Clinical trial results:
A Multicentre, Long-term Safety, Efficacy and Pharmacokinetics Study of Lubiprostone in Paediatric Subjects Aged 6 to <18 years with Functional Constipation

Summary

EudraCT number	2013-004384-31
Trial protocol	BE GB DE ES NL FR PL
Global end of trial date	01 May 2017

Results information

Result version number	v1 (current)
This version publication date	19 August 2017
First version publication date	19 August 2017

Trial information

Trial identification

Sponsor protocol code	SAG/0211PFC-11S1

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Sucampo Pharma Americas LLC
Sponsor organisation address	850 King Farm Blvd, Suite 550, Rockville, United States, MD, 20850
Public contact	Senior Director Regulatory Affairs, Sucampo AG, 41 417263045, hschulze@sucampo.com
Scientific contact	Senior Director Regulatory Affairs, Sucampo AG, 41 417263045, 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	01 May 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 May 2017
Global end of trial reached?	Yes
Global end of trial date	01 May 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the long-term safety, efficacy, and pharmacokinetics of oral lubiprostone 12 or 24 mcg capsules dosed twice daily (BID) when administered orally for 36 weeks in paediatric subjects with functional constipation.

Protection of trial subjects:

none specific

Background therapy:

none

Evidence for comparator:

none. This was a single arm study with lubiprostone as the investigational medicinal product.

Actual start date of recruitment	26 February 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 36
Country: Number of subjects enrolled	Poland: 10
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	United States: 359
Worldwide total number of subjects	418
EEA total number of subjects	59

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)	232
Adolescents (12-17 years)	186
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects who completed the placebo-controlled study SAG/0211PFC-1131 (3 months) were invited to enrol in this open-label long-term safety extension study (9 additional months). Also subjects in the placebo arm were able to participate in this study. The first patient was randomised on 27 March 2013.

Pre-assignment

Screening details:

Subjects must have completed the entire 12-week treatment period during the preceding study SAG/0211PFC-1131, agreed to continue to abstain from concomitant medication (prescribed or OTC) use that could affect gastrointestinal motility, were willing and able to administer rescue medication, if needed, and subject (or parent) must have given consent

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

the study was not blinded.

Arms

Arm title	study arm

Arm description:

This was a single arm study. All patients received lubiprostone. Those who received 12 mcg BID in the preceding study SAG/0211PFC-1131 continued to receive 12 mcg, those who received 24 mcg BID continued with 24 mcg. Those of the placebo arm weighing less than 50 kg received 12 mcg BID and those over 50 kg received 24 mcg BID.

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:

12 or 24 mcg BID. Those patients who received 12 mcg BID in the preceding study SAG/0211PFC-1131 continued to receive 12 mcg BID and those who received 24 mcg BID in the preceding study continued with 24 mcg BID. Patients from the placebo arm of the preceding study received 12 mcg BID when they weighed less than 50 kg, and 24 mcg BID when their weigt was greater than 50 kg.

Number of subjects in period 1	study arm
Started	418
Completed	280
Not completed	138
Consent withdrawn by subject	36
Physician decision	7
Adverse event, non-fatal	18
Pregnancy	2

Lost to follow-up	32
Lack of efficacy	35
Protocol deviation	3
terminated by sponsor	5

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	418	418	
Age categorical			
Subjects had to be 6 to 17 years of age at baseline.			
Units: Subjects			
6-17 years	418	418	
Gender categorical Units: Subjects			
Female	229	229	
Male	189	189	

Subject analysis sets

Subject analysis set title	mITT Population
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

the mITT group comprised all subjects who enroled in the trial, took at least one dose of study medication and had at least one diary entry after treatment initiation.
There was only one subject that did not fulfill these conditions, because of serious compliance issues with potential data integrity impact at the site.

Reporting group values	mITT Population		
Number of subjects	418		
Age categorical			
Subjects had to be 6 to 17 years of age at baseline.			
Units: Subjects			
6-17 years	418		
Gender categorical Units: Subjects			
Female	229		
Male	189		

End points

End points reporting groups

Reporting group title	study arm

Reporting group description:

This was a single arm study. All patients received lubiprostone. Those who received 12 mcg BID in the preceding study SAG/0211PFC-1131 continued to receive 12 mcg, those who received 24 mcg BID continued with 24 mcg. Those of the placebo arm weighing less than 50 kg received 12 mcg BID and those over 50 kg received 24 mcg BID.

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

End point title	Change in number of spontaneous bowel movements (SBM)[1]

End point description:

Monthly and overall change from baseline in Spontaneous Bowel Movement (SBM) frequency.
Here the mean change of overall number of of SBM per week compared to baseline is provided.

End point type	Primary

End point timeframe:

At Months 1 to 9

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Since this was an open-label study, descriptive statistics was used.

End point values	study arm	mITT Population	mITT Population	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	418	418	418	
Units: number of SBM				
arithmetic mean (standard deviation)	1.47 (± 2.01)	1.47 (± 2.01)	1.47 (± 2.01)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Straining

End point title	Straining

End point description:

Monthly and overall change from baseline in straining associated with SBMs.
Here the change from baseline in straining is provided with a mean value of a 5-digit score.

End point type	Other pre-specified

End point timeframe:

Months 1 to 9

End point values	study arm	mITT Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	418	418		
Units: number of straining scale				
arithmetic mean (standard deviation)	-1.27 (± 1.2)	-1.27 (± 1.2)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Stool consistency

End point title	Stool consistency

End point description:

Monthly and overlall change from baseline in stool consistency associated with SBMs.
Here the overall change from baseline in stool consistency id provided as mean value of a 5-point rating scale.

End point type	Other pre-specified

End point timeframe:

Months 1 to 9

End point values	study arm	mITT Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	418	418		
Units: number of stool consistency scale				
arithmetic mean (standard deviation)	0.61 (± 0.81)	0.61 (± 0.81)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Abdominal pain

End point title	Abdominal pain

End point description:

Monthly and overall change from baseline in abdominal pain.
Here the overall change from baseline in abdominal pain is expressed as mean value of a 5-point scale.

End point type	Other pre-specified

End point timeframe:

Months 1 to 9

End point values	study arm	mITT Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	418	418		
Units: number of abdominal pain scale				
arithmetic mean (standard deviation)	-0.73 (± 0.98)	-0.73 (± 0.98)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

9 conscutive months of study treatment followed by 1 month of follow-up

Adverse event reporting additional description:

Patients or caregivers could report AEs at any time. Patients and caregivers were routinely asked about any AEs at each visit.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14

Reporting groups

Reporting group title	Treatment group

Reporting group description:

There was only one arm in this open-label study. All subjects received lubiprostone.

Serious adverse events	Treatment group		
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 418 (3.11%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Conversion disorder			
subjects affected / exposed	1 / 418 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Depressed level of consciousness			
subjects affected / exposed	1 / 418 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Tonsillar haemorrhage			
subjects affected / exposed	1 / 418 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Faecaloma			

subjects affected / exposed	1 / 418 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Irritable bowel syndrome and dehydration			
subjects affected / exposed	1 / 418 (0.24%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	1 / 418 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
faecal incontinence			
subjects affected / exposed	1 / 418 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	3 / 418 (0.72%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Faecaloma and gastritis			
subjects affected / exposed	1 / 418 (0.24%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal obstruction			
subjects affected / exposed	1 / 418 (0.24%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	1 / 418 (0.24%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Treatment group		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	131 / 418 (31.34%)		
Injury, poisoning and procedural complications			
Injury, poisening, procedural complication			
subjects affected / exposed	36 / 418 (8.61%)		
occurrences (all)	36		
Nervous system disorders			
Headache			
subjects affected / exposed	33 / 418 (7.89%)		
occurrences (all)	33		
General disorders and administration site conditions			
Nausea			
subjects affected / exposed	36 / 418 (8.61%)		
occurrences (all)	36		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	47 / 418 (11.24%)		
occurrences (all)	47		
Abdominal pain			
subjects affected / exposed	33 / 418 (7.89%)		
occurrences (all)	33		
Diarrhoea			
subjects affected / exposed	27 / 418 (6.46%)		
occurrences (all)	27		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	31 / 418 (7.42%)		
occurrences (all)	31		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 November 2013	clarification in exclusion criteria regarding pregnancy test, and measures to reduce stress and pain in paeditaric population
05 December 2013	Clarifications on study objectives and endpoints
19 November 2015	Increase number of sites. Some administrative changes and clarifications on inclusion criteria.
20 September 2016	change of sponsor, addition of a legal representative

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

none

Notes: