Clinical trial results:
A 12-week, randomised, double-blind, placebo-controlled trial to evaluate the efficacy and safety of prucalopride in subjects with chronic non-cancer pain suffering from opioid induced constipation

Summary

EudraCT number	2009-015652-20
Trial protocol	BE PL DE CZ FR NL BG GB ES HU
Global end of trial date	13 August 2012

Results information

Result version number	v1 (current)
This version publication date	04 September 2018
First version publication date	31 May 2015

Trial information

Trial identification

Sponsor protocol code	M0001-C301/SPD555-301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01117051
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Shire-Movetis NV
Sponsor organisation address	B-2300 Turnhout, Veedijk, Belgium, 58 (1004)
Public contact	Shire-Movetis Clinical Trials, Shire-Movetis NV, +32 14404390, Shire-Movetis.clinicaltrials@shire.com
Scientific contact	Shire-Movetis Clinical Trials, Shire-Movetis NV, +32 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	13 August 2012
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 August 2012
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of prucalopride versus placebo over 12 weeks of treatment in subjects aged 18 years and older with chronic non-cancer pain, suffering from opioid-induced constipation (OIC).

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice. The subject's informed consent was obtained in writing prior to performing any study-related procedures. Subjects were allowed to take a laxative (bisacodyl DULCOLAX®; Boehringer-Ingelheim) as rescue medication throughout the study, but only if they had not had a bowel movement (BM) in the preceding 48 hours.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 May 2010
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	Netherlands: 1
Country: Number of subjects enrolled	Poland: 11
Country: Number of subjects enrolled	Romania: 11
Country: Number of subjects enrolled	United Kingdom: 27
Country: Number of subjects enrolled	Belgium: 17
Country: Number of subjects enrolled	Bulgaria: 9
Country: Number of subjects enrolled	Czech Republic: 78
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	Hungary: 3
Worldwide total number of subjects	174
EEA total number of subjects	174

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	132
From 65 to 84 years	42
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects were screened and entered a 2-week Run-in Period (or a 3-week Run-in Period if the subject was using agents that influence bowel habit) during which the presence and severity of opioid-induced constipation (OIC) was documented (the subject completed an e-diary).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Placebo matched investigational product.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects received placebo once daily before breakfast for up to 12 weeks.

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

Dosage and administration details:

Matching placebo was administered once daily before breakfast for 12 weeks. Adult subjects ≥18 to <65 years of age took a placebo tablet matching a 2mg prucalopride tablet. Elderly subjects ≥65 years took a placebo tablet matching a 1mg prucalopride tablet. In case of insufficient response, defined as an average of <3 spontaneous bowel movements (SBM)/week during the preceding 2 weeks of treatment at Week 2 or Week 4, the daily dose had to be increased to one placebo tablet matching a 2mg prucalopride tablet. Once the placebo dose was increased to match 2mg once daily the subject stayed on this dose for the remainder of the study. Further increases or decreases in dose were not permitted, ie, no changes in dose occurred at the Week 8 visit or thereafter.

Arm title	Prucalopride

Arm description:

Participants received prucalopride once daily before breakfast for up to 12 weeks.

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

Dosage and administration details:

Prucalopride was administered once daily before breakfast for 12 weeks. Adult subjects ≥18 to <65 years of age took one 2mg tablet. Elderly subjects ≥65 years took one 1mg tablet. In case of insufficient response, defined as an average of <3 spontaneous bowel movements (SBM)/week during the preceding 2 weeks of treatment at Week 2 or Week 4, the daily dose had to be increased to one 2mg tablet. Once the dose was increased to 2mg once daily the subject stayed on this dose for the

remainder of the study. Further increases or decreases in dose were not permitted, ie, no changes in dose occurred at the Week 8 visit or thereafter.

Number of subjects in period 1	Placebo	Prucalopride
Started	86	88
Completed	73	77
Not completed	13	11
Sponsor's decision	3	1
Surgical procedure	-	1
Convenience issue	1	-
Randomised by mistake	-	1
Did not meet in-/exclusion criteria	-	1
Adverse event	4	3
Lost to follow-up	-	1
Withdrawal by subject	5	3

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo once daily before breakfast for up to 12 weeks.	
Reporting group title	Prucalopride
Reporting group description:	
Participants received prucalopride once daily before breakfast for up to 12 weeks.	

Reporting group values	Placebo	Prucalopride	Total
Number of subjects	86	88	174
Age categorical Units: Subjects			
Between >=18 and <65 years	65	67	132
Between >=65 and <75 year	11	11	22
>=75 years	10	10	20
Age continuous Units: years			
arithmetic mean	57.5	56	
standard deviation	± 11.49	± 12.25	-
Gender categorical Units: Subjects			
Female	63	64	127
Male	23	24	47
Region of enrollment Units: Subjects			
Belgium	8	9	17
Bulgaria	4	5	9
Czech Republic	40	38	78
Germany	6	7	13
France	2	2	4
United Kingdom	13	14	27
Hungary	2	1	3
Netherlands	0	1	1
Poland	6	5	11
Romania	5	6	11

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects received placebo once daily before breakfast for up to 12 weeks.	
Reporting group title	Prucalopride
Reporting group description:	
Participants received prucalopride once daily before breakfast for up to 12 weeks.	

Primary: Percent of Subjects With an Average Frequency of >=3 Spontaneous Bowel Movements (SBM) Per Week

End point title	Percent of Subjects With an Average Frequency of >=3 Spontaneous Bowel Movements (SBM) Per Week
End point description:	
A bowel movement (BM) was defined as spontaneous if no laxatives were taken in the 24 hours preceding that BM. This end point analysed the Intent-to-Treat (ITT) population, defined as all subjects who were randomised into the study and who had received at least 1 dose of investigational medication.	
End point type	Primary
End point timeframe:	
12 weeks	

End point values	Placebo	Prucalopride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	86		
Units: percent of subjects				
number (not applicable)	39.8	48.8		

Statistical analyses

Statistical analysis title	Analysis of SBM
Comparison groups	Placebo v Prucalopride
Number of subjects included in analysis	169
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.305
Method	Cochran-Mantel-Haenszel

Secondary: Plasma Concentration of Prucalopride at Week 2

End point title	Plasma Concentration of Prucalopride at Week 2[1]

End point description:

This end point analysed the ITT population, defined as all subjects who were randomised into the study and who had received at least 1 dose of investigational medication. Subjects in the ITT whose post-dose samples were collected outside the 5-hour sampling window were not used in the plasma concentration calculation.

End point type	Secondary

End point timeframe:

Week 2

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a subgroup analysis of the Prucalopride treatment arm. Prucalopride concentration was not assessed for subjects who received placebo.

End point values	Prucalopride			
Subject group type	Reporting group			
Number of subjects analysed	62			
Units: ng/ml				
arithmetic mean (standard deviation)				
Pre-dose 5 hours post-dose	2.827 (± 1.5989) 6.107 (± 2.8839)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of Prucalopride at Week 8

End point title	Plasma Concentration of Prucalopride at Week 8[2]

End point description:

This end point analysed the ITT population, defined as all subjects who were randomised into the study and who had received at least 1 dose of investigational medication. Subjects in the ITT whose post-dose samples were collected outside the 5-hour sampling window were not used in the plasma concentration calculation.

End point type	Secondary

End point timeframe:

Week 8

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a subgroup analysis of the Prucalopride treatment arm. Prucalopride concentration was not assessed for subjects who received placebo.

End point values	Prucalopride			
Subject group type	Reporting group			
Number of subjects analysed	53			
Units: ng/ml				
arithmetic mean (standard deviation)				
Pre-dose 5 hours post-dose	3.179 (± 1.9066) 6.615 (± 2.5758)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

12 weeks

Adverse event reporting additional description:

AEs were assessed for the Safety Population, defined as all subjects who were randomised into the study and who had received at least 1 dose of investigational product.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects received placebo once daily before breakfast for up to 12 weeks.

Reporting group title	Prucalopride

Reporting group description:

Participants received prucalopride once daily before breakfast for up to 12 weeks.

Serious adverse events	Placebo	Prucalopride	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 83 (2.41%)	2 / 86 (2.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 83 (0.00%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Intestinal obstruction			
subjects affected / exposed	0 / 83 (0.00%)	1 / 86 (1.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			

subjects affected / exposed	1 / 83 (1.20%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Hepatitis A			
subjects affected / exposed	1 / 83 (1.20%)	0 / 86 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Placebo	Prucalopride	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 83 (22.89%)	20 / 86 (23.26%)	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 83 (1.20%)	2 / 86 (2.33%)	
occurrences (all)	1	2	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 83 (2.41%)	0 / 86 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 83 (2.41%)	4 / 86 (4.65%)	
occurrences (all)	2	4	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	4 / 83 (4.82%)	2 / 86 (2.33%)	
occurrences (all)	6	3	
Abdominal Pain Upper			
subjects affected / exposed	2 / 83 (2.41%)	3 / 86 (3.49%)	
occurrences (all)	2	3	
Diarrhoea			
subjects affected / exposed	4 / 83 (4.82%)	3 / 86 (3.49%)	
occurrences (all)	4	3	

Flatulence			
subjects affected / exposed	1 / 83 (1.20%)	4 / 86 (4.65%)	
occurrences (all)	1	4	
Nausea			
subjects affected / exposed	5 / 83 (6.02%)	9 / 86 (10.47%)	
occurrences (all)	8	11	
Rectal Haemorrhage			
subjects affected / exposed	2 / 83 (2.41%)	1 / 86 (1.16%)	
occurrences (all)	3	1	
Vomiting			
subjects affected / exposed	3 / 83 (3.61%)	2 / 86 (2.33%)	
occurrences (all)	3	2	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 83 (0.00%)	2 / 86 (2.33%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	1 / 83 (1.20%)	4 / 86 (4.65%)	
occurrences (all)	1	4	
Pain In Extremity			
subjects affected / exposed	2 / 83 (2.41%)	0 / 86 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Influenza			
subjects affected / exposed	1 / 83 (1.20%)	2 / 86 (2.33%)	
occurrences (all)	1	2	
Nasopharyngitis			
subjects affected / exposed	2 / 83 (2.41%)	1 / 86 (1.16%)	
occurrences (all)	2	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 April 2010	The following changes were made to the protocol: * Exclusion criterion 4: Intestinal perforation was added as an organic disorder of the large bowel * Exclusion criterion 10: In the following phrase "serum creatinine concentration greater than 2mg/dL (<180micromole/L)", the "180micromole/L" was deleted * The following was added to the list of prohibitions and restrictions "Women of childbearing potential should be instructed that in case of severe diarrhoea, the efficacy of oral contraceptives may be reduced and the use of an additional contraceptive method is recommended to prevent possible failure of oral contraception (see the prescribing information of the oral contraceptive)."
19 May 2011	Protocol Amendment 2: The pharmacovigilance reporting methods were changed in order to be in line with the sponsor's procedures.
13 January 2012	Protocol Amendment 3:The main reason for this protocol amendment was the lowering of the planned number of subjects to be included in the study from 510 (255 in each treatment arm) to 342 (171 in each treatment arm). Furthermore, several changes were made in order to clarify that it should be included in the subject's medical history in case he/she was lactose intolerant. All subjects with lactose intolerance had to strictly adhere to their diet during the entire study (added to the list of prohibitions and restrictions in Section 3.9) since in subjects with lactose intolerance low doses of lactose could lead to diarrhea (added to Exclusion Criterion 14). In addition, the following changes were made: * Exclusion criterion 4: the wording was changed to clarify that subjects with "insulin-dependent diabetes mellitus, even if adequately controlled" were excluded * Exclusion criterion 10: the serum creatinine lower limit concentration was changed from 2mg/dL to 180micromole/L and the calculated creatinine clearance was changed from 50 to </= 30mL/min * Additional exclusion criterion 16 "subjects who previously used prucalopride" was added * It was clarified in the section on screening failures that these subjects could not be rescreened without prior approval from the sponsor * A paragraph was added to the section on dose regimen and administration period (Section 4.5.1) on what subjects had to do in case they forgot to take their daily dose of investigational product in the morning * The definition of overdose was added to the section of overdose management (Section 4.5.5) * In the section on sample size (Section 6.1), the 2-sided significance level was changed from 1 to 5%.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
13 August 2012	This study was terminated early due to slow recruitment and the fact that the sponsor is no longer pursuing the opioid-induced constipation (OIC) indication.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to the early termination of the study, results should be interpreted with caution.

Notes: