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Human Medicines Division

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Constella

linaclotide

Procedure no: EMEA/H/C/002490/P46/018

Note

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

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Table of contents

List of abbreviations

AE	adverse event
AESI	adverse events of special interest
BMs	bowel movements
BP	blood pressure
CI	confidence interval
CIC	chronic idiopathic constipation
COVID-19	coronavirus disease 2019
CRFs	case report forms
CRO	contract research organization
CSBM	complete spontaneous bowel movement
CSR	clinical study report
DSMB	data safety monitoring board
ECG	electrocardiogram
eDiary	electronic diary
EOS	end of study
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 Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
IRB	institutional review board
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
PCS	potentially clinically significant
PEG	polyethylene glycol
PFC	pediatric functional constipation
PT	preferred term
QTcF QT	Corrected by Fridericia's formula
RR	respiratory rate
SAE	serious adverse event
SAP	statistical analysis plan
SBM	spontaneous bowel movement
SOC	system organ class
TEAE	treatment-emergent adverse event
TESAEs	treatment-emergent serious adverse events
ULN	upper limit of normal

1. Introduction

This submission, filed by the MAH on 22-12-2022, includes a paediatric study submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, referring to an interim study report of study No. LIN-MD-64 (A Phase 3, Multicenter, Randomized, Double-blind, Parallel-group, Safety and Efficacy Study of Linaclotide in Paediatric Participants, ages 6 to 17 years, With Irritable Bowel Syndrome with Constipation (IBS-C) and of Linaclotide versus placebo in Paediatric Participants with Functional Constipation (FC)).

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

The submission of the study report occurred at the same date as the previously reported study LIN-MD-66 (long-term safety study). Due to procedural reasons, the study report for LIN-MD-64 is reported with one month time-distance to the long-term safety study.

2. Summary of data submitted

The MAH states that Study LIN-MD-64 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.

The MAH claims that there are no new data that change or result in a new benefit/risk evaluation. The MAH 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. The interim CSR submitted reports the efficacy results in patients with FC only, but not in those patients with IBS-C.

3. Scientific discussion

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 72µg 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.

The MAH stated that Study LIN-MD-64 is part of the agreed PIP (EMEA-000927-PIP01-10-M06). In accordance with the above-mentioned facts, the applicant 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. Consequently, no changes are proposed to the PI.

Study LIN-MD-64 is a Phase 3, multi-centre, randomized, double-blind, parallel-group, safety and efficacy study of linaclotide in paediatric subjects, aged 6 to 17 years, with IBS-C, and of linaclotide versus placebo in paediatric subjects with FC. The current submission focuses on the final results from

paediatric FC subjects only. Results from the paediatric IBS-C subjects will be reported in a separate subsequent CSR.

3.1. Clinical study LIN-MD-64

The interim CSR for study LIN-MD-64 is focussing on the evaluation of the data for patients with functional constipation only, although the study itself also included patients with IBS-C.

Study LIN-MD-64 is titled as: Phase 3, Multicenter, Randomized, Double-blind, Parallel-group, Safety and Efficacy Study of Linaclotide in Paediatric Participants, Ages 6 to 17 Years, With Irritable Bowel Syndrome with Constipation (IBS-C) and of Linaclotide versus Placebo in Paediatric Participants with Functional Constipation (FC)

Methods

Study participants

The original study protocol included the following inclusion criteria for the population to be studied:

The participants had to meet the modified Rome III criteria for Child/Adolescent FC. In particular, for the patients, for at least 2 months before the Screening Visit, the participant had to have 2 or fewer defecations (with each defecation occurring in the absence of any laxative, suppository, or enema use during the preceding 24 hours) in the toilet per week.

In addition, participants had to meet one or more of the following criteria at least once per week for at least 2 months before the screening visit:

- History of retentive posturing or excessive volitional stool retention
- History of painful or hard BMs
- History of large diameter stools that may obstruct the toilet
- Presence of a large faecal mass in the rectum
- At least 1 episode of faecal incontinence per week

Assessor's comment:

The criteria above were relevant for the study population for which results are included in the submitted interim CSR. It is noted that the requirements were based on the Rome III criteria, despite the fact that – at the time of the planning of the study – Rome IV was already in place

According to the Rome IV criteria, the following would apply:

"Must include two or more of the following occurring at least once per week for a minimum of 1 month with insufficient criteria for a diagnosis of IBS:

- Two or fewer defecations in the toilet per week in a child of a developmental age of at least 4 years
- At least one episode of faecal incontinence per week
- History of retentive posturing or excessive volitional stool retention
- History of painful or hard bowel movements
- Presence of a large faecal mass in the rectum

- History of large diameter stools which can obstruct the toilet
- After appropriate evaluation, the symptoms cannot be fully explained by another medical condition"

It is obvious that the inclusion criteria also appropriately reflect Rome IV, and are rather more "restrictive" with the requirement of the 2-months time-frame as compared to the only one-month time-frame in Rome IV. The inclusion criteria are therefore considered adequate.

With the protocol amendment 1, dated June 2020, the scope of the study was widened to allow patients with IBS-C also into the study. For IBS-C patients, the following inclusion criteria were set up:

Participants had to meet the Rome III criteria for child/adolescent IBS defined as experiencing - at least once per week for at least 2 months before the Screening Visit - abdominal discomfort (an uncomfortable sensation not described as pain) or pain associated with 2 or more of the following at least 25% of the time:

- Improvement with defecation
- Onset associated with a change in frequency of stool
- Onset associated with a change in form (appearance) of stool

In addition, participants had to have an average daytime abdominal pain score of ≥ 1 (at least "a tiny bit") during the 14 days before Visit 3.

Assessor's comment:

No comment necessary. The results of this subgroup will obviously be reported at a later time-point. In the following, no further reference is made to the IBS-C subgroup included in the study.

Treatments

All FC subjects were randomized to a linaclotide 72 µg dose or placebo with a 1:1 allocation ratio. The identity of the investigational product is given in the following table:

Table 1: Identity of Investigational Product:

Study Drug	Dosage Form	Dosage Strength	Manufacturer	Bulk Lot
Linaclotide	Capsules	72 µg	Forest Laboratories Ireland, Limited	D28287, D23247, and D12109
Placebo	Capsules	-	Forest Laboratories Ireland, Limited	D24970, NDA/2019/04/0005, and D07637

Assessor's comment:

It is noted that a capsule formulation was used in the trial. Since "solid" pharmaceutical forms could cause problems with intake, especially in young children, the participant were allowed to take the dose as a "sprinkled dose" with clear instructions with using either applesauce, or bottled water.

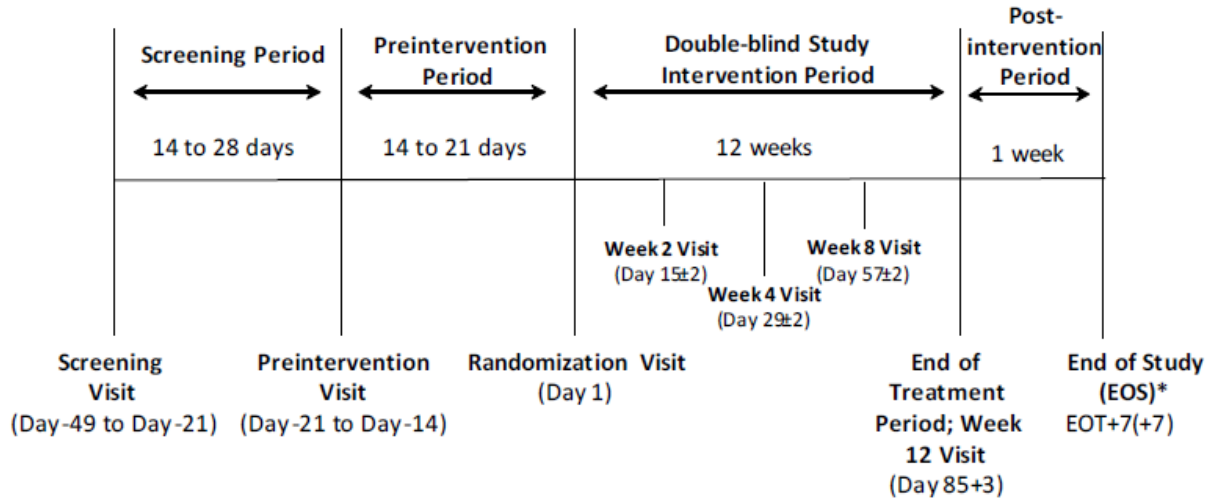
Objective(s)

The primary objective of the trial was defined as "to evaluate the safety and efficacy of 12 weeks of linaclotide therapy in comparison with placebo in paediatric participants aged 6 to 17 years who fulfil modified Rome III Criteria for Child/Adolescent FC". The objectives for the IBS-C population were separately defined.

Study design:

The study included 8 visits and consisted of a 2- to 4-week Screening Period to establish eligibility for study entry, a 2- to 3-week pre-intervention Period to establish baseline values, a 12-week Double-Blind Intervention Period to assess the effects of blinded dosing, followed by a 1-week post-intervention Period, for a total duration of approximately 17 to 20 weeks. The overall study scheme is given in the following figure:

Figure 1: Study design schematic:



* Subjects who rollover to the long-term safety study, Study LIN-MD-66, before the End of Study Visit were not required to have this visit.

Assessor's comment:

No further comment. The study design is appropriate.

Outcomes/endpoints

The protocol defined the following as primary efficacy assessment:

"The primary efficacy assessments, which will be used to determine the primary efficacy endpoint of SBM frequency, are the items assessing BM frequency and rescue medication use."

Bowel movement frequency was to be evaluated with morning and evening e-diaries, asking for the number and timing of stools. A similar evaluation for the rescue medication use was also included.

In addition, the statistical considerations (Chapter 9.1 of the protocol) define the primary evaluation as follows:

"The primary endpoint is change from baseline in 12-week SBM frequency rate (SBMs/week) during the study intervention period." This endpoint definition was also used in the SAP and clear instructions given how to determine a SBM. The SAP clearly stated also the following:

The statistical null hypothesis for the primary endpoint is as follows: linaclotide 72 ug is the same as placebo with respect to the primary efficacy analysis endpoint. This hypothesis will be tested using an analysis of covariance (ANCOVA) model with study intervention, age group (6- 11 years of age and 12-17 years of age) as fixed factors and baseline value as a covariate. Least squares means (LSMs) for each study intervention group, difference in LSMs between linaclotide versus placebo, associated 2-

sided 95% CI for these difference in LSMs, and the corresponding statistical test p-value will be reported.

Assessor's comment:

The mentioned first description is not clear. It is understood that SBMs are to be evaluated on the answer to the question whether any rescue medication has been taken. However, the definition as above obviously refers to a responder-type evaluation, for which the criteria are partially unclear. However, the statistical parts of the protocol more clearly defined the primary endpoint, and the evaluation based on SBM weekly frequency is deemed adequate.

The secondary and additional endpoints comprised the following:

- Stool consistency according to the paediatric Bristol Stool Form Scale (BSFS)
- The number of complete spontaneous bowel movements and sense of incomplete evacuation
- The degree of straining with each bowel movement
- Occurrence and severity of day-time, night-time and 24-hour abdominal pain
- Occurrence and severity of day-time, night-time, and 24-hour abdominal bloating
- Occurrence and frequency of faecal incontinence
- Fulfilment of the modified Rome III criteria (as at inclusion)
- Participants global impression of change and global impression of severity
- Observer reported global impression of change and global severity (only patients aged 6-11).

Assessor's comment:

The secondary and additional efficacy endpoints are deemed adequate. Of note, the BSFS endpoint was evaluated using a change from baseline evaluation as secondary endpoint in confirmatory manner, within a hierarchical approach (to be tested only once the primary endpoint was significant.

All efficacy assessments were determined by responses entered in the electronic diary (eDiary). Given a lack of existing age-appropriate patient-reported outcome (PRO) measures, the sponsors developed a Paediatric FC Symptom Diary (PFCSD), a novel patient-reported eDiary that assesses 7 core signs and symptoms of FC (stool frequency, stool consistency, incomplete evacuation, straining, abdominal pain, abdominal bloating, and faecal incontinence). Development of the PFCSD included input from paediatric patients with FC and their caregivers, and is aligned with FDA's 2009 Guidance for Industry, Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. A PRO dossier summarizing the totality of evidence for use of the PFCSD to support both primary and secondary endpoints relevant to the FC population in the pivotal Study LIN-MD-64 is also submitted with this application.

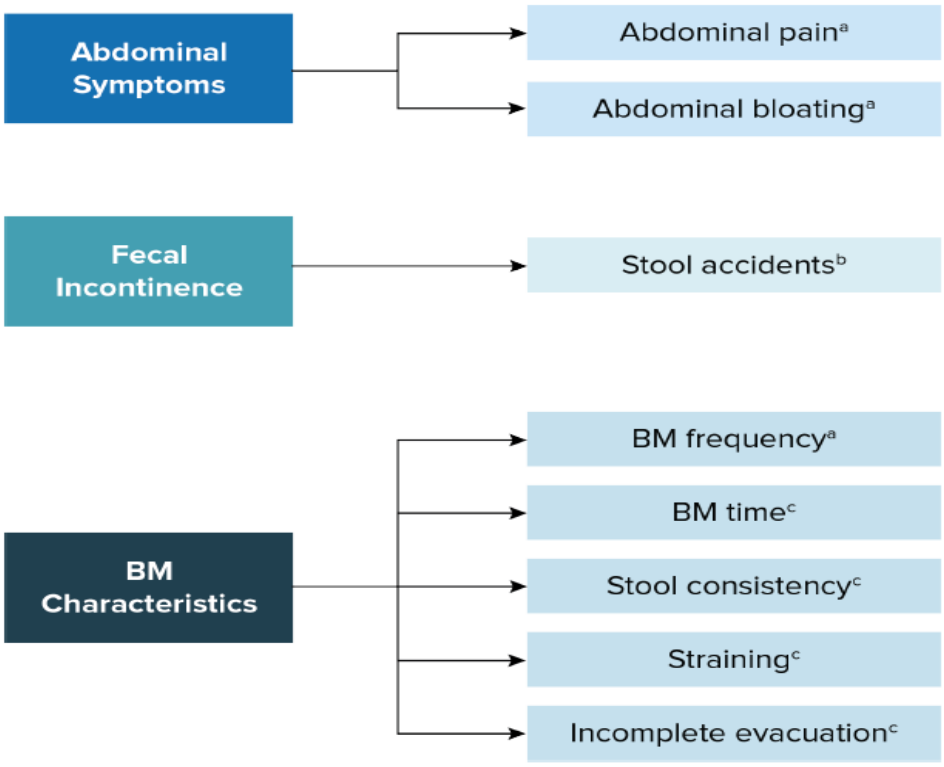
PRO-Dossier submission:

The applicant submits a complete report on the development of the PFCSD (Paediatric Functional Constipation Symptom Diary) a novel patient-reported electronic diary (eDiary) assessing the 7 core symptoms of FC, with input from the Food and Drug Administration's (FDA's) Divisions of Gastroenterology and Clinical Outcome Assessment throughout the development process (i.e., the FDA has reviewed both qualitative and quantitative work to support the content validity and psychometric properties of the eDiary). Although the PFCSD was developed for IBS-C patients also, the submitted dossier refers mainly, or exclusively to the FC population.

The PFCSD includes the scales mentioned above for the following items: The morning and evening reporting of the number of stools, the reporting of the BSFS for each bowel movement, the assessment of completeness of each bowel movement (yes/no), the presence and level of straining (0-4 scale), the presence and severity of abdominal pain (1-4 scale with evaluation in the morning and evening), the presence and severity of abdominal bloating (similar to abdominal pain), and the occurrence of faecal incontinence (yes/no)

The conceptual framework for the PFCSD is shown in the following figure:

Figure 2: PFCSD conceptual framework



BM = bowel movement; PFCSD = Pediatric Functional Constipation Symptom Diary.
[a] Assessed in the morning and evening diary.
[b] Assessed only in the evening diary.
[c] Items asked for each BM reported.

The development and psychometric evaluation of the PFCSD was undertaken in accordance with recommendations outlined in the FDA PRO guidance "Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims", and with frequent input from the FDA. In addition, caregivers of patients with paediatric FC were also interviewed during diary development. As such, the IBS-C patient and FC caregiver qualitative results are presented in the dossier in conjunction with input from FC patient results where relevant. Each of the following steps were completed to inform the rigorous development of the PFCSD:

Step 1: A targeted literature review was undertaken to identify and review the previously undertaken qualitative research on IBS and FC symptoms.

Step 2: An advisory board of expert paediatric gastroenterologists was convened to confirm results of the literature review, inform the development of a conceptual framework, and assist in the development of the PRO measurement strategy

Step 4 included an FDA consultation during which agreement on the plan for the diary development process was achieved.

Stop 4 comprised a concept elicitation phase, during which a total of 31 interview with children and adolescents with a clinical diagnosis of FC, 33 patients with IBS-C, 28 parents/caregivers of FC patients, and 27 caregivers/parents of IBS-C patients were undertaken in order to identify key symptoms and signs.

Step 5 included the item generation, which integrated the steps 1-4

Step 6 was a translatability assessment of the draft items to facilitate future translations of the diary. No changes were made to the draft item pool based on this assessment.

Step 7 included a cognitive debriefing and quantitative pilot study phase. To refine the draft PFCSD items, 3 iterative rounds of cognitive debriefing interviews were conducted with a total of 32 children/adolescents aged 6 through 17 years with PFC and 33 children/adolescents aged 6 through 17 years with IBS-C. In addition to the interviews, each of these participants completed the draft PFCSD for 5 to 9 days to facilitate an initial assessment of its quantitative properties. The main change implemented after cognitive debriefing referred to the implementation of the 2 12-hour recall periods, mainly attributable to the difficulties of understanding the 24-hour period in small children (up to 8 years).

Step 8 was another FDA review procedure, which ended with implementing recommendations from the FDA to remove certain items (deemed to be duplicate), and minor changes to items (e.g. introduction of faces instead of scales only) and instructions, and the development of an interviewer-administered version in order to address concerns regarding the understanding/handling by younger children.

Step 9: Included additional qualitative interviews (n=30) in order to address the FDA concerns and to confirm content and face validity of the changes implemented.

Step 10 included the psychometric evaluation of the scale: The psychometric properties of the initial version of the PFCSD were evaluated using data from the following phase 2 clinical trial: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Safety and Efficacy Study of Linaclotide in Children Ages 6 to 17 Years Who Fulfil Modified Rome III Criteria for Child/Adolescent FC (LIN-MD-62). The properties evaluated referred to inter-item correlation, reliability (test-retest reliability), construct, convergent and divergent validity, known-groups validity and the ability to detect change. Anchors used in this evaluation were based on global severity and global change anchors from patients and caregivers.

Step 11 included again an FDA interaction step: The FDA expressed concerns regarding the global impression items slated for inclusion in phase 3 and the need for additional evidence to support meaningful SBM change. The sponsors agreed to implement the Agency’s recommendations.

Step 12 was the confirmatory psychometric evaluation: The psychometric properties of the final PFCSD were confirmed using data from the submitted (based on the interim CSR) phase 3 study (LIN-MD-64). The properties evaluated referred to test-re-test reliability, construct, convergent and divergent validity, known-groups validity, and the responsiveness/ability to detect change. Responder thresholds were determined for each of the items.

The scale was translated into the following languages: English (Canada), Bulgarian (Bulgaria), Russian (Estonia), Arabic/Hebrew/Russian (Israel), Italian (Italy), Dutch (Netherlands), Russian/Ukrainian (Ukraine), and Spanish (US).

Assessor’s comment:

A complete evaluation of the appropriateness of the instrument is probably not within the scope of this procedure for the following reasons: The study results have been used for the final evaluation/validation of the scale, and usually, the use of newly developed scales as primary endpoint within the same trial used for psychometric validation is not deemed appropriate. Also, this submission is filed with the proposal not to implement any consequences for the current MA in the EU, and therefore, the validity of the instrument appears to be of secondary concern only.

However, the main issue with the PRO is the fact that it is not proposed to be evaluated as a total PFCSD scale, but that each of the items is evaluated separately, similar to the evaluations performed during development. Therefore, the development is not fully understood, and it remains mainly unclear how the final selection of the primary and secondary endpoints has been done, and whether it has any relation to the development of the scale/instrument, and how the "validation exercise" has indeed influenced the selection of the endpoint.

As reported above, the endpoints selected – including the primary and first ("key") secondary endpoint are deemed acceptable, but rather on the basis that BM frequency (including SBM and CSBM) have previously also been used as primary endpoints in comparable trials (including those in the paediatric population), and the BSFS is also not a new development. Moreover, the chosen primary and "key secondary" endpoints were clearly identified as the most important already in the early phases of development of the scale, and can be regarded to matter the most to the patients. Therefore, despite the fact that the final validation step was carried out in this submitted phase 3 study, no concern does arise. Rather, it is considered that the final way of evaluating the endpoints used (e.g. the split of the recall period in two 12-hour periods) has been appropriately substantiated, and supports the use of the items of the PFCSD (but not the total scale though) within a phase 3 study.

Sample size/Statistical Methods

For the primary and secondary efficacy parameters, comparison between linaclotide and placebo were performed using an analysis of covariance (ANCOVA) model with study intervention group and age group (6 to 11 years of age and 12 to 17 years of age) as fixed factors and baseline value as a covariate. Least squares means (LSMs) for each study intervention group, difference in LSMs between linaclotide versus placebo, associated 2-sided 95% confidence interval (CI) for these difference in LSMs, and the corresponding statistical test P value were reported. Study intervention-by-age group interaction were investigated as an exploratory analysis to assess whether the effects of study intervention were consistent across age groups. Sensitivity analyses were performed to assess the robustness of ANCOVA based on an observed case approach.

The sample size of this study was determined based on the primary efficacy endpoint. A total of 326 participants are targeted to be randomized to this study in a 1:1 allocation ratio to receive either linaclotide 72 µg (163 participants) or placebo (163 participants) for 12-weeks of double-blind study intervention period. This sample size was based on the assumption of a 1 point reduction of the SBM rate (based on change from baseline in SBM frequency rate with a 72 µg dose: Phase 2 LIN-MD-62 data, including the 6-11 year age group weighing $\geq$ 35 kg and the 12-17 year age group, and recent adult study MCP-103-309, and assumed standard deviation of 3, and alpha level of 5% (two sided), a 1:1 randomisation, a 2-sample t-test, and a power of 85%.

The protocol additionally defined, that, depending on the enrolment status for FC participants in this study, an IA for futility "may be considered". It further determined that, assuming that this optional futility IA is performed at 50% of information based on using the primary efficacy endpoint for FC participants, a total sample size of 378 FC participants (189 participants in each study intervention group) will need to be randomized to ensure 85% power for the final analysis at a slightly reduced significance level of 4.9% to demonstrate that linaclotide is superior to placebo (based on the same

assumptions as above. The IA was to be performed by an independent DSMB and the DSMB was to give a recommendation for the stop or continuation of the study only. No stopping for efficacy was foreseen and the futility stop was non-binding (with, however, stopping boundaries being set-up). According to the SAP, the interim analysis was to be performed once 189 patients had completed the study intervention. However, finally, the interim analysis was not performed.

For the IBS patients, no interim was foreseen, and obviously no sample size calculation performed.

An estimand framework was included in the protocol and the SAP, with the following definitions:

Population

The target population is participants with FC, ages 6-17 years old, satisfying the inclusion and exclusion criteria as specified in Sections 5.1 and 5.2 of the protocol, respectively. The analysis population is mITT

Variable

The variable is the change from baseline in the participant's 12-week SBM frequency rate (SBMs/week) during the Study Intervention Period as derived from the twice daily eDiary (morning and evening).

Accounting for Intercurrent Events:

Intercurrent events and their handling rules are as follows:

- The BMs for the participants who took a laxative, enema, or suppository on the calendar day of the BM or the calendar day before the BM will not be considered as SBMs for the analysis.
- Participants who discontinue prematurely during but prior to the completion of the double-blind Study Intervention Period will have their eDiary data included up to the morning diary following the last dose date for primary endpoint. SBM frequency rate based on included eDiary data up to morning diary after last dose date will be considered equivalent to the 12-week SBM frequency rate.
- Participants with any intermediate missing diary data during the 12-week study intervention period will have their data included as observed. The SBM frequency rate (SBMs/week) will be calculated based on the available data (as discussed in Section 16.3.4) and this SBM frequency rate will be considered to be equivalent to the rate over the 12-week study intervention period.

Population-level Summary

The population-level summary for the primary endpoint is the difference in primary variable means between the linaclotide dose arm and placebo based on difference in LSMs from the ANCOVA model in main analysis approach.

3 sensitivity analyses were planned for, one under the assumption of values missing at random (MAR), using an MMRM approach) one under the assumption of not-missing-at-random (NMAR), and the third analysis with data imputing missing data with worst response.

Assessor's comment:

Planning assumptions and definition and proposed primary evaluation are deemed adequate. The final study population using a modified ITT is not really an intent-to-treat evaluation, since study (drug) discontinuation before the first entry into the diary post-baseline could be influenced by the study drug. However, the validity of the results usually depends on the number of these early discontinuations, and since the overall number was small (n=2; see below), this deviation can be accepted. The evaluation of the SBM is partly referring to a type of a "composite" estimand, since only

those without rescue intake were included in the counting of the frequency. The premature discontinuation handling is resembling of a treatment policy estimand (without clearly spelling it out) with the primary evaluation being based on a LOCF evaluation. LOCF, however, could be regarded to be problematic, since differential development of the BM frequency could be assumed for active and placebo, in case the active is indeed efficacious. However, assuming that placebo is probably without relevant effects, it seems sufficiently conservative. Also, the planned sensitivity analyses will give additional reassurance.

It is noted that the reporting of statistical methods is insufficiently included in the submitted CSR.

Changes in the conduct of the study:

The original protocol (17 April 2019, 180 subjects randomized) had 1 global amendment, 4 regional amendments, and no administrative changes. The amendments and number of subjects enrolled under the amendment were as follows:

- Regional Amendment EU-1 (03 December 2019 0 subjects)

- Regional Amendment EU-2 (17 April 2020, 0 subjects)

- Global Amendment 1 (05 June 2020, 134 subjects)

- Regional Amendment EU-3 (07 August, 2020, 16 subjects)

- Regional Amendment CA-1 (12 May 2021 0 subjects)

The protocol changes described in the amendments did not affect the interpretation of the study results.

Assessor's comment:

The study report clearly fails to appropriately describe the protocol amendments undertaken and their (potential) implications. From the reported numbers of patients, it appears that the recruited subjects again refer to the FC population only, which is somewhat counterintuitive since the global amendment 1 was introducing the recruitment of IBS-C patients also (similar to the EU-3 amendment which was introducing the IBS-C population separately for Europe again), and it would be clearer when differential numbers for the two indications had been reported. However, considering the final number of 330 patients included, it is obvious that the total number included in the above statements (180+134+16) refer to the FC population only.

Again, the CSR does not properly include an overview on the changes implemented.

Results

Participant flow

The study was conducted at 64 sites, in 7 countries. Overall, 1002 subjects were screened, and 159 subjects discontinued the Screening Period.

Of the subjects who entered the Pre-intervention Period, 331 subjects completed; the most frequent reason for study discontinuation during the Pre-intervention Period was screen failure (433 subjects, 43.2%).

The disposition of all randomized subjects is presented in the following table. A total of 330 subjects were randomized to receive either placebo or linaclotide 72 µg. The majority (88.8%) of subjects completed the Double-blind Study Intervention Period. The most frequent reason for discontinuation during the Double-blind Study Intervention Period was withdrawal by subject (12 subjects, 3.6%). Overall, 140 (42.4%) subjects completed the post-intervention Period. Note, subjects who rolled over to the long-term safety study, Study LIN-MD-66, before the EOS Visit were not required to have this visit. Most subjects (258 subjects, 78.2%) signed informed consent for extension study LIN-MD-66.

Table 2: Disposition of Subjects (All Randomized Subjects)

	Number (%) of Subjects		
	Placebo N = 164	Linaclotide 72 µg N = 166	Total N = 330
Number of subjects treated	164 (100.0)	164 (98.8)	328 (99.4)
Double-Blind Study Intervention Period			
Number of subjects completed Double-Blind Intervention Period	145 (88.4)	148 (89.2)	293 (88.8)
Number of subjects discontinued from Double-Blind Intervention Period	19 (11.6)	18 (10.8)	37 (11.2)
Reasons for Discontinuation from Double-Blind Intervention Period			
Adverse event	2 (1.2)	2 (1.2)	4 (1.2)
Lack of efficacy	1 (0.6)	2 (1.2)	3 (0.9)
Withdrawal by subject	7 (4.3)	5 (3.0)	12 (3.6)
Lost to follow-up	4 (2.4)	0 (0.0)	4 (1.2)
Physician decision	1 (0.6)	1 (0.6)	2 (0.6)
Protocol deviation	0 (0.0)	1 (0.6)	1 (0.3)
Non-compliance with study treatment	0 (0.0)	4 (2.4)	4 (1.2)
Other	4 (2.4)	3 (1.8)	7 (2.1)
Related to COVID-19	6 (3.7)	1 (0.6)	7 (2.1)
Number of subjects signed informed consent for extension Study LIN-MD-66	131 (79.9)	127 (76.5)	258 (78.2)
Number of subjects completed study	144 (87.8)	144 (86.7)	288 (87.3)
Number of subjects discontinued from study	20 (12.2)	22 (13.3)	42 (12.7)

COVID-19 = coronavirus disease 2019

Subjects completed Double-Blind Study Intervention Period but did not participate in Post-intervention period and signed informed consent for LIN-MD-66 extension study are counted as completers in this study.

Cross-reference: Table 14.1-1.2

A total of 7/164 (4.3%) subjects in the placebo group and 1/164 (0.6%) subject in the linaclotide group had study visits impacted by coronavirus disease 2019 (COVID-19) during the study, and 2 subjects had study drug interruption due to COVID-19. A total of 5/164 (3.0%) subjects in the placebo group and 4/164 (2.4%) subjects in the linaclotide group reported treatment-emergent adverse events (TEAEs) COVID-19 in the Safety Population. The pandemic did thus not significantly affect the enrolment and conduct of the study.

The following table shows the protocol deviations, during the study. Overall, the number of protocol deviations was low.

Table 3: Number (%) of Subjects with Significant Deviations (Randomized Population)

	Number (%) of Subjects		
		Linaclotide	
	Placebo	72 µg	Total
Protocol Deviation Category	**N = 164**	**N = 166**	**N = 330**
Overall	**6 (3.7)**	**9 (5.4)**	**15 (4.5)**
Dosed with wrong study intervention (ICH)	1 (0.6)	1 (0.6)	2 (0.6)
Exclusion criteria met (ICH)	1 (0.6)	3 (1.8)	4 (1.2)
Inappropriate use of rescue medication	1 (0.6)	1 (0.6)	2 (0.6)
Inclusion criteria not met (ICH)	1 (0.6)	2 (1.2)	3 (0.9)
Initial informed consent not signed (ICH)	1 (0.6)	0 (0.0)	1 (0.3)
Prohibited concomitant medication taken (ICH)	2 (1.2)	1 (0.6)	3 (0.9)
Withdrawal due to protocol deviation	0 (0.0)	1 (0.6)	1 (0.3)

ICH = International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

Cross-reference: Table 14.1-2.1

The final randomized population consisted of 164 patients in the placebo, and 166 patients in the active treatment group. The mITT population consisted of 164 and 164 patients in the two groups, similar to the safety population. Obviously, two patients discontinued from the study before intake of the study medication.

Assessor's comment:

As can be seen from the tables, the number of screen failures was considerable, and the reasons are not given in this short interim CSR that has been submitted. However, due to the rather strict requirements for the presence of symptoms during the introductory phase, this appears to be the main reason for not being randomised.

As seen from the table for disposition, the number of discontinuations was generally low, including those patients that have discontinued before the first diary entries (n=2). Also, there was obviously a strong adherence to study procedures, intake of medication, etc. since also the number of protocol deviations was rather low.

Baseline data

Demographics were similar across the treatment groups. Overall, the mean age was 11.1 years, 55.2% of subjects were female and 44.8% of subjects were male. White and either Black or African American subjects accounted for 69.8% and 26.2% of subjects, respectively. Most subjects were not Hispanic or Latino (54.9%). The main characteristics are shown in the following table:

Table 4: Demographics, mIIT population

	Number of Subjects		
		Linaclotide	
	Placebo N = 164	72 µg N = 164	Total N = 328
Age (years)			
Mean (SD)	11.1 (2.96)	11.1 (3.33)	11.1 (3.14)
Median	11.0	11.0	11.0
Q1, Q3	9.0, 13.0	8.0, 14.0	8.0, 13.5
Min, Max	6, 17	6, 17	6, 17
Age group, n (%)			
6–11 years of age	91 (55.5)	90 (54.9)	181 (55.2)
12–17 years of age	73 (44.5)	74 (45.1)	147 (44.8)
Sex, n (%)			
Male	78 (47.6)	69 (42.1)	147 (44.8)
Female	86 (52.4)	95 (57.9)	181 (55.2)
Race, n (%)			
White	114 (69.5)	115 (70.1)	229 (69.8)
Black or African American	45 (27.4)	41 (25.0)	86 (26.2)
Asian	2 (1.2)	3 (1.8)	5 (1.5)
American Indian or Alaska Native	1 (0.6)	0 (0.0)	1 (0.3)
Native Hawaiian or other Pacific islander	1 (0.6)	3 (1.8)	4 (1.2)
Multiple[a]	1 (0.6)	2 (1.2)	3 (0.9)
Ethnicity, n (%)			
Hispanic or Latino	77 (47.0)	71 (43.3)	148 (45.1)
Not Hispanic or Latino	87 (53.0)	93 (56.7)	180 (54.9)

Max = maximum; Min = minimum; mITT = modified intent-to-treat; Q = quartile; SD = standard deviation

a. Subjects who reported multiple races are only included in the multiple category, see Table 14.1-4.1.4 for details.

Cross-reference: Table 14.1-4.1.1

Baseline characteristics were generally balanced between treatment groups. Overall, the mean body mass index was 21.81 kg/m2 in the mITT population.

The mean SBM frequency rate (SBMs/week) was 1.217 and the mean complete spontaneous bowel movement (CSBM) frequency rate (CSBMs/week) was 0.565. The mean stool consistency was 2.3, and the mean abdominal pain score around 1 (for 24-hour, night-time and daytime scores), similar to scores for abdominal bloating. Feacal incontinence scores were at 0.07 at baseline.

The most common (≥ 5% overall) medical and surgical history ongoing at screening by Medical Dictionary for Regulatory Activities (MedDRA) (version 25.0) preferred term (PT) in the Safety Population were attention deficit hyperactivity disorder (15.9%), seasonal allergy (14.3%), and asthma (12.5%). The most frequently (≥ 5% overall) reported concomitant medication classes in the Safety Population were centrally acting sympathomimetics (40/328 subjects [12.2%]), piperazine derivatives (26/328 [7.9%]), and selective beta-2-adrenoreceptor agonists (23/328 [7.0%]).

The mean dosing compliance was 97.0% for the placebo group and 97.2% for the linaclotide group during the Double-blind Study Intervention Period. The extent of exposure is given in the following table:

Table 5: Extent of Exposure (Safety Population)

	Placebo N = 164	Linaclotide 72 µg N = 164
Duration of Exposure (Unit = day), n (%)		
1 day	0 (0.0)	0 (0.0)
> 1 - ≤ 14 days	2 (1.2)	5 (3.0)
> 14 - ≤ 28 days	3 (1.8)	5 (3.0)
> 28 - ≤ 56 days	7 (4.3)	2 (1.2)
> 56 - ≤ 96 days	147 (89.6)	150 (91.5)
> 96 days	5 (3.0)	2 (1.2)
Mean (SD)	82.5 (16.23)	81.1 (18.08)
Median	86.0	85.0
Q1, Q3	84.0, 88.0	84.0, 87.0
Min, Max	10, 118	6, 99
n	164	164
Patient-Years	37.05	36.40

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

Cross-reference: Table 14.3-1.1

The mean compliance with completing the eDiary was 87.321% in the placebo group and 84.756% in the linaclotide group during the Pre-intervention Period, 67.466% in the placebo group and 63.729% in the linaclotide group during the Double-blind Study Intervention Period.

Assessor's comment:

The interim CSR only provides abbreviated reports of the baseline characteristics, however, there appear to be no relevant differences between the treatment groups. The reported weekly SBM frequency appears to assure a relevantly affected population, similar to the stool consistency. The scores for pain and bloating were relevantly lower, and this underpins the importance of the stool-frequency and –consistency related endpoints.

The adherence to the electronic diary is somewhat surprisingly low and could of course question the overall validity of the results. In case the study had been submitted for a change in the product information, this had triggered further questions. For the time being, however, this is taken note of, without consequences.

Efficacy results

The primary efficacy analysis demonstrated a statistically significant increase in SBM frequency rate for subjects in the linaclotide group compared to the placebo group. The least square mean difference between the linaclotide and placebo treatment groups for change in overall SBM frequency rate from baseline was 1.170 SBMs/week (95% confidence interval [CI], 0.651–1.689; P < 0.0001). Three

sensitivity analyses were performed to assess the robustness of ANCOVA based on an observed-cases approach with the results confirming the primary analysis (including the "worst-case" analysis).

Additionally, subgroup analyses of the primary endpoint were conducted for the following categories: age group (6 to 11 years group, 12 to 17 years group), region (North American, EU, and other), race (white, non-white), and gender (male, female). Subgroups were interpreted with caution due to limited sample size within each subgroup category. Efficacy results for the primary endpoint within all subgroup analyses were consistent. The 95% CIs for the treatment difference between linaclotide versus placebo in each subgroup (except non-white subgroup and region subgroup with < 10 subjects in each treatment group for EU and other) excluded zero in favour of the linaclotide 72 µg dose group.

Table 6: 12-week SBM frequency rate: Analysis of change from baseline during the study intervention period (mITT population)

	Placebo N = 164	Linaclotide 72 µg N = 164
Intervention Period, n[a]	164	164
Change from Baseline		
Mean (SD)	1.013 (2.032)	2.248 (2.752)
SE	0.159	0.215
Median	0.673	1.531
Q1, Q3	−0.071, 1.715	0.419, 3.451
Min, max	−2.49, 9.97	−2.73, 11.26
n[a]	164	164
Least square estimates[b]		
LS Mean (SE)	1.050 (0.187)	2.220 (0.187)
Versus Placebo		
Difference (SE)	-	1.170 (0.264)
95% CI	-	(0.651, 1.689)
P value	-	< 0.0001

ANCOVA = analysis of covariance; CI = confidence interval; LS = least square; max = maximum; min = minimum; mITT = modified intent-to-treat; SBM = spontaneous bowel movement; SD = standard deviation; SE = standard error; Q = quartile

a. Subjects with analysis values at both baseline and postbaseline during the specified time period.

b. ANCOVA model estimates/t-tests comparing specified treatment groups, controlling for age group and baseline value.

Cross-reference: Table 14.2-1.1

The secondary efficacy endpoint for the stool consistency demonstrated a statistically significant improvement in stool consistency for subjects in the linaclotide group compared to the placebo group. The least square mean difference between the linaclotide and placebo treatment groups was 0.423 (95% CI, 0.208–0.638; P = 0.0001). The sensitivity analyses with mixed-effects model for repeated measures (missing at random) and worst response imputation with ANCOVA model were performed for the secondary efficacy endpoint to assess the robustness of the results based on an observed cases approach. Similar results for the change from baseline in 12-week stool consistency were observed in the 2 sensitivity analyses.

The overall results are given in the following table:

Table 7: 12-Week Stool Consistency: Summary of Analysis of Change from Baseline During the Study Intervention Period (mITT Population)

	Placebo N = 164	Linaclotide 72 µg N = 164
Intervention Period, n[a]	132	135
Change from Baseline		
Mean (SD)	0.679 (1.148)	1.130 (1.272)
SE	0.100	0.110
Median	0.659	1.065
Q1, Q3	−0.080, 1.462	0.333, 1.944
Min, max	−2.33, 3.13	−3.00, 5.54
n[a]	132	135
Least square estimates[b]		
LS Mean (SE)	0.685 (0.078)	1.108 (0.077)
Versus placebo		
Difference (SE)	-	0.423 (0.109)
95% CI	-	(0.208, 0.638)
P value	-	0.0001

ANCOVA = analysis of covariance; CI =confidence interval; LS = least square; Max = maximum; Min = minimum; mITT = modified intent-to-treat; Q = quartile SD = standard deviation; SE = standard error

a. Subjects with analysis values at both baseline and postbaseline during the specified time period.

b. ANCOVA model estimates/t-tests comparing specified treatment groups, controlling for age group and baseline value.

Cross-reference: Table 14.2-2.1

The submitted interim CSR does not include the detailed results of the other secondary endpoints, but has the results only included as appendix tables. The following reports a selection of these endpdoints:

Table 8: Selected secondary endpoints – mITT population

Secondary efficacy variable (if not indicated otherwise: change from baseline)	Placebo n=164	Linaclotide 72 µg n=164	Difference (90% CI; p-value)
12-week CSBM frequency	0.901	1.875	0.955 (0.508, 1.403) <0.0001
Overall SBM responder (%)	33.5	36.0	2.4 (-7.9, 12.7) 0.6489
Abdominal pain based on morning and evening assessments	-0.337	-0.404	-0.069 (-0.213, 0.075) 0.3473
Straining	-0.818	-1.128	-0.441 (-0.652, -0.231 <0.0001
Abdominal bloating based on morning and evening assessments	-0.341	-0.530	-0.161 (-0.304, -0.019) 0.0265

Proportion of subjects who report using rescue medicine (responder, %)	60.4	51.8	-8.5 (-19.2, 2.2) 0.1212
Subjects not fulfilling modified Rome III criteria	11.0	11.0	n.r.

As an addition to the overall responder rate, the applicant has analysed the weekly SBM responder rates, where the linaclotide group showed a greater percentage of subjects in weekly SBM responders (defined as a subject who had an SBM increase ≥ 2 in the SBM weekly rate from baseline for any week in the Study Intervention Period) compared to the placebo group at Weeks 1, 3, 4, 6, 7, 9, 11, and 12 (nominal P value < 0.05), with weekly SBM responders ranging from 29.7% to 41.4% for the linaclotide group and 19.5% to 28.4% for the placebo group.

The percentage of subjects with at least 1 SBM within 24 or 48 hours after the first dose of study drug was higher in the linaclotide group than in the placebo group (nominal P value < 0.05) with 50 (30.5%) subjects versus 34 (20.7%) subjects having symptom relief (i.e., at least one SBM) within 24 hours and 93 (56.7%) subjects versus 63 (38.4%) subjects having symptom relief within 48 hours.

Assessor's comment:

The results of the study clearly show that the study was successful in a methodological sense, since the primary and key secondary (hierarchically tested in confirmatory manner) endpoints were showing highly statistically significant results. However, when considering all endpoints, the results rather appear like a "mixed bag" with significant results with regard to the numerical evaluation of bowel-movement related endpoints (frequency and consistency), but rather poor results when a responder-type endpoint (such as the SBM responders) were evaluated. A similar picture is derived from the other symptoms, when no relevant effects on bloating and abdominal pain are seen, but straining is significantly reduced. The rather disappointing part of the results are completed by showing no effect on the presence of fulfilment of the Rome III criteria and the overall use of rescue medication.

The results also have to be seen on the evaluation of the proposed responder thresholds derived in the PRO (PFCSD) validation exercise, which determined the SBM frequency responder threshold a 2.0 (which was then used in the responder analysis as above), the CSBM responder threshold at 1.0 (thus, the mean change was very close to the responder threshold, which appears to be a relevant change overall), for abdominal pain and bloating at (lowest threshold proposed) -0.4 (the mean changes were less than -0.1 in both symptoms, which consequently appears to be clinically not relevant), for straining at -0.60 (the mean change was about -0.4, and it remains unclear whether this is relevant, and would need a responder analysis), and for stool consistency at 0.7 to 1.3 (in the results, not even the lower threshold was achieved for the mean change (which was around 0.4), but this would also need to be evaluated in a responder analyses to put the result into context).

In summary, while the study is successful for its primary and key secondary endpoints, there remain relevant doubts about the clinical relevance of the treatment effects. Also the effects of the treatment appear to be restricted to the influence on bowel movements (frequency and consistency), and the symptoms associated with stooling (straining), but rather minor effects on associated symptoms such as bloating and abdominal pain. This is not really surprising, since the baseline severity of these symptoms were not very high, and the symptoms rather play a minor role in functional constipation overall.

Since the applicant does not draw any consequences for the EU product information, it is currently not considered necessary to request additional analyses, or argumentation on clinical relevance of the treatment effects.

Treatment of functional constipation even in minors is not a field of unmet medical need, and the decision of the applicant not to pursue the FC indication, neither in adults nor in children can therefore be accepted.

Subgroup analyses:

Additionally, subgroup analyses of the primary and secondary endpoints were conducted for the following categories: age group (6 to 11 years group, 12 to 17 years group), region (North American, EU, and other), race (white, non-white), and gender (male, female). Subgroup analyses results should be interpreted with caution due to limited sample size within each subgroup category. Efficacy results for the primary and secondary endpoints within all subgroup analyses were consistent. The 95% CIs for the treatment difference between linaclotide versus placebo in each subgroup (except non-white subgroup.

Safety results

For the exposure, it is referred to the above table 5, which demonstrates that exposure was quite similar in the two treatment groups. The safety was evaluated in the safety population, and included AEs, AEs of special interest (AESIs), laboratory parameters, and vital signs (including ECG).

Adverse events.

The overall number and percentage of subjects who reported AEs are summarized in the following table. AEs were reported for 28 subjects (17.1%) in the linaclotide group and for 35 subjects (21.3%) in the placebo group. The majority of AEs in each treatment group were non-serious. Treatment-emergent serious adverse events (TESAEs) were reported for 2 subjects (1.2%) in the linaclotide group and 2 subjects (1.2%) in the placebo group.

AEs leading to study treatment discontinuation were reported for 2 subjects (1.2%) in the linaclotide group and for 3 subjects (1.8%) in the placebo group. No AEs leading to death were reported.

Table 9: Overall Number (%) of Subjects with AEs (Safety Population)

	Number (%) of Subjects	
AE Category	Placebo N = 164	Linaclotide 72 µg N = 164
All TEAEs	35 (21.3)	28 (17.1)
Treatment-related TEAE	5 (3.0)	9 (5.5)
Deaths	0 (0.0)	0 (0.0)
TESAE	2 (1.2)	2 (1.2)
Treatment-related TESAE	0 (0.0)	1 (0.6)
TEAE Leading to Study Treatment Discontinuation from Study	3 (1.8)	2 (1.2)

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event

MedDRA version 25.0 was used to code AE terms.

Cross-Reference: Table 14.3-2.1

The following table displays the TEAEs occurring in more than 1 patient (=1.2%) according to SOC and PT.

Table 10: TEAEs occurring in more than 1 patient: Number (%) of participants (SOC and PT); safety population:

System Organ Class Preferred Term	Placebo (n=164)	Linaclotide 72 µg, n=164
Gastrointestinal disorders	7 (4.3)	11 (6.7)
Diarrhoea	3 (1.8)	7 (4.3)
Nausea	0	2 (1.2)
Vomiting	2 (1.2)	0
Infections and Infestations	15 (9.1)	9 (5.5)
COVID-19	5 (3.0)	4 (2.4)
Influenza	2 (1.2)	1 (0.6)
Upper resp.tract infection	2 (1.2)	1 (0.6)
Pharyngitis streptococcal	2 (1.2)	1 (0.6)
Nervous system disorders	4 (2.4)	2 (1.2)
Headache	2 (1.2)	2 (1.2)
Investigations	4 (2.4)	2 (1.2)
SARS-Cov-2 test pos.	3 (1.8)	0
Respiratory, thoracic and mediastinal disorders	4 (2.4)	2 (1.2)
Cough	3 (1.8)	1 (0.6)

Oropharyngeal pain	2 (1.2)	0
Skin and subcutaneous tissue disorders	4 (2.4)	2 (1.2)
General disorders and administration site conditions	2 (1.2)	2 (1.2)
Pyrexia	2 (1.2)	0
Hepatobiliary disorders	0	1 (0.6)
Metabolism and nutrition disorders	0	1 (0.6)
Psychiatric disorders	2 (1.2)	0
Reproductive system and breast disorders	2 (1.2)	0
Cardiac disorders	1 (0.6)	0
Injury, poisoning and procedural complications	1 (0.6)	0
Renal and urinary disorders	1 (0.6)	0

As seen from the table, the most frequent AEs were diarrhoea in the linaclotide group, and COVID-19 in the placebo group.

The most frequent treatment-related TEAE reported during the intervention period by PT was diarrhea reported in 2/164 (1.2%) subjects in the placebo group and 6/164 (3.7%) in the linaclotide group. The overview on the related TEAEs is given in the following table:

Table 11: Treatment-related TEAEs: Number (%) of subjects by SOC and PT (safety population)

	Number (%) of Subjects	
SOC PT	Placebo N = 164	Linaclotide 72 µg N = 164
Subjects with at least one treatment-related TEAE	**5 (3.0)**	**9 (5.5)**
Gastrointestinal disorders	3 (1.8)	8 (4.9)
Diarrhoea	2 (1.2)	6 (3.7)
Nausea	0	2 (1.2)
Abdominal discomfort	0	1 (0.6)
Abdominal distension	1 (0.6)	0
Infections and infestations	0	1 (0.6)
COVID-19	0	1 (0.6)
Metabolism and nutrition disorders	0	1 (0.6)
Dehydration	0	1 (0.6)
Nervous system disorders	2 (1.2)	0
Dizziness	1 (0.6)	0
Headache	1 (0.6)	0

AE = adverse event; COVID-19 = coronavirus disease 2019; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; SOC = System Organ Class; TEAE: treatment-emergent adverse event

MedDRA version 25.0 was used to code AE terms.

The majority of TEAEs reported were considered mild or moderate in severity. Overall, 2/164 (1.2%) subjects in the placebo group and 3/164 (1.8%) subjects in the linaclotide group experienced severe TEAEs during the study. Severe TEAEs of suicide attempt and suicidal ideation were reported in the placebo group and diarrhoea, faecaloma, pulmonary artery stenosis, and dehydration were reported in the linaclotide group. Severe events of diarrhoea and dehydration were reported in 1 subject and were considered by the investigator to be related to study drug

There were no deaths during the study.

Overall, a total of 4/328 (1.2%) subjects reported ≥ 1 TESAEs: 2/164 (1.2%) in the placebo group and 2/164 (1.2%) in the linaclotide group. TESAEs of suicide attempt (in 2 subjects) and suicidal ideation were reported in the placebo group, and diarrhoea and faecaloma were reported in the linaclotide group. All serious adverse events (SAEs) were considered not related to study drug, except for a TESAE of diarrhoea in 1 subject in the linaclotide group.

This subject was a 17 year old female who developed diarrhoea after 10 days of active treatment. The medical history of the subject included chronic constipation, IBS, ovarian cysts, eczema, migraine, allergies (food, chemicals), generalized anxiety disorder, and urinary tract infection. Concomitant medication included aripiprazole, sertraline, Senna, macrogol, sex hormone preparations, and fluconazole. After 10 days of treatment, the subject experienced severe diarrhoea, and study medication intake was stopped. The patient was hospitalized for 1 day.

Subject presented to ER with dizziness, headache and nausea in the setting of approximately 1.5-week history of diarrhoea after starting the study drug. The subject reported the diarrhoea started the same day as starting the study drug with 3-5 episodes of diarrhoea per day, occasionally bloody, but more

streaks. The subject began feeling lightheaded, dizzy, nausea and dehydrated 2 day later. Initially she was able to eat, but over the past week she had reported decreasing intake due to nausea. The subject also endorsed intermittent burning urination since starting the medication. Physical examination revealed no findings, and the patient was treated with IV fluids for dehydration. There were no relevant laboratory value abnormalities except for low bicarbonate (see also below). No signs for infection were detected. The diarrhoea continued but improved during hospital stay and she was discharged the next day. 5 days later the patient presented again in the clinical and was well. The event was considered resolved.

Assessor's comment:

The assessment of the relatedness of the SAEs is agreed with. The event of faecaloma (occurring at about 1 month of treatment) is of course related to the underlying disease, but somehow also expresses a treatment failure.

Overall, 5/328 (1.5%) subjects (3/164 (1.8%) subjects in the placebo group and 2/164 (1.2%) subjects in the linaclotide group) experienced AEs leading to discontinuation of study drug. TEAEs leading to discontinuation of study drug in the placebo group were suicide attempt (in 2 subjects), suicidal ideation, and COVID-19. TEAEs leading to discontinuation of study drug in the linaclotide group were diarrhoea, faecaloma, nausea, and dehydration.

AESIs (i.e., significant volume depletion and/or significant electrolyte abnormalities and/or ECG abnormalities that were considered by the investigator or sponsor to be related to diarrhoea) were reported for 1/164 (0.6%) subject in the linaclotide group during the study. The 17-year-old subject experienced severe diarrhoea which led to hospitalization accompanied by dehydration on Day 10 of double-blind intervention period, requiring intravenous fluids (the case described above). The AESI was reported as resolved without sequalae on Day 11 and led to study discontinuation.

Laboratory evaluations:

The incidences of laboratory test results that were identified as potentially clinically significant (PCS) based on the criteria defined in the SAP are presented in the following table. There were no unexpected changes of clinical relevance in the study. The most frequent (occurring in $\geq$ 5 subjects) PCS values were observed for albumin (> 1.1 $\times$ upper limit of normal [ULN]) and monocytes absolute cell count (< 0.5× ULN), neither of which was associated with concomitant reports of diarrhoea. There was a clinically significant low value of bicarbonate for a subject following an event of diarrhoea that met AESI criteria.

Table 12: Number of Subjects with Potentially Clinically Significant Postbaseline Laboratory Values During the Double-blind Intervention Period (Safety Population)

Parameter (unit) PCS Criterion	Placebo N = 164 n/N1 (%)	Linaclotide 72 µg N = 164 n/N1 (%)
Hematology		
Eosinophils absolute cell count (10^9/L)		
> 3 × ULN	2/142 (1.4)	3/147 (2.0)
Hematocrit (Ratio)		
< 0.9 × LLN	2/142 (1.4)	2/146 (1.4)
Hemoglobin (g/L)		
< 0.9 × LLN	1/141 (0.7)	1/144 (0.7)
Monocytes, absolute cell count (10^9/L)		
< 0.5 × LLN	3/137 (2.2)	6/142 (4.2)
Neutrophils, absolute cell count (10^9/L)		
< 0.8 × LLN	0/142 (0.0)	2/147 (1.4)
Red blood cell count (10^{12}/L)		
< 0.9 × LLN	0/142 (0.0)	2/148 (1.4)
Chemistry		
ALT (U/L)		
≥ 3 × ULN	0/142 (0.0)	2/150 (1.3)
Albumin (g/L)		
> 1.1 × ULN	5/136 (3.7)	5/149 (3.4)
Alkaline phosphatase (U/L)		
Age 6-12 (inclusive) male and female; Age 13-15 (inclusive), male: ≥ 1.2 × ULN	2/111 (1.8)	1/105 (1.0)
Bicarbonate (HCO3) (mmol/L)		
< 0.9 × LLN	3/137 (2.2)	2/149 (1.3)
Creatinine (umol/L)		
> 1.3 × ULN	1/142 (0.7)	0/149 (0.0)
Glucose, non-fasting (mmol/L)		
< 0.8 × LLN	0/144 (0.0)	1/152 (0.7)
Potassium (mmol/L)		
> 1.1 × ULN	1/141 (0.7)	1/148 (0.7)

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

Notes: N1 (percentage denominator) = Participants with non-missing non-PCS baseline and ≥1 postbaseline parameter assessment during double-blind treatment period.

For alkaline phosphatase criteria, denominator in the percentage calculation included number of participants in the specific age group and gender of interest with non-missing non-PCS baseline and ≥1 postbaseline parameter assessment during double-blind treatment period.

Cross-reference: Table 14.3-4.1

Vital signs:

Descriptive statistics for height, vital signs (ie, temperature, body weight, respiratory rate [RR], and supine pulse rate, supine systolic and diastolic blood pressure [BP]) and changes from baseline values were evaluated. There were no unexpected changes of clinical relevance.

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.

Table 13: Number of subjects with PCS post-baseline vital sign values during the double-blind intervention period (safety population).

Parameter (unit) PCS Criterion	Placebo N = 164 n/N1 (%)	Linaclotide 72 µg N = 164 n/N1 (%)
Systolic Blood Pressure (mmHg) (Supine)		
Age 6–11 (inclusive): ≤ 80 and Decrease ≥ 20	0/90 (0.0)	1/86 (1.2)
Age 6–11 (inclusive): ≥ 140 and Increase ≥ 20	1/90 (1.1)	0/86 (0.0)
Age 12–17 (inclusive): ≤ 90 and Decrease ≥ 20	1/72 (1.4)	0/74 (0.0)
Age 12–17 (inclusive): ≥ 155 and Increase ≥ 20	0/72 (0.0)	0/74 (0.0)
Standing - Supine Systolic Blood Pressure (mmHg)		
≤ -20 and Decrease ≥ 10	5/162 (3.1)	2/160 (1.3)
Diastolic Blood Pressure (mmHg) (Supine)		
Age 6–11 (inclusive): ≤ 40 and Decrease ≥ 15	0/90 (0.0)	0/86 (0.0)
Age 6–11 (inclusive): ≥ 95 and Increase ≥ 15	2/90 (2.2)	0/86 (0.0)
Age 12–17 (inclusive): ≤ 45 and Decrease ≥ 15	0/72 (0.0)	0/74 (0.0)
Age 12–17 (inclusive): ≥ 105 and Increase ≥ 15	0/72 (0.0)	0/74 (0.0)
Standing - Supine Diastolic Blood Pressure (mmHg)		
≤ −10 and Decrease ≥ 10	14/162 (8.6)	14/160 (8.8)
Pulse Rate (beats/min) (Supine)		
Age 6–11 (inclusive): ≤ 50 and Decrease ≥ 15	0/90 (0.0)	0/86 (0.0)
Age 6–11 (inclusive): ≥ 140 and Increase ≥ 15	0/90 (0.0)	0/86 (0.0)
Age 12–17 (inclusive): ≤ 40 and Decrease ≥ 15	0/72 (0.0)	0/74 (0.0)
Age 12–17 (inclusive): ≥ 120 and Increase ≥ 15	0/72 (0.0)	0/74 (0.0)
Standing - Supine Pulse Rate (beats/min)		
≥ 20 and Increase ≥ 10	24/162 (14.8)	20/160 (12.5)
Weight (kg)		
Decrease of ≥ 5%	6/162 (3.7)	7/160 (4.4)
Increase of ≥ 5%	41/162 (25.3)	37/160 (23.1)

PCS = potentially clinically significant

Notes: N1 (percentage denominator) = Participants with non-missing non-PCS baseline and ≥1 postbaseline parameter assessment. For specific age dependent criteria, participants in that specific age group of interest with non-missing non-PCS baseline and ≥1 postbaseline parameter assessment included for the denominator.

The incidences of ECG parameters that were identified as PCS based were evaluated on the criteria defined in the SAP and included PR interval, QRS duration, and QTcF inverval. No subjects experienced PCS postbaseline ECG parameters of QRS duration, PR interval, or QTcF interval.

The applicant concludes that linaclotide is well tolerated in paediatric subjects with a safety profile consistent with prior linaclotide studies in adults with CIC and IBS-C. There were no new safety signals observed in paediatric subjects. Overall, linaclotide was well tolerated across 6 to 17-year-olds.

Assessor's comment:

The overall conclusions of the study report are agreed with. The known safety profile of the compound has been confirmed in the paediatric FC population.

Discussion on clinical aspects

The applicant has submitted an interim analysis of the efficacy and safety study in children aged 6-17 LIN-MD-64. While this study included both FC as well as IBS-C patients, the submitted study report includes the evaluation of the patients with FC only.

The study included a patient population with functional constipation at the start of the study, which can be considered representative of an FC population in need for pharmaceutical treatment, and the inclusion criteria, as well as procedures for evaluation of the fulfilment of the study inclusion criteria are considered appropriate.

The study was a 3-month, placebo-controlled study, which evaluated as main endpoints the frequency and consistency of bowel movements. Both the choice of the primary endpoints, as well as the mode of evaluation are considered appropriate. Secondary endpoints also included additional symptoms of or associated with constipation such as straining at defaecation, bloating and abdominal pain.

The results of the study indicated an overall treatment success with clear (statistically significant) effects on the frequency of bowel movements (both those being SBMs as well as CSBMs) and on stool consistency. However, the overall results are currently not considered full convincing with regard to their clinical meaningfulness. This refers to the stool consistency (where the mean difference was far from the minimally important difference determined for this parameter) and the results of the evaluation of the associated symptoms, for which partially non-significant results were achieved. While the latter can be partly be attributed to the fact that symptoms such as bloating and abdominal pain do not play a prominent role in FC, there are even concerns on the clinical relevance of the main results, since a responder evaluation even in the most clearly statistically significant endpoint, the SBM rate, not only missed statistical significance, but also did not show a clinically relevant difference to placebo.

The applicant has overall submitted only an abbreviated study report, which does not fully display the results in appropriate manner, and refers to a high extent to appendix tables and displays only. Similarly, the submitted clinical overview is only a very brief and rather uncritical document. This is both probably owed to the fact that the applicant does not intend to implement any changes into the European license for the compound, which is currently licensed for the treatment of IBS-C in adults only. There is obviously no intent to market the compound also in functional constipation, neither in adults nor in children. This decision can be accepted based on the fact that there is clearly no unmet medical need whatsoever for the treatment of functional constipation both for adults as well as children. Therefore, the "no-consequence" conclusions of the applicant are accepted.

The results of the patients included with IBS-C into study LIN-MD-64, however, may potentially need re-consideration for changes of the product information, and are awaited.

The safety evaluation of the presented study mainly confirmed the known safety profile of the compound with the mainstay of adverse reactions related to the local effects in the gastrointestinal tract. There was one serious event of special interested, which was a case of severe diarrhoea in an adolescent being hospitalised. Nevertheless, the overall rate of adverse events and adverse reactions was low during the study, and the safety results of the study do overall not influence the risk-benefit profile in the licensed indication.

4. Overall conclusion

The applicant has submitted the results of an interim evaluation of study LIN-MD-64 which is a randomised, double-blind efficacy and safety study in children and adolescents aged 6-17 with functional constipation or IBS-C. For the purpose of this interim evaluation, the results of the FC population only were submitted. The study was formally a successful study with regard to efficacy, however, would need further evaluation with regard to the evaluation of clinical meaningfulness of the study results, in case the applicant would have proposed changes to the currently approved product information in the EU, which is, however, not the case. The safety evaluation in this study was rather unremarkable, and confirmed an acceptable safety profile in the paediatric population for a treatment duration of 3 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**