



## 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-<br>Polyethylene glycol<br>(PEG) | Polyethylene glycol<br>(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-<br>Polyethylene glycol<br>(PEG) | Polyethylene glycol<br>(PEG)-Prucalopride |
|--------------------------------|---|---|
|                                |   |   |
| Started                        | 6   | 6   |
| Completed                      | 6   | 6   |

## Baseline characteristics

### Reporting groups

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

## End points

### End points reporting groups

|  |  |
|--|--|
| Reporting group title  | Prucalopride-Polyethylene glycol (PEG) |
| Reporting group description:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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).<br>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:<br>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:<br>The mean amplitude of all HAPCs was calculated as the sum of the mean amplitude for each HAPC divided by the number of HAPCs.<br>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:<br>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:<br>1-The medical monitor was changed<br>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<br>3-The original text on the packaging of the investigational product was corrected<br>4-Additional wording was added on the timing of colonic multiple sensor catheter placement<br>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"<br>5-Minor editorial changes were performed |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported