Clinical trial results:
A multicentre, randomised, plcebo-controlled, double-blind study of the efficacy, safety, and pharmacekinetics of lubiprostone in paediatric subjects aged >=6 years to <18 years with functional constipation

Summary

EudraCT number	2013-003468-30
Trial protocol	BE GB DE ES NL PL FR
Global end of trial date	27 July 2016

Results information

Result version number	v2 (current)
This version publication date	06 December 2017
First version publication date	10 May 2017
Version creation reason	• Correction of full data set • Changes to summary attachments We noted a number of errors included in this register, which we would need to correct.

Trial information

Trial identification

Sponsor protocol code	SAG/0211PFC-1131

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02766777
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sucampo AG
Sponsor organisation address	Baarerstrasse 22, Zug, Switzerland, 6300
Public contact	Hermann Schulze, PhD, Sucampo AG, 41 41-726-3030, hschulze@sucampo.com
Scientific contact	Hermann Schulze, PhD, Sucampo AG, 41 41-726-3030, hschulze@sucampo.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000245-PIP01-08
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 March 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 July 2016
Global end of trial reached?	Yes
Global end of trial date	27 July 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy, safety and pharmacokinetics of oral lubiprostone 12 or 24 mcg capsules dosed twice daily (based on subject body weight at baseline) as compared to matching placebo, when administered orally for 12 weeks in paediatric subjects with functional constipation.

To evaluate the measurement characteristics of the paediatric functional constipation clinical outcome assessments, including observer-reported outcomes and patient-reported outcomes instruments.

Protection of trial subjects:

No specific measures were put in place.

Background therapy:

Background therapy was not allowed and had to be discontinued before randomisation. However, in the event that no bowel movement occurred within a 3-day period, the use of rescue medication was permitted as per the instructions of the investigator.

Evidence for comparator:

No active comparator was use. This was a placebo-controlled study.

Actual start date of recruitment	25 November 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	9 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 46
Country: Number of subjects enrolled	Poland: 11
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Canada: 12
Country: Number of subjects enrolled	United States: 522
Worldwide total number of subjects	606
EEA total number of subjects	72

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)	279
Adolescents (12-17 years)	327
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The total trial duration was 16 weeks, consisting of a screening phase (2 weeks), treatment phase (12 weeks) and a follow-up phase (2 weeks). Subjects had to be between 6 and 17 years old at the time of screening. Subjects had to fulfill the modified Rome III Diagnostic Criteria for Childhood Functional Constipation (Child/Adolescent; Section H3a)

Pre-assignment

Screening details:

Subjects fulfilling the inclusion criteria were screened 2 weeks prior to the treatment phase. During this time, subjects had to discontinue prior concomitant medications that would affect gastrointestinal motility. If subjects took a fibre supplement (Metamucil®, PerDiem®, Fybogel), usage must have been at a stable dose and schedule for 30 days.

Period 1

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

Blinding implementation details:

None specific. The IMPs were all looking identical.

Arms

Are arms mutually exclusive?	Yes
Arm title	Verum

Arm description:

Lubiprostone 12 or 24 mcg, depending on subject's body weight at baseline

Arm type	Experimental
Investigational medicinal product name	Lubiprostone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Subjects with a body weight <50 kg at baseline received Lubiprostone 12 mcg BID for 12 weeks. If the dose was safe but did not show any efficacy at Week 1, dosage was increased to 24 mcg BID.

Subjects with a body weight >50 kg at baseline received Lubiprostone 24 mcg BID for 12 weeks. If the dose was unsafe at Week 1, dosage was decreased to 12 mcg BID.

Arm title	Placebo

Arm description:

Matching placebo

Arm type	Placebo
Investigational medicinal product name	Placebo to lubiprostone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:
one placebo capsule BID for 12 weeks.

Number of subjects in period 1	Verum	Placebo
Started	404	202
Completed	339	166
Not completed	65	36
Physician decision	7	2
Adverse event, non-fatal	17	6
withdrawal by subject	21	16
non-compliance with study drug	2	3
Lost to follow-up	9	2
Lack of efficacy	4	3
terminated by sponsor	2	1
not specified	3	3

Baseline characteristics

Reporting groups	
Reporting group title	Verum
Reporting group description:	
Lubiprostone 12 or 24 mcg, depending on subject's body weight at baseline	
Reporting group title	Placebo
Reporting group description:	
Matching placebo	

Reporting group values	Verum	Placebo	Total
Number of subjects	404	202	606
Age categorical Units: Subjects			
Children (2-11 years)	196	95	291
Adolescents (12-17 years)	208	107	315
Gender categorical Units: Subjects			
Female	217	110	327
Male	187	92	279
Body weight			
below and above 50 kg			
Units: Subjects			
<50 kg	239	113	352
>50 kg	165	89	254

Subject analysis sets	
Subject analysis set title	mITT verum
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
mITT population receiving lubiprostone	
Subject analysis set title	mITT Placebo
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
mITT population receiving placebo	

Reporting group values	mITT verum	mITT Placebo	
Number of subjects	399	195	
Age categorical Units: Subjects			
Children (2-11 years)	193	92	
Adolescents (12-17 years)	206	103	
Gender categorical Units: Subjects			
Female	216	106	
Male	183	89	

Body weight			
below and above 50 kg			
Units: Subjects			
<50 kg	236	109	
>50 kg	163	86	

End points

End points reporting groups

Reporting group title	Verum
Reporting group description: Lubiprostone 12 or 24 mcg, depending on subject's body weight at baseline	
Reporting group title	Placebo
Reporting group description: Matching placebo	
Subject analysis set title	mITT verum
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: mITT population receiving lubiprostone	
Subject analysis set title	mITT Placebo
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: mITT population receiving placebo	

Primary: Change in rate of spontaneous bowel movements (SBM)

End point title	Change in rate of spontaneous bowel movements (SBM)
End point description: The primary efficacy endpoint was the overall SBM response rate of subjects who received oral lubiprostone capsules 12 mcg or 24 mcg BID compared with matching placebo BID administered orally for 12 weeks to subjects with PFC aged ≥6 years to <18 years in the mITT Population.	
End point type	Primary
End point timeframe: at Week 12	

End point values	Verum	Placebo	mITT verum	mITT Placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	404	202	399	195
Units: percent				
number (not applicable)	19	14.4	19	14.4

Statistical analyses

Statistical analysis title	Cochran-Mantel-Haenzel
Statistical analysis description: For the primary efficacy endpoint of overall SBM response, the Cochran-Mantel-Haenzel (CMH) test stratifying by, baseline SBM frequency (<1.5 or ≥1.5) was to be used for the comparison between the placebo group and the overall lubiprostone group.	
Comparison groups	Placebo v Verum

Number of subjects included in analysis	606
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.1609 [1]
Method	Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.56
upper limit	10.94
Variability estimate	Standard deviation

Notes:

[1] - primary endpoint was not met.

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 14 weeks	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0
Reporting groups	
Reporting group title	Verum
Reporting group description: this group received Lubiprostone 12 or 24 mcg.	
Reporting group title	Placebo arm
Reporting group description: this group received placebo	

Serious adverse events	Verum	Placebo arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 404 (2.72%)	7 / 202 (3.47%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 404 (0.25%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 404 (0.25%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Faecaloma			
subjects affected / exposed	4 / 404 (0.99%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

Hand-foot-and-mouth disease			
subjects affected / exposed	1 / 404 (0.25%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 404 (0.25%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	1 / 404 (0.25%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	1 / 404 (0.25%)	0 / 202 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression			
subjects affected / exposed	1 / 404 (0.25%)	0 / 202 (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	Verum	Placebo arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	239 / 404 (59.16%)	114 / 202 (56.44%)	
Investigations			
Investigation			
subjects affected / exposed	37 / 404 (9.16%)	14 / 202 (6.93%)	
occurrences (all)	37	14	
Nervous system disorders			
Headache			
subjects affected / exposed	34 / 404 (8.42%)	10 / 202 (4.95%)	
occurrences (all)	34	10	

Gastrointestinal disorders			
Nausea			
subjects affected / exposed	57 / 404 (14.11%)	14 / 202 (6.93%)	
occurrences (all)	57	14	
Vomiting			
subjects affected / exposed	45 / 404 (11.14%)	12 / 202 (5.94%)	
occurrences (all)	45	12	
Abdominal pain			
subjects affected / exposed	42 / 404 (10.40%)	23 / 202 (11.39%)	
occurrences (all)	42	23	
Diarrhoea			
subjects affected / exposed	28 / 404 (6.93%)	6 / 202 (2.97%)	
occurrences (all)	28	6	
Abdominal pain upper			
subjects affected / exposed	20 / 404 (4.95%)	6 / 202 (2.97%)	
occurrences (all)	20	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 October 2013	• Update in Biostatistician and Medical Monitor personnel; • Update in contact information for SAE reporting; • Update to the eligibility criteria associated with bowel movement characteristics; • Change in the primary endpoint to overall SBM response based on FDA's recommendation; and • Addition of events of special interest (chest pain, dyspnea, hepatotoxicity/liver enzyme increased, anaphylaxis).
26 November 2013	• Clarification of contraception specifications.
15 April 2014	• Added evaluation of measurement characteristics of the PFC clinical outcome measure assessments; and • Clarified eligibility to DXA subgroup;
14 April 2015	• Update to Medical Monitor personnel information in Europe; and • Eligibility update to allow subjects with a concurrent diagnosis of IBS.
02 September 2015	• Eligibility update to exclude subjects with concurrent diagnosis of IBS.
25 September 2015	• Revision of dose escalation instructions to require dose escalation by Investigator for subjects who may benefit from a higher dose of study medication.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported