Clinical trial results:
A 12-week, Randomised, Double-blind, Placebo-controlled Trial to Evaluate the Efficacy, Quality of Life, Safety and Tolerability of Prucalopride in Male Subjects With Chronic Constipation

Summary

EudraCT number	2009-015719-42
Trial protocol	BE DE CZ GB FR NL BG DK
Global end of trial date	25 October 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	SPD555-302

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01147926
WHO universal trial number (UTN)	-
Other trial identifiers	Study Number: M0001-C302

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)	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	25 October 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 October 2013
Was the trial ended prematurely?	No

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 male subjects with chronic constipation.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation of Good Clinical Practice (GCP), 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	23 September 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: 10
Country: Number of subjects enrolled	Poland: 56
Country: Number of subjects enrolled	United Kingdom: 24
Country: Number of subjects enrolled	Belgium: 20
Country: Number of subjects enrolled	Bulgaria: 18
Country: Number of subjects enrolled	Czech Republic: 29
Country: Number of subjects enrolled	Denmark: 41
Country: Number of subjects enrolled	France: 41
Country: Number of subjects enrolled	Germany: 21
Country: Number of subjects enrolled	Romania: 114
Worldwide total number of subjects	374
EEA total number of subjects	374

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)	222
From 65 to 84 years	145
85 years and over	7

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Out of a total of 553 subjects screened, 374 were randomized and 370 were treated with study drug. Reasons for 4 'randomized subjects but not treated': 2 subjects withdrew consent (1 each in placebo and prucalopride groups), 1 subject was non-compliant in prucalopride group, and 1 subject did not meet selection criteria in prucalopride group.

Pre-assignment period milestones

Number of subjects started	374
Number of subjects completed	370

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 2
Reason: Number of subjects	Non-compliance: 1
Reason: Number of subjects	Did not meet selection criteria: 1

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, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo matched to Prucalopride tablet orally once daily.

Arm type	Placebo
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 received oral dose of placebo matching with prucalopride once daily.

Arm title	Prucalopride

Arm description:

Prucalopride 2 milligram (mg) tablet orally once daily for subjects greater than or equal to (≥) 18 to less than (<) 65 years; 1 mg once daily orally for subjects ≥65 years, and in case of insufficient response, increased to 2 mg once daily orally at Week 2 or Week 4.

Arm type	Experimental

Investigational medicinal product name	Prucalopride
Investigational medicinal product code	M0001, SPD555
Other name	Resolor®
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received prucalopride 2 mg once daily orally (subjects ≥18 to <65 years); 1 mg once daily orally (subjects ≥65 years), and in case of insufficient response, increased to 2 mg once daily orally at Week 2 or Week 4.

Number of subjects in period 1[1]	Placebo	Prucalopride
Started	186	184
Completed	160	158
Not completed	26	26
Consent withdrawn by subject	8	9
Too busy, no time for study	1	-
Sponsor's Decision	-	1
Principal investigator left hospital	1	3
Adverse Event	7	6
Colonoscopy result	-	1
Selection criteria not met	3	-
Subject non-compliant	5	3
Lost to follow-up	-	2
Went on holiday	-	1
Lack of efficacy	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 period included only treated subjects, the worldwide number enrolled in the trial differs with the number of subjects reported in the baseline period.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo matched to Prucalopride tablet orally once daily.	
Reporting group title	Prucalopride
Reporting group description:	
Prucalopride 2 milligram (mg) tablet orally once daily for subjects greater than or equal to (≥) 18 to less than (<) 65 years; 1 mg once daily orally for subjects ≥65 years, and in case of insufficient response, increased to 2 mg once daily orally at Week 2 or Week 4.	

Reporting group values	Placebo	Prucalopride	Total
Number of subjects	186	184	370
Age categorical			
Safety population was defined as all subjects randomized into the study, who took at least 1 dose of investigational product based on information from the e-diary and/or tablet count (compliance) documented on the electronic case report form (eCRF). The Safety Population is equivalent to an Intent-to-treat (ITT) Population.			
Units: Subjects			
Less than 65 years	115	104	219
Between 65 and 75 years	39	43	82
75 years and above	32	37	69
Age continuous			
Safety population was defined as all subjects randomized into the study, who took at least 1 dose of investigational product based on information from the e-diary and/or tablet count (compliance) documented on the eCRF. The Safety Population is equivalent to an ITT Population.			
Units: years			
arithmetic mean	58.5	58.4	
standard deviation	± 16.28	± 17.57	-
Gender categorical			
Safety population was defined as all subjects randomized into the study, who took at least 1 dose of investigational product based on information from the e-diary and/or tablet count (compliance) documented on the eCRF. The Safety Population is equivalent to an ITT Population.			
Units: Subjects			
Male	186	184	370

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo matched to Prucalopride tablet orally once daily.	
Reporting group title	Prucalopride
Reporting group description:	
Prucalopride 2 milligram (mg) tablet orally once daily for subjects greater than or equal to (≥) 18 to less than (<) 65 years; 1 mg once daily orally for subjects ≥65 years, and in case of insufficient response, increased to 2 mg once daily orally at Week 2 or Week 4.	

Primary: The Percentage of Subjects With an Average of ≥3 Spontaneous Complete Bowel Movements (SCBM) Per Week

End point title	The Percentage of Subjects With an Average of ≥3 Spontaneous Complete Bowel Movements (SCBM) Per Week
End point description:	
Spontaneous Bowel Movements defined as a bowel movement that was not preceded within a period of 24 hours by the intake of a laxative agent or by the use of an enema. Modified Intent-to-treat Population (mITT) included all subjects randomized into the study except those excluded due to a major GCP breach at one site, who took at least 1 dose of the investigational product.	
End point type	Primary
End point timeframe:	
Over 12-week treatment period	

End point values	Placebo	Prucalopride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	181	177		
Units: percentage of subjects				
number (not applicable)	17.7	37.9		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Placebo v Prucalopride
Number of subjects included in analysis	358
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel

Secondary: Percentage of Subjects With an Average Weekly Frequency of at Least 3

SCBM Per Week and an Increase of ≥ 1 SCBM Per Week for ≥ 75% of the 12-week Treatment Period and ≥ 75% of the Last Third of the 12-week Treatment Period

End point title	Percentage of Subjects With an Average Weekly Frequency of at Least 3 SCBM Per Week and an Increase of ≥ 1 SCBM Per Week for ≥ 75% of the 12-week Treatment Period and ≥ 75% of the Last Third of the 12-week Treatment Period

End point description:

mITT population included all subjects randomized into the study except those excluded due to a major GCP breach at one site, who took at least 1 dose of the investigational product.

End point type	Secondary

End point timeframe:

Over 12-week treatment period

End point values	Placebo	Prucalopride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	181	177		
Units: percentage of subjects				
number (not applicable)	12.2	27.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With an Increase of at Least 1 SCBM Per Week

End point title	Percentage of Subjects With an Increase of at Least 1 SCBM Per Week

End point description:

mITT population included all subjects randomized into the study except those excluded due to a major GCP breach at one site, who took at least 1 dose of the investigational product.

End point type	Secondary

End point timeframe:

Over 12-week treatment period

End point values	Placebo	Prucalopride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	181	177		
Units: percentage of subjects				
number (not applicable)	45.3	53.7		

Statistical analyses

No statistical analyses for this end point

Secondary: SCBM Per Week

End point title	SCBM Per Week

End point description:

mITT population included all subjects randomized into the study except those excluded due to a major GCP breach at one site, who took at least 1 dose of the investigational product.

End point type	Secondary

End point timeframe:

Over 12-week treatment period

End point values	Placebo	Prucalopride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	172[1]	170[2]		
Units: SCBM per week				
arithmetic mean (standard deviation)	1.8 (± 1.91)	2.6 (± 2.4)		

Notes:

[1] - Not all subjects in the mITT population had data for this outcome.

[2] - Not all subjects in the mITT population had data for this outcome.

Statistical analyses

No statistical analyses for this end point

Secondary: Percent spontaneous bowel movements (SBM) With a Consistency of Normal and Hard/Very Hard

End point title	Percent spontaneous bowel movements (SBM) With a Consistency of Normal and Hard/Very Hard

End point description:

Consistency measured using the 7-point Bristol scale where 1-2 indicate constipation (=hard/very hard), 3-4 are ideal stools (=normal), and 5-7 tending toward diarrhea. mITT population included all subjects randomized into the study except those excluded due to a major GCP breach at one site, who took at least 1 dose of the investigational product.

End point type	Secondary

End point timeframe:

Over 12-week treatment period

End point values	Placebo	Prucalopride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167[3]	170[4]		
Units: percentage of SBM				
arithmetic mean (standard deviation)				
Normal consistency	50.8 (± 30.21)	47.5 (± 31.7)		
Hard/Very hard consistency	31.9 (± 29.86)	26.9 (± 28.27)		

Notes:

[3] - Not all subjects in the mITT population had data for this outcome.

[4] - Not all subjects in the mITT population had data for this outcome.

Statistical analyses

No statistical analyses for this end point

Secondary: Percent SCBM With No Straining and Severe/Very Severe Straining

End point title	Percent SCBM With No Straining and Severe/Very Severe Straining

End point description:

Straining was evaluated on a 5-point scale (0=none, 1=mild, 2=moderate, 3=severe, or 4=very severe). mITT population included all subjects randomized into the study except those excluded due to a major GCP breach at one site, who took at least 1 dose of the investigational product.

End point type	Secondary

End point timeframe:

Over 12 week treatment period

End point values	Placebo	Prucalopride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167[5]	170[6]		
Units: percentage of SBM				
arithmetic mean (standard deviation)				
No straining	9.5 (± 16.23)	9.7 (± 17.4)		
Severe/Very severe straining	23.7 (± 27.62)	20.6 (± 27.33)		

Notes:

[5] - Not all subjects in the mITT population had data for this outcome.

[6] - Not all subjects in the mITT population had data for this outcome.

Statistical analyses

No statistical analyses for this end point

Secondary: Percent SBM With Sensation of Complete Evacuation

End point title	Percent SBM With Sensation of Complete Evacuation

End point description:

mITT population included all subjects randomized into the study except those excluded due to a major GCP breach at one site, who took at least 1 dose of the investigational product.

End point type	Secondary

End point timeframe:

Over 12 week treatment period

End point values	Placebo	Prucalopride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167[7]	170[8]		
Units: percentage of SBM				
arithmetic mean (standard deviation)	43.2 (± 32.9)	46.7 (± 34.19)		

Notes:

[7] - Not all subjects in the mITT population had data for this outcome.

[8] - Not all subjects in the mITT population had data for this outcome.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First SCBM After Investigational Product Intake on Day 1

End point title	Time to First SCBM After Investigational Product Intake on Day 1

End point description:

mITT population included all subjects randomized into the study except those excluded due to a major GCP breach at one site, who took at least 1 dose of the investigational product.

End point type	Secondary

End point timeframe:

Day 1

End point values	Placebo	Prucalopride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	181	177		
Units: hours				
median (confidence interval 95%)	218.9 (143.93 to 291.43)	110.3 (70.8 to 172.77)		

Statistical analyses

No statistical analyses for this end point

Secondary: Bisacodyl Tablets Taken Per Week

End point title	Bisacodyl Tablets Taken Per Week

End point description:

mITT population included all subjects randomized into the study except those excluded due to a major GCP breach at one site, who took at least 1 dose of the investigational product.

End point type	Secondary

End point timeframe:

Over 12 week treatment period

End point values	Placebo	Prucalopride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	172[9]	170[10]		
Units: tablets/week				
arithmetic mean (standard deviation)	1 (± 1.76)	0.6 (± 1.56)		

Notes:

[9] - Not all subjects in the mITT population had data for this outcome.

[10] - Not all subjects in the mITT population had data for this outcome.

Statistical analyses

No statistical analyses for this end point

Secondary: Days With Rescue Medication Taken Per Week

End point title	Days With Rescue Medication Taken Per Week

End point description:

mITT population included all subjects randomized into the study except those excluded due to a major GCP breach at one site, who took at least 1 dose of the investigational product.

End point type	Secondary

End point timeframe:

Over 12-week treatment period

End point values	Placebo	Prucalopride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	172[11]	170[12]		
Units: days/week				
arithmetic mean (standard deviation)	0.6 (± 0.94)	0.3 (± 0.69)		

Notes:

[11] - Not all subjects in the mITT population had data for this outcome.

[12] - Not all subjects in the mITT population had data for this outcome.

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Subjects With an Improvement of ≥ 1 Point on the Patient Assessment of Constipation – Symptom (PAC-SYM) Questionnaire Total Score at Final On-Treatment Assessment

End point title	Percent of Subjects With an Improvement of ≥ 1 Point on the Patient Assessment of Constipation – Symptom (PAC-SYM) Questionnaire Total Score at Final On-Treatment Assessment

End point description:

The PAC-SYM is a validated 12-item questionnaire for the evaluation of severity of symptoms of constipation in subjects with constipation. Items were rated on a 5-point Likert scale: 0=absent, 1=mild, 2=moderate, 3=severe, 4=very severe. Total score ranged from 0 to 48. Lower scores indicate improvement in symptoms. A 1-point improvement in PAC-SYM total score was considered clinically meaningful. mITT population included all subjects randomized into the study except those excluded due to a major GCP breach at one site, who took at least 1 dose of the investigational product.

End point type	Secondary

End point timeframe:

Over 12-week treatment period

End point values	Placebo	Prucalopride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171[13]	169[14]		
Units: percentage of subjects				
number (not applicable)	30.4	34.9		

Notes:

[13] - Not all subjects in the mITT population had data for this outcome.

[14] - Not all subjects in the mITT population had data for this outcome.

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Subjects With an Improvement of ≥ 1 Point on the Patient Assessment of Constipation - Quality of Life (PAC-QOL) Total Score at Final On-Treatment Assessment

End point title	Percent of Subjects With an Improvement of ≥ 1 Point on the Patient Assessment of Constipation - Quality of Life (PAC-QOL) Total Score at Final On-Treatment Assessment

End point description:

The PAC-QOL is a validated 28-item questionnaire for the evaluation of quality of life in subjects with constipation. Items were rated on a 5-point Likert scale: 0=not at all/none of the time, 1=a little bit/a little bit of the time, 2=moderately/some of the time, 3=quite a bit/most of the time, 4=extremely/all of the time. Total score ranged from 0-112. Lower scores indicate improvement in symptoms. A 1-point improvement in PAC-QOL total score was considered clinically meaningful. mITT population included all subjects randomized into the study except those excluded due to a major GCP breach at one site, who took at least 1 dose of the investigational product.

End point type	Secondary

End point timeframe:

Over 12-week treatment period

End point values	Placebo	Prucalopride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171[15]	169[16]		
Units: percentage of subjects				
number (not applicable)	32.7	40.2		

Notes:

[15] - Not all subjects in the mITT population had data for this outcome.

[16] - Not all subjects in the mITT population had data for this outcome.

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Subjects on the Subject Global Evaluation on Severity of Constipation Score Rating Constipation as Severe to Very Severe at Final On-Treatment Assessment

End point title	Percent of Subjects on the Subject Global Evaluation on

	Severity of Constipation Score Rating Constipation as Severe to Very Severe at Final On-Treatment Assessment

End point description:

Subject was asked to rate the severity of his constipation using a 5-point Likert scale: 0=absent, 1=mild, 2=moderate, 3=severe, 4=very severe. mITT population included all subjects randomized into the study except those excluded due to a major GCP breach at one site, who took at least 1 dose of the investigational product.

End point type	Secondary

End point timeframe:

Over 12-week treatment period

End point values	Placebo	Prucalopride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171[17]	169[18]		
Units: percentage of subjects				
number (not applicable)	30.4	21.9		

Notes:

[17] - Not all subjects in the mITT population had data for this outcome.

[18] - Not all subjects in the mITT population had data for this outcome.

Statistical analyses

No statistical analyses for this end point

Secondary: Percent of Subjects on the Subject Global Evaluation on Efficacy of Treatment Score Rating Treatment as Quite a Bit to Extremely Effective at Final On-Treatment Assessment

End point title	Percent of Subjects on the Subject Global Evaluation on Efficacy of Treatment Score Rating Treatment as Quite a Bit to Extremely Effective at Final On-Treatment Assessment

End point description:

The subject was asked to rate his global evaluation of the efficacy of treatment using the following 5-point scale:
0=not at all effective
1=a little bit effective
2=moderately effective
3=quite a bit effective
4=extremely effective.
mITT population included all subjects randomized into the study except those excluded due to a major GCP breach at one site, who took at least 1 dose of the investigational product.

End point type	Secondary

End point timeframe:

Over 12-week treatment period

End point values	Placebo	Prucalopride		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	171[19]	169[20]		
Units: percentage of subjects				
number (not applicable)	30.4	46.7		

Notes:

[19] - Not all subjects in the mITT population had data for this outcome.

[20] - Not all subjects in the mITT population had data for this outcome.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline up to Week 12	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Placebo matched to Prucalopride tablet orally once daily.	
Reporting group title	Prucalopride
Reporting group description:	
Prucalopride 2 mg tablet orally once daily for subjects ≥18 to <65 years; 1 mg once daily orally for subjects ≥65 years, and in case of insufficient response, increased to 2 mg once daily orally at Week 2 or Week 4.	

Serious adverse events	Placebo	Prucalopride	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 186 (2.15%)	1 / 184 (0.54%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
GLOTTIS CARCINOMA			
subjects affected / exposed	1 / 186 (0.54%)	0 / 184 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
LOWER LIMB FRACTURE			
subjects affected / exposed	1 / 186 (0.54%)	0 / 184 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
ATRIAL FIBRILLATION			
subjects affected / exposed	0 / 186 (0.00%)	1 / 184 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

MYOCARDIAL ISCHAEMIA			
subjects affected / exposed	1 / 186 (0.54%)	0 / 184 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
ATELECTASIS			
subjects affected / exposed	1 / 186 (0.54%)	0 / 184 (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: 5 %

Non-serious adverse events	Placebo	Prucalopride	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 186 (11.29%)	37 / 184 (20.11%)	
Nervous system disorders			
HEADACHE			
subjects affected / exposed	7 / 186 (3.76%)	17 / 184 (9.24%)	
occurrences (all)	8	18	
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	11 / 186 (5.91%)	8 / 184 (4.35%)	
occurrences (all)	12	11	
DIARRHOEA			
subjects affected / exposed	3 / 186 (1.61%)	12 / 184 (6.52%)	
occurrences (all)	3	16	
NAUSEA			
subjects affected / exposed	4 / 186 (2.15%)	11 / 184 (5.98%)	
occurrences (all)	4	12	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 April 2011	1. A colonoscopy/sigmoidoscopy was added at the Screening Visit (Visit 1) in subjects for which organic disorders needed to be ruled out (these subjects had a 4-week Run-in Period) 2. Study duration was prolonged up to 16 weeks to allow for a possible 4-week Run-in Period 3. Inclusion criterion was reworded to specify that subjects with a history of on average less than or equal to 2 SBM/week that resulted in a feeling of complete evacuation were to be excluded 4. Subjects with insulin-dependent diabetes mellitus should always be excluded, also if they were under appropriate medical therapy. In addition, for all other conditions listed in this exclusion criterion, the following was added: if a subject was experiencing chronic constipation prior to the onset of the condition and the constipation had not been worsened by the condition, the subject was eligible for screening. However, if the constipation had started after the onset of the condition and the relation between both could not be excluded (it was not certain whether it was secondary to it or not), or when the constipation had worsened after the onset of 1 of the above conditions, the subject was not allowed to be screened for this study 5. Summarized information on excluded conditions of the gastrointestinal tract. In addition, it was specified in which circumstances an endoscopy or radiologic bowel evaluation was required 6. An exclusion criterion was added to exclude subjects who previously used prucalopride 7. It was clarified that serious adverse events needed to be reported within 1 working day (instead of within 24 hours)
11 August 2011	1. Exclusion Criterion was reworded to reflect clinical practice and to allow for clinical judgment in those instances when a repeat procedure would be indicated. Colonoscopy and/or sigmoidoscopy with or without barium enema (depending on age) was performed in this study to prevent subjects from being randomized into the study with primarily obstructive or inflammatory disease as the cause of constipation. A procedure within 5 years was sufficient to screen subjects for serious colonic disease and to remove polyps. In clinical practice, removal of a polyp would not warrant repeat colonoscopy prior to a 5-year time point unless there were special circumstances 2. Updated from milligram per deciliter to micromole per liter, to reflect the current International System of Units for serum creatinine concentration. Also, the creatinine clearance cut-off was changed from 50 milliliter per minute (mL/min) to 30 mL/min to be in line with the Summary of Product Characteristics which mentions that subjects with severe renal impairment (creatinine clearance less than or equal to 30mL/min) had to start at a dose of 1 mg 3. Subjects could not be rescreened without prior approval from the sponsor 4. It was clarified that subjects received 1 package of bisacodyl at the Screening Visit (Visit 1) and from then on, they received bisacodyl as required 5. The timing of dosing was specified in Dose Regimen and Administration Period and instructions were added on what to do in case of a missed dose 6. The relatedness categories were updated to the dichotomized categories “related” (includes very likely, probably, and possibly related) and “not related” (includes doubtful and not related) 6. The time period prior to the start of investigational product during which no bisacodyl could be used was changed from “48 hours before the start of the Double-blind Treatment (Visit)” to “24 hours before the start of Double-blind Treatment (morning after Visit 2)"

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported