethylene glycol (PEG)	Polyethylene glycol (PEG)-Prucalopride	Total
Number of subjects	7	6	13
Age categorical Units: Subjects			
18-64 years	7	6	13
Age continuous Units: years arithmetic mean standard deviation	40.3 ± 11.04	35.2 ± 13.18	-
Gender categorical Units: Subjects			
Female	7	6	13
Male	0	0	0
Region of Enrollment Units: Subjects			
United States	7	6	13

## End points

### End points reporting groups

Reporting group title	Prucalopride-Polyethylene glycol (PEG)
Reporting group description: A single dose of prucalopride in the first period followed by 2 doses of PEG 3350 plus electrolytes in the second period.	
Reporting group title	Polyethylene glycol (PEG)-Prucalopride
Reporting group description: Two doses of PEG 3350 plus electrolytes in the first period followed by a single dose of prucalopride in the second period.	
Reporting group title	Prucalopride-Polyethylene glycol (PEG)
Reporting group description: A single dose of prucalopride in the first period followed by 2 doses of PEG 3350 plus electrolytes in the second period.	
Reporting group title	Polyethylene glycol (PEG)-Prucalopride
Reporting group description: Two doses of PEG 3350 plus electrolytes in the first period followed by a single dose of prucalopride in the second period.	
Subject analysis set title	Prucalopride
Subject analysis set type	Full analysis
Subject analysis set description: A single dose of 2mg prucalopride, administered orally as tablets with 125mL of water on Day 1.	
Subject analysis set title	PEG 3350
Subject analysis set type	Full analysis
Subject analysis set description: 13.8g polyethylene glycol (PEG) 3350 with sodium bicarbonate, sodium chloride, and potassium chloride as a solution in water. Administered twice orally on Day 1 (once in the morning and once prior to lunch).	

### Primary: The Number of High-Amplitude Propagating Contractions (HAPC)

End point title	The Number of High-Amplitude Propagating Contractions (HAPC)
End point description: Manometry recordings were read by an experienced gastroenterologist who was blinded to the treatment each subject received. The tracings were analyzed using computer-based validated software. HAPC and manometry data were available for every sensor as well as average values for each HAPC and manometry time point. The primary outcome analysis of HAPC data used the following threshold: Mean amplitude $\geq 100$ mmHg and extension $\geq 20$ cm (9 sensors). This end point analyzed the Pharmacodynamic Analysis Set, which consisted of all randomized subjects who had taken at least 1 dose of investigational product and who had 1 evaluable manometry assessment (minimum of 4 hours of manometry recordings from the intake of investigational product) for each treatment period.	
End point type	Primary
End point timeframe: Over 12 hours post-dose	

End point values	Prucalopride	PEG 3350		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	12		
Units: Number of HAPC with amplitude $\geq 100\text{mmHg}$				
least squares mean (standard error)	8.7 ( $\pm$ 2.06)	2.9 ( $\pm$ 2.06)		

## Statistical analyses

Statistical analysis title	Analysis of HPACs
Comparison groups	PEG 3350 v Prucalopride
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.012
Method	Linear Mixed-Effect Models Analysis
Parameter estimate	Mean difference (final values)
Point estimate	5.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.6
upper limit	9.9

## Secondary: Area Under The Concentration Curve (AUC) of All HAPCs

End point title	Area Under The Concentration Curve (AUC) of All HAPCs
End point description:	<p>The AUC of all HAPCs during the first 12 hours after treatment was calculated as the sum of the AUC at all sensors of each HAPC at the <math>\geq 100\text{mmHg}</math> and <math>\geq 20\text{cm}</math> threshold.</p> <p>This end point analyzed the Pharmacodynamic Analysis Set, which consisted of all randomized subjects who had taken at least 1 dose of investigational product and who had 1 evaluable manometry assessment (minimum of 4 hours of manometry recordings from the intake of investigational product) for each treatment period.</p>
End point type	Secondary
End point timeframe:	
Over 12 hours post-dose	

End point values	Prucalopride	PEG 3350		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	6		
Units: mmHg.sec				
least squares mean (standard error)	110204.1 ( $\pm$ 28279.91)	41152.7 ( $\pm$ 34432.61)		



## Statistical analyses

<b>Statistical analysis title</b>	Analysis of AUC of All HAPCs
Comparison groups	PEG 3350 v Prucalopride
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.079
Method	Linear Mixed-Effect Models Analysis
Parameter estimate	Mean difference (final values)
Point estimate	69051.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12004.5
upper limit	150107.3

## Secondary: The Mean Amplitude of HAPC

End point title	The Mean Amplitude of HAPC
End point description: The mean amplitude of all HAPCs was calculated as the sum of the mean amplitude for each HAPC divided by the number of HAPCs. This end point analyzed the Pharmacodynamic Analysis Set, which consisted of all randomized subjects who had taken at least 1 dose of investigational product and who had 1 evaluable manometry assessment (minimum of 4 hours of manometry recordings from the intake of investigational product) for each treatment period.	
End point type	Secondary
End point timeframe: Over 12 hours post-dose	

<b>End point values</b>	Prucalopride	PEG 3350		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	6		
Units: mmHg				
least squares mean (standard error)	199 (± 15.15)	189.8 (± 19.56)		

## Statistical analyses

<b>Statistical analysis title</b>	Analysis of Mean Amplitude of HAPC
Comparison groups	Prucalopride v PEG 3350
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.717
Method	Linear Mixed-Effect Models Analysis
Parameter estimate	Mean difference (final values)
Point estimate	9.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-45.3
upper limit	63.7

### Secondary: Time to First HAPC

End point title	Time to First HAPC
End point description:	
The median (95% confidence interval) time to first HAPC after administration of investigational product with amplitude $\geq 100$ mmHg and extension $\geq 20$ cm.	
This end point analyzed the Pharmacodynamic Analysis Set, which included all subjects in the Safety Analysis Set who had 1 evaluable manometry assessment (minimum of 4 hours of manometry recordings from the intake of investigational product) for each treatment period.	
In the PEG 3350 group, the median time to first HAPC after administration of investigational product with amplitude $\geq 100$ mmHg and extension $\geq 20$ cm could not be calculated as only 6 subjects had HAPCs that met this threshold.	
End point type	Secondary
End point timeframe:	
Over 12 hours post-dose	

<b>End point values</b>	Prucalopride			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: hours				
median (confidence interval 95%)	4.5 (1.5 to 9.3)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Propagation Velocity of HAPC

End point title	Propagation Velocity of HAPC
End point description:	
Propagation velocity was calculated as the extension divided by the duration for each HAPC. Mean propagation velocity is the sum of the propagation velocities divided by the number of HAPCs.	

This end point analyzed the Pharmacodynamic Analysis Set, which consisted of all randomized subjects who had taken at least 1 dose of investigational product and who had 1 evaluable manometry assessment (minimum of 4 hours of manometry recordings from the intake of investigational product) for each treatment period.

End point type	Secondary
End point timeframe:	
Over 12 hours post-dose	

End point values	Prucalopride	PEG 3350		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	6		
Units: cm/sec				
least squares mean (standard error)	0.467 ( $\pm$ 0.0803)	0.646 ( $\pm$ 0.1074)		

## Statistical analyses

Statistical analysis title	Analysis of Propagation Velocity of HAPC
Comparison groups	Prucalopride v PEG 3350
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.18
Method	Linear Mixed-Effect Models Analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.179
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.465
upper limit	0.107

## Secondary: Duration of HAPC

End point title	Duration of HAPC
End point description:	
The mean duration of all HAPCs was calculated as the sum of the duration of each HAPC divided by the number of HAPCs.	
This end point analyzed the Pharmacodynamic Analysis Set, which consisted of all randomized subjects who had taken at least 1 dose of investigational product and who had 1 evaluable manometry assessment (minimum of 4 hours of manometry recordings from the intake of investigational product) for each treatment period.	
End point type	Secondary
End point timeframe:	
Over 12 hours post-dose	

End point values	Prucalopride	PEG 3350		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	6		
Units: sec				
least squares mean (standard error)	84.9 ( $\pm$ 8.05)	69.1 ( $\pm$ 10.75)		

## Statistical analyses

Statistical analysis title	Analysis of Duration of HAPC
Comparison groups	Prucalopride v PEG 3350
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.225
Method	Linear Mixed-Effect Models Analysis
Parameter estimate	Mean difference (final values)
Point estimate	15.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.6
upper limit	44.3

## Secondary: Motility Index

End point title	Motility Index
End point description:	
Motility index (mmHg) was summarized for the following 3 time points: pre-dose, 0-5 hours post-dose, and 5-12 hours post-dose. The motility index is defined as the natural logarithm of all peak amplitudes of every contraction +1.	
This end point analyzed the Pharmacodynamic Analysis Set, which consisted of all randomized subjects who had taken at least 1 dose of investigational product and who had 1 evaluable manometry assessment (minimum of 4 hours of manometry recordings from the intake of investigational product) for each treatment period.	
End point type	Secondary
End point timeframe:	
Over 12 hours post-dose	

End point values	Prucalopride	PEG 3350		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	11		
Units: mmHg				
least squares mean (standard error)				
Pre-dose	9.467 (± 0.4668)	8.312 (± 0.4403)		
0-5 hours post-dose	13.661 (± 0.3221)	13.349 (± 0.352)		
5-12 hours post-dose	14.208 (± 0.2976)	14.39 (± 0.2489)		

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to 35 days

Assessment type	Systematic
-----------------	------------

### Dictionary used

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

Dictionary version	15.1
--------------------	------

### Reporting groups

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

Reporting group description:

A single dose of 2mg prucalopride, administered orally as tablets with 125mL of water on Day 1.

Reporting group title	Polyethylene Glycol
-----------------------	---------------------

Reporting group description:

13.8g polyethylene glycol (PEG) 3350 with sodium bicarbonate, sodium chloride, and potassium chloride as a solution in water. Administered twice orally on Day 1 (once in the morning and once prior to lunch).

Serious adverse events	Prucalopride	Polyethylene Glycol	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Prucalopride	Polyethylene Glycol	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 13 (23.08%)	0 / 12 (0.00%)	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 13 (15.38%)	0 / 12 (0.00%)	
occurrences (all)	2	0	
Diarrhoea			

subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
Rectal haemorrhage			
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences (all)	1	0	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 September 2012	The general amendment included the following changes: 1-The medical monitor was changed 2-Due to concerns regarding the original lengthy fasting period between Day -2 and Day 1, dinner was added to Day -2 and Day -1, and an afternoon snack was added to Day -1 3-The original text on the packaging of the investigational product was corrected 4-Additional wording was added on the timing of colonic multiple sensor catheter placement 5-The original text on the reporting period for SAEs was changed from "must occur within one business day" to "must occur within 24 hours" 5-Minor editorial changes were performed

Notes:

---

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported