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Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Constella

linaclotide

Procedure no: EMEA/H/C/002490/P46/019

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

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List of abbreviations

AE	adverse event
AESI	adverse event of special interest
CIC	chronic idiopathic constipation
COVID-19	coronavirus disease - 2019
CSR	clinical study report
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
EOT	End-of Treatment
EU	European Union
FC	functional constipation
GC-C	guanylate cyclase subtype C
GCP	Good Clinical Practice
IBS-C	irritable bowel syndrome with constipation
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
PCS	potentially clinically significant
PEG	polyethylene glycol
PFC	paediatric functional constipation
PT	preferred term
QTc	QT interval corrected for heart rate
QTcF	QT corrected by Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States

1. Introduction

On 22-12-2022, the MAH submitted interim results of a paediatric study submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. The interim study report corresponds to study No. LIN-MD-66 (Long-term safety study or oral linaclotide administered to paediatric participants with function constipation (FC) or irritable bowel syndrome with constipation (IBS-C)).

A short critical expert overview has also been provided with this submission.

2. Summary of data submitted

The MAH states that Study LIN-MD-66 is part of the Linaclotide PIP 000927-PIP01-10-M06 (pending M07 EC decision for PIP modification). The applicant also states that there are no regulatory consequences identified by the MAH with this study.

There are no new data that change or result in a new benefit/risk evaluation. The applicant confirms that there are no regulatory consequences identified with this study and that there is no new data that changes or results in a new benefit/risk evaluation. Consequently, no changes are proposed to the Constella PI.

3. Scientific discussion

3.1. Clinical aspects

Introduction

Linaclotide, a 14-amino acid peptide that acts on the apical surface of epithelial cells in the intestinal lumen to stimulate the receptor guanylate cyclase subtype C (GC-C), is currently approved in a wide variety of countries across the world with approval in the EU dated 26/12/2012. The product is currently licensed in the EU for the indication:

"Constella is indicated for the symptomatic treatment of moderate to severe irritable bowel syndrome with constipation (IBS-C) in adults".
The compound is also licensed for the indication chronic idiopathic constipation in the US, Canada, Japan; Australia; New Zealand; Saudi Arabia; and Mexico (with doses of 72 µg and 145 µg daily), and the MAH intends to modify the currently approved indication in the US to include functional constipation (FC) in children and adolescents 6-17 years of age.

Since the FC indication is not licensed in the EU, there is no intention to include the extension of the patient population into the European license.

Study LIN-MD-66 is a Phase 3, long-term safety study of oral linaclotide administered to paediatric subjects, ages 6 to 17 years, with FC or IBS-C, who completed study intervention in Studies LIN-MD-62, LIN-MD-63, or LIN-MD-64 based on the individual study criteria. The current submission focuses on the interim results for paediatric FC subjects only (from the lead-in Studies LIN-MD-62 and LIN-MD-64) as of the data cut-off date of 15 July 2022. Results for paediatric IBS-C subjects (from the lead-in Studies LIN-MD-63 and LIN-MD-64) will be reported in separate subsequent CSRs.

3.2. Clinical study LIN-MD-66

The study with the title "A Long-term Safety Study of Oral Linaclotide Administered to Paediatric Participants with Functional Constipation (FC) or Irritable Bowel Syndrome with Constipation (IBS-C)" was conducted in 55 sites in 4 countries (USA, Canada, Israel and the Netherlands).

The submitted interim clinical study report (CSR) focuses on paediatric functional constipation (PFC) subjects only. Results from the IBS-C subjects will be reported in a separate subsequent CSR. The submitted interim analysis had a data cut-off date of 15 July 2022.

Methods

Study participants

The study was to enrol paediatric subjects (6 to 17 years of age) with FC or IBS-C who completed study intervention in Studies LIN-MD-62, LIN-MD-63, or LIN MD-64 based on the individual study criteria.

Treatments

Eligible subjects 6 to 11 years of age received linaclotide 72 µg once daily, and subjects 12 to 17 years of age were randomized in a 1:1 ratio to linaclotide 72 µg or 145 µg once daily for 24 weeks based on their age at the time of enrolment into Study LIN-MD-66.

Subjects who turned 18 years of age during or after completing the lead-in study, were eligible if they enrolled within 28 days (inclusive) of the last day of study intervention in the lead-in study. Such subjects were dosed as 17-year-old subjects.

Objective(s)

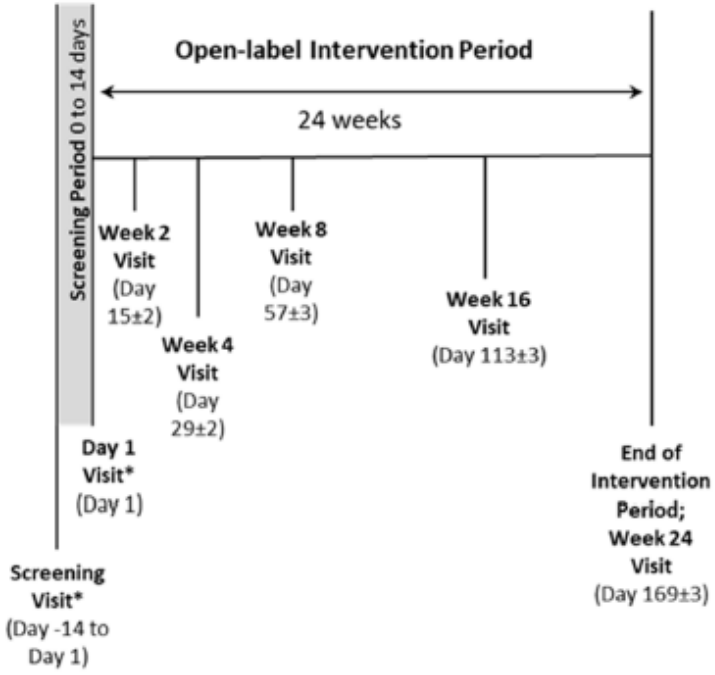
The objective of the trial was stated as "to assess the long-term safety of linaclotide in paediatric subjects with FC (total exposure with linaclotide for 24 weeks) who have completed Studies LIN-MD-62 or LIN-MD-64" according to the submitted interim CSR.

The study protocol defines the objectives more extensively as: "The objective of this study is to assess the long-term safety of linaclotide in paediatric participants with FC (total exposure with linaclotide for 24 weeks) or IBS-C (total exposure with linaclotide for 52 weeks) who have completed Study LIN-MD-62, LIN-MD-63, or LIN-MD- 64.

Study design:

For the reported subjects with PFC, the study was to consist of 7 visits, including a 0- to 14-day Screening Period and 24 weeks of study intervention. The Screening Visit may have been the same as the End-of-Treatment Visit or End-of-Study Visit of the subject's lead-in study. The overall design/study plan is shown in the following figure:

Figure 1: Study design schematic.



For subjects who enrolled in Study LIN-MD-66 on the same day as their End-of Treatment (EOT) visit in Study LIN-MD-64, the EOT visit may have been combined with the Screening (Visit 1). For subjects who enroll within ≤ 28 days (inclusive) from last study intervention (Visit 7) in the Study LIN-MD-64, the Screening Visit (Visit 1) and Day 1 (Visit 2) procedures may have been combined, with the exception of subjects who are positive for fecal impaction assessment at the Screening Visit.

Outcomes/endpoints

According to the protocol, no endpoints are specified for this long-term safety study. The safety assessments, however, were to include monitoring of adverse events (AEs), clinical laboratory assessments (clinical chemistry, complete blood count [CBC], urinalysis), vital sign measurements (including postural vital signs), electrocardiograms (ECGs), physical examinations, height, and weight.

The following efficacy evaluation/endpoint was collected during the study: Rome III criteria were assessed by the investigator at the Screening Visit (Visit 1) and at the end of the study intervention period during the EOT Visit (Visit 7) as an additional efficacy assessment. This endpoint was introduced with the Protocol Amendment 1, dated June 2020. This protocol amendment also included that patients with IBS-C could be enrolled into the study (from the lead-in study LIN-MD-64).

The following safety evaluations were performed during the study: monitoring of AEs, adverse events of special interest (AESIs), clinical laboratory assessments (clinical chemistry, complete blood count, urinalysis), vital sign measurements (including postural vital signs), electrocardiograms (ECGs), physical examinations, height, and weight.

AESIs were defined as significant volume depletion and/or significant electrolyte abnormalities and/or ECG abnormalities that are considered by the investigator or sponsor to be related to diarrhoea.

Assessor's comment:

Since this is an interim CSR only, not all deviations of the CSR in relation to the protocol will be reported in the following. The deviations are based on the fact that for this submission, only the FC population with the previous studies LIN-MD-62 and LIN-MD-64 are included.

Sample size/Statistical Methods

At least 120 subjects with PFC or IBS-C were planned to be enrolled to receive linaclotide study intervention; however, the actual number of subjects in this study was determined to depend on the number of subjects who complete study intervention in the lead-in study (LIN-MD-62, LIN-MD-64, or LIN-MD-63) and enrol into this open-label extension study after fulfilling the eligibility criteria.

No sample size calculation or statistical methods other than descriptive statistics were specified.

Changes in the conduct of the study:

The original protocol (15 July 2019, 97 subjects) had 2 global amendments, 2 regional amendments, and no administrative changes. The amendments and number of subjects enrolled under each amendment were as follows:

- Global Amendment 1 (10 June 2020, 175 subjects)
- Regional Amendment 1, EU-1 (13 February 2020, 0 subjects)
- Regional Amendment 2, EU-2 (07 August 2020, 2 subjects)
- Global Amendment 2 (30 April 2021, 9 subjects)

Assessor's comment:

As reported above, the global amendment No. 1 related to the inclusion of the IBS-C subjects rolling over from study LIN-MD-64. These subjects are not included in the submitted CSR.

Results

Participant flow

The study was conducted at 55 sites, in 4 countries (US, Canada, Israel, and the Netherlands). Overall, 285 subjects with PFC were screened, and 283 subjects were enrolled in the study. Of the subjects who entered the Treatment Period, a total of 282 subjects received either 72 µg or 145 µg linaclotide and 83.7% completed the study drug (administration). The most frequent reasons for discontinuation from study drug were lost to follow-up (9 subjects, 3.2%) and withdrawal by subject (6 subjects, 2.1%). The disposition of subjects is given in the following table:

Table 1: Disposition of subjects (screened population).

Disposition	Linaclotide 72 µg n (%)	Linaclotide 145 µg n (%)	Total n (%)
Number of subjects enrolled open-label intervention period	210 (100.0)	73 (100.0)	283 (100.0)
Number of subjects treated and received placebo in lead-in study	106 (50.5)	30 (41.1)	136 (48.1)
Number of subjects treated	210 (100.0)	72 (98.6)	282 (99.6)
Number of subjects ongoing at data cutoff	18 (8.6)	4 (5.5)	22 (7.8)
Number of subjects who completed study drug	175 (83.3)	62 (84.9)	237 (83.7)
Number of subjects who discontinued from study drug	17 (8.1)	7 (9.6)	24 (8.5)
Reasons for discontinuation			
Adverse event	1 (0.5)	1 (1.4)	2 (0.7)
Withdrawal by subject	2 (1.0)	4 (5.5)	6 (2.1)
Lost to follow-up	7 (3.3)	2 (2.7)	9 (3.2)
Pregnancy	1 (0.5)	0	1 (0.4)
Death	0	0	0
Physician decision	2 (1.0)	0	2 (0.7)
Protocol deviation	1 (0.5)	0	1 (0.4)
Non-compliance with study drug	0	0	0
Study terminated by the sponsor	0	0	0
Site terminated by the sponsor	0	0	0
Lack of efficacy	2 (1.0)	0	2 (0.7)
Other	1 (0.5)	0	1 (0.4)
Related to COVID-19	0	0	0

COVID-19 = coronavirus disease – 2019.

Assessor's comment:

The enrolment into the study from the two feeder studies was almost complete. Of note is also the fact that the number of subjects discontinuing the study due to identified reasons relating to the study drug appears to be very small, with 2 patients with "lack of efficacy", and 2 with "adverse events".

The influence of the Covid pandemic on the study was rather minor: Overall, 1 (0.4%) subject had a visit impacted by coronavirus disease - 2019 (COVID-19), and 1 (0.4%) subject had a COVID-19-related treatment interruption. Both were in the 72 µg group.

There were overall 7 patients with protocol deviations (2.5%), of which 4 did not meet the inclusion criteria, and one each did not sign the ICF, was dosed with the wrong study treatment, or was withdrawn due to a protocol deviation.

Baseline data

Overall, the mean age of the study participants reported was 11.5 years and 55.0% of the subjects were female. White and Black/African American subjects accounted for 68.4% and 27.0% of subjects, respectively, and a little less than half of all subjects were Hispanic or Latino. The main baseline demographic characteristics are shown in the following table:

Table 2: Baseline demographics (safety population).

Parameter	Linaclotide 72 µg (N = 210) n (%)	Linaclotide 145 µg (N = 72) n (%)	Total (N = 282) n (%)
Age (years)			
Mean (SD)	10.6 (2.96)	14.2 (1.79)	11.5 (3.13)
Median	10.0	14.0	12.0
Min, max	6, 18	12, 18	6, 18
Age group, n (%)			
6-11 years	140 (66.7)	0	140 (49.6)
12-18 years	70 (33.3)	72 (100)	142 (50.4)
Sex, n (%)			
Male	95 (45.2)	32 (44.4)	127 (45.0)
Female	115 (54.8)	40 (55.6)	155 (55.0)
Race, n (%)			
White	142 (67.6)	51 (70.8)	193 (68.4)
Black or African American	59 (28.1)	17 (23.6)	76 (27.0)
Asian	2 (1.0)	3 (4.2)	5 (1.8)
American Indian or Alaska Native	2 (1.0)	0	2 (0.7)
Native Hawaiian or Other Pacific Islander	2 (1.0)	0	2 (0.7)
Multiple[a]	3 (1.4)	1 (1.4)	4 (1.4)
Ethnicity, n (%)			
Hispanic or Latino	92 (43.8)	36 (50.0)	128 (45.4)
Not Hispanic or Latino	118 (56.2)	36 (50.0)	154 (54.6)

Max = maximum; Min = minimum; SD = standard deviation

a. Subjects who reported multiple races are only included in the multiple category.

Mean body mass index in the Safety Population was 20.69 kg/m2 in the 6- to 11-year-old group and 24.38 kg/m2 in the 12- to 18-year-old group. The most frequently reported (≥ 5% overall) medical and surgical history by Medical Dictionary for Regulatory Activities (MedDRA) (version 25.0) preferred term (PT) in the Safety Population were attention deficit hyperactivity disorder (15.2%), seasonal allergy and asthma (14.9% each), and obesity (5.7%). The most frequently reported (≥ 5% overall) concomitant medication classes in the Safety Population were centrally acting sympathomimetics (13.1%), piperazine derivatives (8.9%), selective beta-2-adrenoreceptor agonists (6.0%), other antihistamines for systemic use (5.3%), and leukotriene receptor antagonists (5.0%)

Treatment compliance during the study was high with 97.7% in the 72µg group, and 98.4% in the 145 µg group. The overall extent of exposure during the study is presented in the following table:

Table 3: Extent of Exposure (safety population).

	Linaclotide 72 µg (N = 210)	Linaclotide 145 µg (N = 72)	Total (N = 282)
Duration of exposure (weeks), n (%)			
≤ 4	3 (1.4)	1 (1.4)	4 (1.4)
> 4 - ≤ 8	6 (2.9)	2 (2.8)	8 (2.8)
> 8 - ≤ 12	6 (2.9)	3 (4.2)	9 (3.2)
> 12 - ≤ 18	14 (6.7)	3 (4.2)	17 (6.0)
> 18 - ≤ 24	45 (21.4)	18 (25.0)	63 (22.3)
> 24	136 (64.8)	45 (62.5)	181 (64.2)
Mean (SD)	22.7 (5.21)	22.6 (5.21)	22.6 (5.20)
Median	24.1	24.1	24.1
Min, Max	1, 34	4, 27	1, 34
Patient-years	91.28	31.13	122.41

Max = maximum; Min = minimum; SD = standard deviation

Note: Exposure weeks = (date of last dose of study intervention - date of first dose of study intervention +1)/7 in this study.

Efficacy results

For the efficacy evaluation, the number and percentage of subjects not fulfilling the Rome III criteria (for functional constipation) are reported as follows:

Table 4: Subjects not fulfilling the modified Rome III criteria (safety population).

	Linaclotide 72 µg (N = 210) n/N (%)	Linaclotide 145 µg (N = 72) n/N (%)	Total (N = 282) n/N (%)
Screening			
Yes	13/74 (17.6)	4/25 (16.0)	17/99 (17.2)
No	61/74 (82.4)	21/25 (84.0)	82/99 (82.8)
End of Open-Label Study Treatment			
Yes	45/74 (60.8)	16/25 (64.0)	61/99 (61.6)
No	29/74 (39.2)	9/25 (36.0)	38/99 (38.4)

Note: This table includes only subjects with complete data sets for this endpoint. Collection of Rome III criteria data was added in Protocol Amendment 1 after approximately 97 subjects had already been enrolled in the study and for which Rome III criteria data were not collected.

Of note are the facts that data from 97 patients are missing in this analysis, since for these patients, which were enrolled before the implementation of protocol amandment 1, no baseline data were available. For the table above, no missing data were imputed, and data were summarized as observed.

Assessor's comment:

The rate of patients suffering from FC was 82.8% (total) at the start of the study, which was decreased to 38.4% at the end of the study, which indicates a relevant change. However, since this is an open-label study, it remains unclear whether this reflects natural history/fluctuation of the disease, or a true treatment effect. Since this is primarily a safety study, the question, however, appears less relevant. There were obviously no relevant differences between the two treatment groups. A percentage of more than 80% having FC (after they had undergone treatment in the preceding studies LIN-MD-63 and LIN-MD-64) could be regarded to be rather high. However, previous randomisation and doses are not known.

Safety results

- Adverse events:

Overall, a total of 52/282 subjects (18.4%) experienced at least 1 TEAE, including 37/210 (17.6%) subjects in the 72 µg group and 15/72 (20.8%) subjects in the 145 µg group. Most AEs were mild in severity, and 13/210 (6.2%) subjects and 6/72 (8.3%) had treatment-related AEs in the 72 µg and 145 µg groups, respectively. There were no deaths or AESIs, and few serious adverse events (SAEs) or AEs leading to discontinuation of study drug. An overview of TEAEs by exposure-adjusted incidence rate per 100 patient-years is also presented in the following table:

Table 5: Overview of Adverse Events by Number (%) of Subjects and by Exposure-adjusted Incidence Rate per 100 Patient-Years (Safety Population).

	Linaclotide					
	72 µg N = 210		145 µg N = 72		Total N = 282	
	n (%)	n/PYs[a] (n/100 PYs)	n (%)	n/PYs[a] (n/100 PYs)	n (%)	n/PYs[a] (n/100 PYs)
TEAE	37 (17.6)	37/80.9 (45.7)	15 (20.8)	15/26.7 (56.1)	52 (18.4)	52/107.6 (48.3)
Treatment-related TEAEs	13 (6.2)	13/87.0 (14.9)	6 (8.3)	6/29.9 (20.1)	19 (6.7)	19/116.9 (16.3)
TESAE	2 (1.0)	2/90.7 (2.2)	0	0/31.1	2 (0.7)	2/121.8 (1.6)
Deaths	0	0/91.3	0	0/31.1	0	0/122.4
TEAEs leading to study drug discontinuation	1 (0.5)	1/91.3 (1.1)	1 (1.4)	1/31.1 (3.2)	2 (0.7)	2/122.4 (1.6)
AESI[b]	0	0/91.3	0	0/31.1	0	0/122.4

AESI = adverse event of special interest; PY = patient-years; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse events

a. PYs = Total of exposure time at risk (days) divided by 365.25 and rounded to 1 decimal place.

b. AESIs include events of significant volume depletion and/or significant electrolyte abnormalities and/or electrocardiogram abnormalities that are considered by the investigator or sponsor to be related to diarrhea.

The most frequently reported (≥5% of subjects in either treatment group) TEAE during the treatment period by PT was diarrhoea. Adverse events of diarrhoea were reported by 12/210 [5.7%] subjects in the 72 µg group and 4/72 [5.6%] subjects in the 145 µg group. Of these subjects, 2 had 2 events of diarrhoea, and all others had 1 event. The most frequently reported TEAEs by exposure-adjusted incidence rate per 100 patient-years are presented in the following table:

Table 6: Treatment-Emergent Adverse Events Reported by ⩾ 2% of Subjects in Either Treatment Group by Number (%) of Subjects and Exposure-Adjusted Incidence Rate per 100 Patient-Years by Preferred Term (Safety Population)

	Linaclotide					
	72 µg N = 210		145 µg N = 72		Total N = 282	
Preferred Term	n (%)	n/PYs[a] (n/100 PYs)	n (%)	n/PYs[a] (n/100 PYs)	n (%)	n/PYs[a] (n/100 PYs)
Subjects with at least one TEAE	17 (8.1)	37/80.9 (45.7)	10 (13.9)	15/26.7 (56.1)	27 (9.6)	52/107.6 (48.3)
Diarrhoea	12 (5.7)	12/88.0 (13.6)	4 (5.6)	4/30.3 (13.2)	16 (5.7)	16/118.3 (13.5)
Abdominal pain	6 (2.9)	6/89.9 (6.7)	1 (1.4)	1/31.1 (3.2)	7 (2.5)	7/121.0 (5.8)
Flatulence	3 (1.4)	3/90.3 (3.3)	2 (2.8)	2/30.5 (6.6)	5 (1.8)	5/120.7 (4.1)
Abdominal pain upper	1 (0.5)	1/91.0 (1.1)	2 (2.8)	2/30.8 (6.5)	3 (1.1)	3/121.8 (2.5)
Blood creatinine increased	1 (0.5)	1/91.3 (1.1)	2 (2.8)	2/30.7 (6.5)	3 (1.1)	3/122.0 (2.5)
Gastrooesophageal reflux disease	1 (0.5)	1/91.0 (1.1)	2 (2.8)	2/30.4 (6.6)	3 (1.1)	3/121.4 (2.5)
Circumcision [m]	0	0/40.5	1 (3.1)	1/13.7 (7.3)	1 (0.8)	1/54.2 (1.8)
Vulvovaginal mycotic infection [f]	0	0/50.8	1 (2.5)	1/16.8 (6.0)	1 (0.6)	1/67.6 (1.5)

[f] = event specific to female subjects; [m] = event specific to male subjects; MedDRA = Medical Dictionary for Regulatory Activities; PY = patient-years; TEAE = treatment-emergent adverse event

a. PYs = Total of exposure time at risk (days) divided by 365.25 and rounded to 1 decimal place.

Note: Adverse event terms were coded using MedDRA version 25.0.

Most TEAEs were not considered treatment related. Of the treatment-related TEAEs, the most frequently reported treatment-related TEAEs during the treatment period by PT was diarrhoea (10/210 [4.8%] subjects in the 72 µg group and 4/72 [5.6%] subjects in the 145 µg group)

An evaluation of the related events is shown in the following table:

Table 7: Treatment-related TEAEs by System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term	Linaclotide 72 µg N = 210 n (%)	Linaclotide 145 µg N = 72 n (%)	Linaclotide Total N = 282 n (%)
Subject with at least one treatment-related TEAE	13 (6.2)	6 (8.3)	19 (6.7)
Gastrointestinal disorders	13 (6.2)	6 (8.3)	19 (6.7)
Diarrhoea	10 (4.8)	4 (5.6)	14 (5.0)
Flatulence	3 (1.4)	2 (2.8)	5 (1.8)
Abdominal pain	3 (1.4)	1 (1.4)	4 (1.4)
Abdominal pain upper	0	1 (1.4)	1 (0.4)
Abdominal discomfort	1 (0.5)	0	1 (0.4)
Metabolism and nutrition disorders	1 (0.5)	0	1 (0.4)
Dehydration	1 (0.5)	0	1 (0.4)

MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.
Note: Adverse event terms were coded using MedDRA version 25.0.

Assessor's comment:

The overall character of events, and especially those assessed as being treatment-related refer to local gastrointestinal effects, and therefore fully reflect the known safety profile for adults.

Most TEAEs were mild in severity. Two of 210 (1.0%) subjects in the 72 µg group and 1/72 (1.4%) subject in the 145 µg group experienced severe TEAEs. Severe TEAEs included the following MedDRA PTs: constipation and disruptive mood dysregulation disorder (both reported by the same subject) and pyelonephritis in the 72 µg group and flatulence in the 145 µg group. All 3 events in the 72 µg group were SAEs and considered not related to study drug, while flatulence in the 145 µg group was non-serious and considered related. All severe events were resolved.

Overall, 2 (0.7%) subjects (1 subject in each dose group) had moderate events of diarrhoea and no subjects had severe events of diarrhoea

- Deaths and SAEs

There were no deaths during the study.

Overall, 2/282 (0.7%) subjects (both in the 72 µg group) experienced at least 1 SAE during the study. One subject had 2 SAEs, severe constipation and severe disruptive mood dysregulation disorder, and 1 subject had severe pyelonephritis. There were no SAEs reported in the 145 µg group. All SAEs resolved, and none were considered related to study drug or led to discontinuation of study drug. No SAE of diarrhoea was reported.

Overall, 2/282 (0.7%) subjects experienced at least 1 AE that led to discontinuation of study drug. One (0.5%) subject in the 72 µg group had mild events of diarrhoea and dehydration that led to discontinuation of study drug. One (1.4%) subject in the 145 µg group had moderate events of abdominal pain and diarrhoea that led to discontinuation of study drug. None of the events were serious, and all were considered by the investigator to be related to study drug.

No AESIs (significant volume depletion and/or significant electrolyte abnormalities and/or ECG abnormalities that are considered by the investigator or sponsor to be related to diarrhoea) were reported.

- Laboratory Evaluations

All comparisons were done and presented according to the two age groups 6-11 and 12-18. There were no noticeable differences in laboratory findings between the age subgroups other than the potentially clinically significant (PCS) albumin values as presented below.

There were no unexpected changes of clinical relevance for haematology, chemistry as well as urine analyses. Similarly, the evaluation of shifts from baseline to the end of treatment did not reveal unexpected changes of clinical relevance.

The individual cases of PCS post-baseline abnormalities are presented in the following table.

The most frequently reported (≥ 2% subjects overall) PCS values were observed for magnesium (> 1.1 × upper limit of normal [ULN]), albumin (> 1.1 × ULN), and monocytes absolute cell count (< 0.5 × lower limit of normal). Regarding magnesium, it should be noted that, among those subjects with post-baseline PCS magnesium findings (> 1.1 × ULN), most of these subjects (13/16) had magnesium levels at baseline that, while not reaching PCS levels, were above the ULN.

Table 8: Number (%) of Subjects with Potentially Clinically Significant Post-baseline Laboratory Parameters Values (Safety Population)

Parameter PCS Criterion	Linaclotide 72 µg N = 210 n/N (%)	 145 µg N = 72 n/N (%)	 Total N = 282 n/N (%)
Hematology			
Eosinophils absolute cell count, > 3 × ULN	2/168 (1.2)	1/61 (1.6)	3/229 (1.3)
Hematocrit, < 0.9 × LLN	0/167	2/62 (3.2)	2/229 (0.9)
Hemoglobin, < 0.9 × LLN	1/166 (0.6)	1/61 (1.6)	2/227 (0.9)
Monocytes absolute cell count, < 0.5 × LLN	6/163 (3.7)	2/60 (3.3)	8/223 (3.6)
Neutrophils absolute cell count, < 0.8 × LLN	1/168 (0.6)	0/62	1/230 (0.4)
Red blood cell count, < 0.9 × LLN	1/168 (0.6)	1/61 (1.6)	2/229 (0.9)
White blood cell count, < 0.7 × LLN	1/166 (0.6)	0/62	1/228 (0.4)
Chemistry			
ALT, ≥ 3 × ULN	1/173 (0.6)	0/62	1/235 (0.4)
Albumin, > 1.1 × ULN	2/169 (1.2)	7/60 (11.7)	9/229 (3.9)
Alkaline phosphatase, ≥ 1.2 × ULN (age 6 to 12 [inclusive] male and female, 13 to 15 [inclusive] male)	2/137 (1.5)	0/28	2/165 (1.2)
Bicarbonate, < 0.9 × LLN	3/169 (1.8)	1/59 (1.7)	4/228 (1.8)
Creatinine, > 1.3 × ULN	1/174 (0.6)	2/62 (3.2)	3/236 (1.3)
Glucose, > 1.4 × ULN	2/172 (1.2)	0/62	2/234 (0.9)
Potassium, > 1.1 × ULN	1/170 (0.6)	0/61	1/231 (0.4)
Magnesium, > 1.1 × ULN	12/156 (7.7)	4/57 (7.0)	16/213 (7.5)

ALT = alanine aminotransferase; LLN = lower limit of normal; PCS = potentially clinically significant; ULN = upper limit of normal

N (percentage denominator) = Subjects with non-missing non-PCS baseline and ≥1 postbaseline parameter assessment. For alkaline phosphatase criteria, the denominator in the percentage calculation included the number of subjects in the specific age group and gender of interest with non-missing non-PCS baseline and ≥1 postbaseline parameter assessment.

No subject met the laboratory criteria for potential Hy's Law.

- Vital Signs, Physical Findings, and Other Observations

There were no unexpected changes of clinical relevance for vital signs (supine systolic and diastolic blood pressure, supine pulse rate, respiration rate, and temperature).

The incidences of all vital sign parameters that were identified as PCS based on the criteria defined in the SAP are presented in the following table. There were no unexpected changes of clinical relevance.

Table 9: Number (%) of Subjects with Post-baseline Potentially Clinically Significant Vital Sign Values (Safety Population)

Parameter PCS Criterion	Linaclotide 72 µg N = 210 n/N (%)	 145 µg N = 72 n/N (%)	 Total N = 282 n/N (%)
Systolic blood pressure (mmHg) (supine)			
Age 6–11 (inclusive): ≤ 80 and decrease ≥ 20	1/135 (0.7)	0/0	1/135 (0.7)
Age 6–11 (inclusive): ≥ 140 and increase ≥ 20	0/135	0/0	0/135
Age 12–18 (inclusive): ≤ 90 and decrease ≥ 20	1/70 (1.4)	0/70	1/140 (0.7)
Age 12–18 (inclusive): ≥ 155 and increase ≥ 20	0/70	0/70	0/140
Standing - supine systolic blood pressure (mmHg)			
≤ -20 and decrease ≥ 10	6/205 (2.9)	0/70	6/275 (2.2)
Diastolic blood pressure (mmHg) (supine)			
Age 6–11 (inclusive): ≤ 40 and decrease ≥ 15	0/135	0/0	0/135
Age 6–11 (inclusive): ≥ 95 and increase ≥ 15	0/135	0/0	0/135
Age 12–18 (inclusive): ≤ 45 and decrease ≥ 15	0/70	0/70	0/140
Age 12–18 (inclusive): ≥ 105 and increase ≥ 15	0/70	0/70	0/140
Standing - supine diastolic blood pressure (mmHg)			
≤ −10 and decrease ≥ 10	10/205 (4.9)	6/70 (8.6)	16/275 (5.8)
Pulse rate (beats/min) (supine)			
Age 6–11 (inclusive): ≤ 50 and decrease ≥ 15	0/135	0/0	0/135
Age 6–11 (inclusive): ≥ 140 and increase ≥ 15	0/135	0/0	0/135
Age 12–18 (inclusive): ≤ 40 and decrease ≥ 15	0/70	0/70	0/140
Age 12–18 (inclusive): ≥ 120 and increase ≥ 15	0/70	0/70	0/140
Standing - supine pulse rate (beats/min)			
≥ 20 and increase ≥ 10	37/205 (18.0)	10/70 (14.3)	47/275 (17.1)
Weight (kg)			
Decrease of ≥ 5%	15/205 (7.3)	7/70 (10.0)	22/275 (8.0)
Increase of ≥ 5%	124/205 (60.5)	24/70 (34.3)	148/275 (53.8)

Min = minimum; PCS = potentially clinically significant

N (percentage denominator) = Subjects with non-missing non-PCS baseline and ≥1 postbaseline parameter assessment. For specific age-dependent criteria, subjects in that specific age group of interest with non-missing non-PCS baseline and ≥1 postbaseline parameter assessment were included for the denominator.

With regard to ECG evaluations, no subject had an abnormal, clinically significant overall ECG interpretation at baseline or at the End of Study, and there were no unexpected changes of clinical relevance. No subject experienced PCS post-baseline ECG parameters of QRS interval, PR interval and QT corrected by Fridericia's formula (QTcF).

- Other events:

As of the data cut-off date for this report, 1 pregnancy has been reported in a 16-year-old in the 72 µg group. The subject had been exposed to study drug at conception and continued taking study drug inconsistently for approximately 3 months, at which point she discontinued from treatment. The

subject gave birth with no issues or complications at 38 weeks of pregnancy, and the foetal outcome was normal.

The applicant concludes that linaclotide was well tolerated in paediatric subjects aged 6 to 17 years with FC. The safety profile was consistent with previous linaclotide studies in adults with CIC and IBS-C. Long-term safety evaluation of linaclotide in subjects with PFC indicated no new safety signals.

Assessor's comment:

The overall conclusions of the MAH are agreed with.

3.3. Discussion on clinical aspects

The applicant has submitted an interim analysis of the long-term open-label safety study LIN-MD-66, which analysed the study population included after the finalisation of the preceding studies LIN-MD-62 and LIN-MD-64, which themselves included patients with functional constipation.

The included patient population was a population aged 6-17 years at the time of inclusion, and the reported observation time was for 24 weeks. Patients were treated in two dose groups, with the patients aged 6-11 receiving a 72 µg dose, and those aged 12-17 receiving either 72 µg or 145 µg daily dose.

The primary objective of the trial was to collect safety information in the paediatric population, and a single efficacy evaluation (endpoint) was only introduced by protocol amendment, when the trial was already ongoing.

While the trial is adequate to collect relevant safety data for the compound in the FC population, the reporting of efficacy is restricted to an endpoint which is difficult to assess and – due to the open label design – does not allow a conclusion on efficacy to be made. No differences between the dose-groups could be found for this single efficacy parameter, and there was not reporting of the different dose-groups in the 11–17 year-old population and the two randomised dose-groups at this age. Since the conclusions on efficacy are limited anyway, a concern about the missing reporting is not raised.

The safety evaluation was overall rather unremarkable, and there were no unexpected adverse events that were assessed as being related to the intake of study medication. Overall, the rate of adverse events was low, and mainly mild in intensity, and fully reflected the safety profile in the adult population, which had already revealed that the mainstay of adverse events is related to effects on the gastrointestinal tract.

No new safety concerns emerged from the overall evaluation of safety from this study.

4. Overall conclusion

The applicant has submitted the results of an interim evaluation of study LIN-MD-66 which is a long-term safety study in a mixed population of patients with IBS-C and FC. For the purpose of this interim evaluation, the results of the FC population only were submitted. A limited evaluation of efficacy was included in the submission, which did not allow any further conclusion on efficacy due to the design of the study, but which also does not stand in contrast to results previously reported for this population. The safety evaluation in this study was rather unremarkable and confirmed an acceptable safety profile in the paediatric population for a treatment duration of at least 6 months. The safety profile appears to be overall very similar to the known safety profile of the compound in adults.

The indication functional constipation is not licensed in the EU, and the applicant does obviously not pursue this indication in the EU neither for adults, nor for the paediatric population.

The submission is therefore correctly presented as having no consequences for the existing license in the EU.

The overall benefit-risk ratio remains unchanged.

PAM fulfilled

No regulatory action required.