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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/P46/020

Note

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

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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	02.12.2024	02.12.2024	☐
☐	CHMP Rapporteur Assessment Report	06.01.2025	06.01.2025	☐
☐	CHMP members comments	20.01.2025	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	23.01.2025	n/a	☐
☐	CHMP adoption of conclusions:	30.01.2025	30.01.2025	☐
☐	CHMP Rapporteur Assessment Report	07.05.2025	17.04.2025	☐
☐	CHMP members comments	12.05.2025	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	15.05.2025	n/a	☐
☒	CHMP adoption of conclusions:	22.05.2025	22.05.2025	☐

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List of abbreviations

AE	adverse event
AESI	adverse event of special interest
CIC	chronic idiopathic constipation
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	pediatric 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 12 November 2024 the MAH submitted a final study report for the completed paediatric study LIN-MD-64 for Constella (Linaclotide), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. The submission focusses on the results of the patients included with a diagnosis of irritable bowel syndrome with Constipation (IBS-C). An interim report for study LIN-MD-64 was previously submitted under procedure P46 018.

This study is not part of the linaclotide PIP (EMEA-000927-PIP01-10-M08) or relating to a PAM, since IBS-C studies are not included in the PIP, however it is a post marketing requirement with the FDA.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

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). In the US, the compound is approved for the treatment of functional constipation in paediatric patients aged 6-17 years (with the 72µg dose).

Study LIN-MD-64 is part of the agreed PIP (EMEA-000927-PIP01-10-M06), however, the investigation of children with IBS-C was not part of this PIP but is a post-marketing requirement to the US FDA.

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 IBS-C subjects only. Results from the paediatric FC subjects have been reported in a separate CSR and been evaluated in the previous Art 46 procedure P46 018.

The Applicant/MAH states that there are no regulatory consequences identified by the MAH with this study and that there is no new data that changes or results in a new benefit/risk evaluation. Consequently, no changes were made to the Constella PI.

Linaclotide, a first-in-class, 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). Linaclotide is an agonist of GC-C, a key regulator of intestinal secretory function in mammals, found on the luminal surface of the intestinal epithelial cells. Linaclotide acts locally in the intestine and has limited permeability, resulting in very low absolute oral bioavailability across all species tested (≤ 0.2%).

Irritable bowel syndrome is characterized by symptoms of abdominal discomfort or pain associated with altered bowel movement characteristics. In adults, the Rome III criteria classify irritable bowel syndrome (IBS) by subtypes of IBS-C, IBS-D, mixed IBS, and unsubtyped IBS, depending on stool consistency. In pediatric patients, although IBS subtypes are encountered in clinical practice,

classifications based on stool consistency were not specified in the Rome criteria at the time of planning the submitted study.

Based on non-extensive available data, the overall estimated prevalence of IBS in the pediatric population varies across studies and study methodologies. In two prevalence studies, IBS was estimated to range from 2.8% to 5.1% among United States (US) children 4 to 18 years of age, with approximately half of these patients affected by the IBS-C subtype. Additionally, another study estimated the prevalence rate of IBS in younger children to about half the observed rate in adolescents (8% in younger children in comparison to 17% in adolescents). More recent epidemiology studies have observed prevalence rates of IBS in 6% to 14% of younger patients and 22% to 35% of adolescents.

The submitted study report therefore concludes that there is a clear unmet medical need for treatment of IBS-C in paediatric patients, since there are no approved pharmacological therapies (in the US).

2.2. Information on the pharmaceutical formulation used in the study

The pharmaceutical formulations used are similar to the commercially available formulations in the US with the strengths 145 µg and 290 µg.

2.3. Clinical aspects

2.3.1. Introduction

This submission is reporting the results of study LIN-MD-64 in patients aged 7-17 years diagnosed with IBS-C. The reported results are a "substudy" of the LIN-MD-64 study, which also included patients aged 6-17 with FC.

2.3.2. Clinical study LIN-MD-64

The interim CSR for study LIN-MD-64 is focussing on the evaluation of the data for patients with IBS-C.

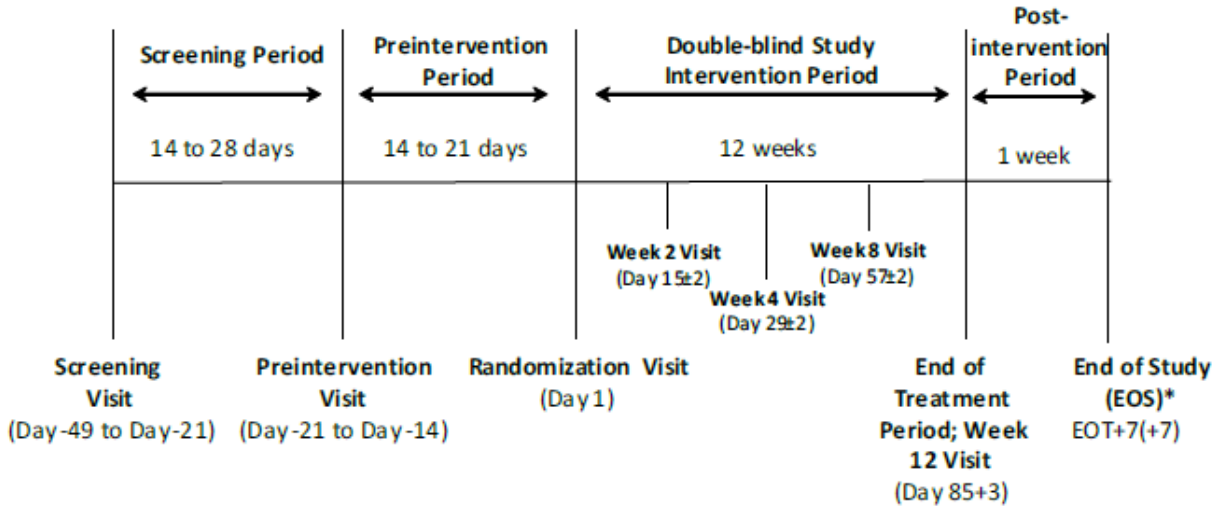
Study LIN-MD-64 is titled as: Phase 3, Multicenter, Randomized, Double-blind, Parallel-group, Safety and Efficacy Study of Linaclotide in Pediatric Participants, Ages 6 to 17 Years, With Irritable Bowel Syndrome with Constipation (IBS-C) and of Linaclotide versus Placebo in Pediatric Participants with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

Methods

The objective for IBS-C subjects was to evaluate the safety and efficacy of 12 weeks of linaclotide therapy in pediatric subjects aged 7 to 17 years with IBS-C (i.e., fulfil modified Rome III Criteria for Child/Adolescent IBS). The study was to compare the safety and efficacy of the two lincalotide doses of 145 µg and 290 µg.

The study included a total of 8 visits and was planned to be approximately 17 to 20 weeks in duration: a 2 to 4-week Screening Period, a 2- to 3-week pre-intervention period, a 12-week- double-blind Study Intervention Period, followed by a 1-week. The overall design is shown 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.

All IBS-C subjects were randomized to 145 µg or 290 µg linaclotide with a 1:1 allocation ratio.

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

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:

The inclusion criteria for the FC population are not discussed here again. For the IBS-C population, it has to be noted that the chosen criteria are not fully in line with the current childhood and adolescent criteria for IBS according to the ROME IV consensus. These are the following:

"Must include all of the following and must be fulfilled for at least 2 months prior to diagnosis:

Abdominal pain at least 4 days per month over at least 2 months associated with one or more of the following:

- Related to defecation
- A change in frequency of stool
- A change in form (appearance) of stool
- In children with abdominal pain and constipation, the pain does not resolve with resolution of the constipation (children in whom the pain resolves have functional constipation, not IBS)
- After appropriate evaluation, the symptoms cannot be fully explained by another medical condition

It is also not fully clear whether the FC criteria were also applicable to the IBS-C population, but this must be assumed, otherwise, it would not make sense to label the patients as IBS with constipation. However, it has to be noted that neither the Rome III, nor the current Rome IV criteria are recommending a subtyping in paediatric IBS.

The Rome III criteria, as well as the modifications chosen by the MAH appear to be less strict as compared to the Rome IV criteria. This has potentially mainly got to do with the fact that the concept of "abdominal discomfort" has been abandoned by the Rome IV consensus. However, the criterion that the pain in those with constipation and pain must not resolve, appears to be in contrast to the previous criterion that the Rome III criteria require the improvement with defaecation of the pain. The MAH does not really discuss these differences, and its potential implications, which seems understandable from the view that the submission of the data is not intended to have an influence on the current status of the product in the EU. This, could, however, be of value once the MAH intends to extend the current adult indication to the paediatric population. For the time being, the differences between the inclusion criteria used, and the current Rome IV criteria are noted, but further questions do not need to be addressed at this time-point.

Treatments

The following table shows the treatments administered to all patients, including those with FC. It should be noted that patients with IBS-C were administered the linaclotide capsule formulations with the strength of 145 and 290 µg only.

Table 1: Identity of Investigational Product

Study Drug	Dosage Form	Formulation	Manufacturer	Bulk Lot
Placebo[a]	Capsules	-	Forest Laboratories Ireland, Limited	1798229, NDA/2019/04/0005, D07637
Linaclotide[a]	Capsules	72 µg	Forest Laboratories Ireland, Limited	1780864-SR03268, D28287, D30657, D23247, D12109
Linaclotide[b]	Capsules	145 µg	Forest Laboratories Ireland, Limited	1780865-SR03261, 1000523585, D27197, D30002, D23067
Linaclotide[b]	Capsules	290 µg	Forest Laboratories Ireland, Limited	1647748, 1780866-SR03268, 1000548092, D28288, D30550, D23068

a. All subjects with FC were randomized to 72 µg or placebo.

b. All subjects with IBS-C were randomized to 145 µg or 290 µg linaclotide.

Notes: This table identifies all investigational products used in Study LIN-MD-64.

Objective(s)

See above.

Outcomes/endpoints

The following efficacy evaluations/endpoints were collected during the study for the FC population:

- SBM (spontaneous bowel movements) – Evaluation of daytime and night-time
- Use of rescue medication (yes/no; day- and night-time)
- 7-point ordinal p-BSFS (paediatric Bristol Stool Form Scale),
- Daily assessments measuring complete evacuation ((CSBM) Question: When you pooped, did it feel like there was more poop left inside that didn't come out?)
- Straining with BMs (5-point Liker scale from "0- not hard at all" to "4 – I pushed very hard")
- Abdominal pain (daytime and nighttime, and combination; yes/no and if present using a 4-point Likert scale
- Abdominal bloating (daytime and nighttime, each with yes/no, and if present with 4-point Likert scale)
- Fecal incontinence (yes/no)
- Modified Rome III criteria global change and global severity items (5-item Likert scales).

The items defined as primary efficacy endpoints were the BM frequency, and the rescue medication use for the FC population.

With amendment I, the efficacy endpoints for the IBS-C population were defined as:

Primary efficacy endpoint:

- APS response in 6/12 weeks (combined daytime and nighttime abdominal pain and SBM+2)

A 6/12 weeks APS + 2 responder is a participant who meets the weekly APS + 2 responder criteria for at least 6 out of the 12 weeks of the intervention period. A weekly APS +2 responder is a participant who has an increase of at least 2 in the SBM weekly rate from baseline, AND a decrease of at least 30% in the mean abdominal pain score from baseline, during that study intervention week.

The secondary endpoints were defined as:

- Change from baseline in 12-week SBM frequency rate (SBMs/week) during the study intervention period
- Change from baseline in 12-week abdominal pain (combined daytime and nighttime symptoms) during the study intervention period
- Change from baseline in 12-week stool consistency during the study intervention period
- 6/12 weeks SBM + 2 responder
- 6/12 weeks abdominal pain (combined daytime and nighttime symptoms) responder

Sample size

There were no pre-conceived statistical hypotheses to be evaluated in the IBS-C population. The proposed sample size was based on practical considerations but was assuming a similar response to treatment as in adults and was calculated using a Bayesian approach (see below). The conclusion was that 50 patients in each of the study arms could be adequate to "inform the prescriber" regarding the safe and efficacious use of the compound in the paediatric population.

Randomisation and blinding (masking)

The study was conducted in double-blind fashion. All IBS-C subjects were randomized to 145 µg or 290 µg linaclotide with a 1:1 allocation ratio. The treatments administered were described above. A separate randomization code list was generated for the IBS-C population.

Statistical Methods

As mentioned above, the IBS-C population was explorative in character. There were no preconceived statistical hypotheses to be assessed in this study for the IBS-C population.

Nevertheless, the following definitions were included for the estimands in the protocol:

The intercurrent events were given with the following items and handling: The intake of rescue medication will have the consequence of not being considered a SBM responder; discontinuation from the study will be handled as non-response in the weeks following discontinuation. Similarly, eDiary responses following the onset of dose de-escalation will not be included. The participants with dose de-escalation will be considered non-responders for the subsequent study intervention weeks. Patients with less than 4 completed diary days per analysis week will also be considered non-responders.

The protocol additionally determined that a Bayesian analysis will be performed for the primary efficacy endpoint using adult IBS-C data (studies MCP-103-202, MCP-103-303, and LIN-MD-31) to inform the prior distribution of response in pediatric IBS-C patients. The 2.5 percentile of posterior distribution for the APS+2 responder rate for linaclotide 290 µg was to be compared separately with the pooled placebo APS + 2 responder rate and with the upper limit of 95% CI of the pooled placebo responder rate from contributing adult studies. The details of the Bayesian analysis will be provided in a separate analysis plan.

Assessor's comment:

Corresponding to the character of the primary endpoint, a composite strategy was chosen for the primary evaluation. This estimand is adequate for a confirmatory study. However, whether it is a sensible approach – especially to choose a responder-type endpoint – for an explorative exercise remains somewhat questionable.

No detailed comments are given with regard to the Bayesian approach. This is understood – as worded in the protocol – as an exploratory analysis only. However, details are given in the SAP only which is not considered fully appropriate. The attitude of the study report submitted, as well as the potential submission for the FDA leave unclear whether a claim (for the US) for treatment of children is made out of these data to extend the IBS-C indication to children and adolescents (aged 7 years and older).

At least a full discussion of the results achieved in the adult population, and the transferability and comparison of the results of the adult studies with the presented study would normally be expected before any kind of such approach could be considered. Such a discussion was, however, neither included in the study report, nor in the clinical overview.

Since, however, there is obviously no plan of the Applicant to come forward with a proposal to extend the use of the product in the EU in the IBS-C indication to children, the details of this are not further discussed.

Results

The study was conducted at 33 sites in the US. Overall, 367 subjects were screened, and 69 subjects discontinued participation during the Screening Period. Of the subjects who entered the Pre-intervention Period, 108 subjects completed; the most frequent reason for study discontinuation during the Pre-intervention Period was screen failure (174 subjects).

Participant flow

The following table gives and overview on the participant flow:

Table 2: Disposition of Subjects (All Randomized Subjects; IBS-C population)

	Number (%) of Subjects		
	Linaclotide 145 µg N = 55	**Linaclotide 290 µg N = 53**	**Total N = 108**
Number of subjects treated	55 (100.0)	53 (100.0)	108 (100.0)
Double-Blind Study Intervention Period			
Number of subjects completed Double-Blind Intervention Period	52 (94.5)	46 (86.8)	98 (90.7)
Number of subjects discontinued from Double-Blind Intervention Period	3 (5.5)	7 (13.2)	10 (9.3)
Reasons for Discontinuation from Double-Blind Intervention Period			
Lack of efficacy	0 (0.0)	1 (1.9)	1 (0.9)
Withdrawal by subject	1 (1.8)	5 (9.4)	6 (5.6)
Lost to follow-up	1 (1.8)	0 (0.0)	1 (0.9)
Physician decision	1 (1.8)	0 (0.0)	1 (0.9)
Other	0 (0.0)	1 (1.9)	1 (0.9)
Related to COVID-19	1 (1.8)	0 (0.0)	1 (0.9)
Number of subjects signed informed consent for extension Study LIN-MD-66	45 (81.8)	36 (67.9)	81 (75.0)
Number of subjects completed study	50 (90.9)	46 (86.8)	96 (88.9)
Number of subjects discontinued from study	5 (9.1)	7 (13.2)	12 (11.1)

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

An additional 8 subjects were enrolled to replace the 8 subjects that were incorrectly randomized due to not meeting the abdominal pain criterion. The 8 incorrectly randomized subjects were excluded from the efficacy analyses but were included in the safety analyses. A further 2 patients were identified with major protocol violation when taking prohibited concomitant medication.

The analysed populations are given in the following table:

Table 3: Analysis Populations

Table 5. Analysis Populations

Population	Number of Subjects		
	Linaclotide 145 µg	Linaclotide 290 µg	Total
Screened Population, N	-	-	367
Randomized Population, N	55	53	108
Modified Intent-to-Treat Population, N	53	47	100
Safety Population, N	55	53	108

Screened Population = all subjects who underwent the Screening Visit (Visit 1) and received a subject identification number.

Randomized Population = all subjects in the Screened Population who were randomized to a study intervention group.

Modified Intent-to-Treat Population = all subjects in the Randomized Population who received at least 1 dose of double-blind study intervention, excluding 8 subjects due to significant noncompliance with the study protocol and/or an electronic clinical outcome assessment issue related to the inclusion criterion.

Safety Population = all subjects in the Randomized Population who took at least 1 dose of double-blind study intervention.

Cross-reference: Table 14.1-3.1, SAP Appendix 16.1-9.1

Assessor's comment:

The mITT population obviously excludes the erroneously included patients from the primary efficacy analysis, which is not in accordance with the ITT principle and would not be acceptable in a confirmatory study. In the context of this study, this is just noted.

Recruitment

The study started with the first patient visit on 02 December 2020 and ended with the last subject last visit on 29 May 2024.

Baseline data

The following table summarises the main baseline characteristics of the mITT population:

Table 4: Demographics, mITT Population

	Number of Subjects		
	Linaclotide 145 µg N = 53	Linaclotide 290 µg N = 47	Total N = 100
Age (years)			
Mean (SD)	12.7 (3.19)	12.6 (2.80)	12.6 (3.00)
Median	13.0	13.0	13.0
Min, Max	7, 17	7, 17	7, 17
Age group, n (%)			
7–11 years of age	22 (41.5)	18 (38.3)	40 (40.0)
12–17 years of age	31 (58.5)	29 (61.7)	60 (60.0)
Sex, n (%)			
Male	23 (43.4)	16 (34.0)	39 (39.0)
Female	30 (56.6)	31 (66.0)	61 (61.0)
Race, n (%)			
White	38 (71.7)	32 (68.1)	70 (70.0)
Black or African American	13 (24.5)	11 (23.4)	24 (24.0)
Asian	2 (3.8)	1 (2.1)	3 (3.0)
Multiple[a]	0 (0.0)	1 (2.1)	1 (1.0)
Missing	0 (0.0)	2 (4.3)	2 (2.0)
Ethnicity, n (%)			
Hispanic or Latino	18 (34.0)	14 (29.8)	32 (32.0)
Not Hispanic or Latino	35 (66.0)	33 (70.2)	68 (68.0)

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

Overall, the mean body mass index was 21.92 kg/m2 in the mITT Population. The mean SBM frequency rate (SBMs/week) was 1.303 and the mean CSBM frequency rate (CSBMs/week) was 0.449.

The most common (≥ 5% overall) medical and surgical history ongoing at screening by MedDRA (version 27.0) PT in the Safety Population were seasonal allergy (13.9%), attention deficit hyperactivity disorder (11.1%), asthma (8.3%), anxiety (6.5%), dysmenorrhea (6.2%), insomnia (5.6%), gastroesophageal reflux disease (5.6%), and migraine (5.6%)

The most frequently (≥ 5% overall) reported concomitant medication classes in the Safety Population were centrally acting sympathomimetics (10.2%), propionic acid derivatives (9.3%), selective beta-2-adrenoreceptor agonists (7.4%), and piperazine derivatives (7.4%)

Efficacy results

Primary endpoint evaluation:

The proportion of pediatric subjects achieving response on the primary endpoint was similar between both linaclotide treatment groups, 22.6% in the linaclotide 145 µg treatment group and 23.4% in the linaclotide 290 µg treatment group.

Based on the determination that IBS-C signs and symptoms and patient response to linaclotide treatment are similar between adult and pediatric populations, the primary statistical analysis was comprised of a partial extrapolation approach utilizing a Bayesian method. Following this approach, information was borrowed from the adult IBS-C population in a Phase 2b study MCP-103-202 and Phase 3 registration studies LIN-MD-31 and MCP-103-302.

Two statistical analyses within the Bayesian framework were conducted. First, the 2.5th percentile for each effective sample size was calculated and compared to the prespecified 18% threshold (the upper bound of 95% CI of the adult linaclotide response rate estimate from the meta-analysis). Superiority was to be claimed if the 2.5th percentile exceeds 18%. Second, the probability that the responder rate of linaclotide is > 18% was also calculated.

The proportion of responders in both treatment groups was numerically higher than the prespecified thresholds of 18% and 16% (the point estimate of adult placebo response rate estimated from the meta-analysis). When compared to the pre-specified threshold of 18%, statistical superiority was not demonstrated in linaclotide 145 µg or 290 µg treatment groups based on the Bayesian analysis when borrowing adult linaclotide subject data ranging from 6 to 18 subjects.

Table 5: Primary Efficacy Analysis, Proportion of Subjects with 6/12 Weeks APS (Abdominal Pain and SBM) + 2 Responder (mITT Population)

	Linaclotide 145 µg N = 53		**Linaclotide 290 µg N = 47**	
Responder rate, n/N1 (%)	12/53 (22.6)		11/47 (23.4)	
	2.5th Percentile[a]	Probability > 18%[a]	2.5th Percentile[a]	Probability > 18%[a]
w = 0.0067	14.3	87.2%	14.5	88.9%
w = 0.008	14.6	88.5%	14.8	90.1%
w = 0.010	15.0	90.2%	15.3	91.7%
w = 0.012	15.5	91.7%	15.7	93.0%
w = 0.014	15.9	93.0%	16.2	94.1%
w = 0.016	16.3	94.1%	16.6	95.1%
w = 0.018	16.6	95.0%	17.0	95.9%
w = 0.02	17.0	95.8%	17.4	96.6%

a. Lower 2.5th percentile and probability are calculated from the posterior Beta(X + w*a, N - X + w*b) distribution, where a = 340 and b = 550.

Five supplemental/sensitivity analyses were performed to assess the robustness of the Bayesian analysis on an observed-cases approach. These analyses were consistent with the primary analysis.

Supplemental/sensitivity analysis 4 assessed the effect of missing eDiary data and supported achieving statistical significance for the primary efficacy endpoint, above the pre-specified threshold of 18%, when missing weekly SBM or abdominal pain scores were imputed using multiple imputation assuming missing at random. The APS+2 responder rates were 34.1% (95% CI: 20.8%-47.4%) and 38.9% (95% CI: 23.8%-54.0%) in the linaclotide 145 µg and 290 µg treatment group, respectively.

Additional post-hoc anlayses were conducted to evaluate the impact of varying the original requirement of twice daily eDiary entries, for a minimum of 4 days in an analysis week, to be considered as a responder. Given the frequency of subjects missing either the morning or the evening eDiary entry in a 24-hour period, and to enhance utilization of all the available eDiary data collected, the first posthoc analysis required the subject to have at least 8 completed eDiary entries in the analysis week (either

morning or evening) to be considered a responder. Given that daytime symptoms (captured in the evening eDiary entries) are the most clinically relevant to IBS-C, a diagnosis not characterized by night-time symptoms, the second post-hoc analysis required the subject to have at least 4 completed evening eDiary entries in the analysis week to be considered a responder.

The results from both analyses demonstrated statistical superiority when compared to the pre-specified threshold of 18%, based on the Bayesian analysis when borrowing adult linaclotide subject data ranging from 6 to 18 subjects and the frequentist approach, comparing the lower bound of the 95% CI with the prespecified threshold of 18%.

Secondary endpoints:

The results for the evaluation of the secondary endpoints are given in the following table:

Table 6: Secondary Efficacy EndPoint Analyses (mITT Population)

Endpoint	Linaclotide 145 µg N = 53		Linaclotide 290 µg N = 47	
12-week SBM frequency rate, change from baseline	**Baseline**	**Change from baseline**	**Baseline**	**Change from baseline**
Mean (SD)	1.339 (0.8396)	2.347 (3.3335)	1.263 (0.8978)	2.747 (2.8861)
Median	1.448	1.482	1.448	1.555
Q1, Q3	0.483, 1.931	0.469, 2.968	0.483, 1.931	0.802, 4.129
Min, Max	0.00, 2.90	-2.64, 18.39	0.00, 2.90	-1.54, 10.95
n[a]	53	53	47	47
12-week abdominal pain based on morning and evening assessments, change from baseline	**Baseline**	**Change from baseline**	**Baseline**	**Change from baseline**
Mean (SD)	1.944 (0.7674)	-0.837 (0.9313)	1.920 (0.8409)	-0.837 (0.8809)
Median	1.821	-0.942	1.571	-0.798
Q1, Q3	1.300, 2.567	-1.310, -0.396	1.250, 2.633	-1.252, -0.229
Min, Max	0.87, 4.00	-2.83, 2.76	0.87, 4.00	-3.39, 0.78
n[a]	53	53	47	47
12-week stool consistency, change from baseline	**Baseline**	**Change from baseline**	**Baseline**	**Change from baseline**
Mean (SD)	2.460 (0.9490)	0.979 (1.2900)	2.792 (1.0734)	1.358 (1.1288)
Median	2.333	1.125	2.600	1.323
Q1, Q3	2.000, 3.000	0.114, 1.980	2.000, 3.167	0.690, 2.299
Min, Max	1.00, 6.00	-1.90, 3.52	1.00, 5.25	-1.86, 3.60
n[a]	47	47	39	39
6/12 weeks SBM + 2 responder[b]				
Responder rate, n/N1 (%)		16/53 (30.2)		14/47 (29.8)
6/12 weeks abdominal pain responder[c]				
Responder rate, n/N1 (%)		26/53 (49.1)		20/47 (42.6)

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

b. A weekly SBM + 2 responder is defined as an increase of at least 2 in the SBM weekly rate from baseline during that study intervention week. A 6/12 weeks SBM + 2 responder is defined as meeting the weekly SBM + 2 responder criteria for at least 6 out of the 12 weeks of the study intervention period. A subject had to have at least 4 completed eDiary days (completed both morning [i.e., nighttime symptoms] and evening eDiary entries [i.e., daytime symptoms] on the same day) in the analysis week to be

considered as a responder for that week and otherwise, was considered as non-responder for that week. Efficacy responses following onset of dose de-escalation are not included in the analysis.

c. A weekly abdominal pain responder is defined as a decrease of at least 30% in the mean abdominal pain score (combination daytime and nighttime) from baseline during that study intervention week. A 6/12 weeks abdominal pain responder is defined as meeting the weekly abdominal pain responder criteria for at least 6 out of the 12 weeks of the study intervention period. A subject had to have at least 4 completed diary days in the analysis week to be considered as a responder for that week and otherwise, was considered as non-responder for that week. Efficacy responses following onset of dose de-escalation are not included in the analysis.

Assessor's comment:

The SAP did include the meta-analysis for the three adult studies envisaged to form the basis of the estimation of the placebo responder rate. The studies MCP-103-202, MCP-103-302, and LIN-MD-31, a meta-analysis was conducted to obtain an estimate for adult placebo effect related to 6/12 weeks APS + 2 responder rate. The estimated 6/12 Weeks APS + 2 responder rate for placebo was 0.16 and upper bound of 95% confidence interval (CI) of the placebo responder rate was 0.18. While it is unknown how the MAH calculated the responder rates in the dose-finding study MCP-103-202 (since responder type evaluations were not included in the data included in the EPAR), the IBS-relief responder rates for the study LIN-MD-31 are given as 37% for linaclotide, and 18.5% for placebo, and with 37.2% and 16.9% for study MCP-103-302. The difference between the linaclotide responder rates in adults and paediatric patients is obvious and rather prominent. It could, however, be speculated that it is attributable to the incomplete diary data, showing the APS+2 responder rates increased to 34.1% (95% CI: 20.8%-47.4%) and 38.9% (95% CI: 23.8%-54.0%) in the linaclotide 145 µg and 290 µg treatment group, respectively, when a multiple imputation strategy was used for the missing diary entries. However, the question whether a comparable efficacy could be concluded in comparison to adults will remain unresolved since this is only an explorative analysis within an explorative study and no justification is given that the imputation method used can be considered adequate.

For the secondary endpoints, the comparisons between the two doses did also not show relevant differences, and, due to the lack of a concomitant placebo treatment, cannot really be assessed for their clinical relevance.

Efficacy conclusions as presented by the Applicant:

The proportion of paediatric subjects achieving response on the primary endpoint (6/12 weeks APS (abdominal pain and SBM) + 2 responder) was 12/53 (22.6%) and 11/47 (23.4%) in the linaclotide 145 µg and 290 µg treatment groups, respectively.

The proportion of responders in both treatment groups was numerically higher than the pre-specified thresholds of 18% (the upper bound of 95% CI of the adult linaclotide response rate estimate from the meta-analysis) and 16% (the point estimate of adult placebo response rate estimated from the meta-analysis), statistical superiority, however, was not met for the 18% threshold.

Five pre-specified supplemental/sensitivity analyses were performed to assess the robustness of the Bayesian analysis on an observed-cases approach and were consistent with the primary efficacy results. Of the 5 pre-specified analyses, supplemental/sensitivity analysis 4 (multiple imputation of missing eDiary data), achieved a statistically significantly higher responder rate than the pre-specified threshold of 18%.

Assessor's comment:

While the endpoints used in the studies in the adult population and in this study may not be fully comparable, the placebo response rates do in fact correspond to the thresholds given in the SAP. However, whether based on these data a conclusion on similar response in adults and children would be adequate, is at least questionable, since the factual responder rates for active treatment were

relevantly higher in adults than those observed in the paediatric population. The question on clinical relevance would immediately need to be raised, in case this study was intended to form the basis of a submission for the extension of the indication IBS-C to the paediatric population.

Since, however, the primary objective was not achieved, a further discussion on the appropriateness on the inclusion criteria, the statistical methods applied, the extrapolation exercise that formed the basis of the analysis, as well as the study conduct, and evaluation, does not seem to be necessary.

Based on the submitted study report, the study, while being inconclusive, is accepted not to be used to change the current licensing status of the compound, or at least not adequate to form the basis of approval of the paediatric IBS-C indication.

Safety results

The overall number and percentage of subjects reporting AEs is given in the following table:

Table 7: Overall Number (%) of Subjects with AEs (Safety Population)

	Number (%) of Subjects		
TEAE Category	**Linaclotide 145 µg N = 55 n(%)**	**Linaclotide 290 µg N = 53 n(%)**	**Total N = 108 n(%)**
All TEAEs	11 (20.0)	8 (15.1)	19 (17.6)
Treatment-related TEAE	3 (5.5)	3 (5.7)	6 (5.6)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)
TESAE	0 (0.0)	0 (0.0)	0 (0.0)
Treatment-related TESAE	0 (0.0)	0 (0.0)	0 (0.0)
TEAE Leading to Study Treatment Discontinuation from Study	0 (0.0)	0 (0.0)	0 (0.0)

Cross-Reference: Table 14.3-2.1

The number and percentage of subjects who reported TEAEs (occurring in ≥ 2% of subjects in any treatment group) by MedDRA PT in the Safety Population is presented in the following table. Diarrhoea rates were similar between the 145 µg and 290 µg linaclotide treatment groups.

Table 8: TEAEs Occurring in ≥ 2% of Subjects in Any Treatment Group by MedDRA PT (Safety Population)

PT	Number (%) of Subjects: Linaclotide 145 µg N = 55 n(%)	Number (%) of Subjects: Linaclotide 290 µg N = 53 n(%)
Subjects with at least one TEAE	11 (20.0)	8 (15.1)
Diarrhoea	4 (7.3)	4 (7.5)
Abdominal pain	2 (3.6)	0 (0.0)
Constipation	2 (3.6)	0 (0.0)
Polycystic ovarian syndrome[a]	1 (3.2)	0 (0.0)

a. Event specific to female; gender-specific percentages are relative to the number of subjects with the corresponding gender.

Cross-Reference: Table 14.3-2.2.1

The number and percentage of subjects who reported treatment-related TEAEs by MedDRA SOC and PT in the Safety Population is presented in the next table:

Table 9: Treatment-related TEAEs: Number (%) of Subjects by MedDRA SOC and PT (Safety Population)

SOC PT	Number (%) of Subjects: Linaclotide 145 µg N = 55 n(%)	Number (%) of Subjects: Linaclotide 290 µg N = 53 n(%)
Subjects with at least one treatment-related TEAE	3 (5.5)	3 (5.7)
Gastrointestinal disorders	3 (5.5)	3 (5.7)
Diarrhoea	3 (5.5)	3 (5.7)
Abdominal pain	1 (1.8)	0 (0.0)
Constipation	1 (1.8)	0 (0.0)
Nausea	1 (1.8)	0 (0.0)
Investigations	1 (1.8)	0 (0.0)
Weight decreased	1 (1.8)	0 (0.0)

Cross-Reference: Table 14.3-2.4.1

All TEAEs reported were considered mild or moderate in severity. No severe TEAEs were reported in the linaclotide treatment groups.

There were no deaths or SAES during the study, and no subjects experienced AEs leading to discontinuation of the study drug.

No 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 diarrhea) were reported during the study.

The course off clinical laboratory evaluations was unremarkable.

The reporting of vital signs did not include unexpected changes. the number of subjects with a potentially clinically significant change is reported in more detail and shows that there were 1 case with a decrease in standing supine systolic blood pressure (between 10 and 20 mmHg), 3 cases of a standing-supine diastolic blood pressure change betw3een -10 and +10, 1 patient with an increase in pulse rate to higher or equal than 140 (with an increase in 15 or more). Moreover, there were 11 patients with an increase between 10 and 20 in the standing-supine pulse rate. Weight decrease of equal to or more than 5% was observed in 5 patients, while a weight increase equal to or more than 5% occurred in 28 patients.

Safety conclusion as of the MAH:

Linaclotide was well tolerated across 7 to 17-year-olds with IBS-C. There were no reported deaths, TESAEs, or AESIs during the study. All TEAEs reported were considered mild or moderate in severity, with none leading to discontinuation of study drug.

Overall, no new safety signals were identified. The safety profile of linaclotide in pediatric subjects is consistent with prior pediatric and adult studies with linaclotide.

Assessor's comment:

The overall safety results with regard to AEs appears to be unremarkable and show a similar AE profile as in adults. Especially, there appears to be no relevant increase in rates of diarrhoea as compared to adults, and there is no dose-response relationship with regard to occurrence of diarrhoea. In a submission intended to extend treatment to children, it would be expected that a more elaborate discussion of the case with blood pressure decrease, pulse increase, as well as weight decrease would be included. For the time being, this is noted, and the MAH made aware on this fact for any potential future submission regarding the paediatric population.

2.3.3. Discussion on clinical aspects

The MAH has submitted the results of one (sub)-study in paediatric patients aged 7-17 years in the indication IBS-C. This study LIN-MD64 was a randomised, partially placebo-controlled study of linaclotide in both FC and IBS-C populations, comparing the two doses of 145µg and 290 µg in the IBS-C subpopulation. The results of the study in the FC population have previously been evaluated.

The IBS-C part of the study was conducted as a double-blind study in an explorative manner only with no pre-determined hypothesis and an arbitrary number of IBS-C subjects included. The statistical analysis performed was nevertheless pre-planned and was done using Bayesian methodology and compared the responder rates achieved with the meta-analytic placebo rate from the adult population, setting the pre-determined placebo responder rate to 18%.

Patients with IBS-C were included based on "modified Rome III criteria" which appear to be partly outdated comparing the criteria with the currently available Rome IV criteria. Also, subtyping of IBS in paediatric patients is not part of the Rome consensus, and therefore, the diagnosis of IBS-C is somewhat subjective only.

The study was conducted with 108 patients included of which 100 only were included in the evaluation, and the analysis was mainly based on the evaluation of responder type endpoints with the combined abdominal pain and change in bowel movement frequency endpoint. The primary evaluation showed that the study could not achieve its goal with demonstrating superiority above the assumed 18% placebo responder rates, achieving 22.6% and 23.4% responder rates in the two treatment groups. There were some additional analyses showing that the result was somewhat dependent on the completeness of the diary data, indicating that the responder rates could be higher than just above

20%. However, with the primary results achieved, the effect above the (assumed) placebo rate appears to be marginal and not clinically relevant.

3. Rapporteur's overall conclusion and recommendation

The MAH has submitted additional data from study LIN-MD-64 of which the data for the FC population had previously been presented. The submitted additional study report included the data for the paediatric population diagnosed with IBS-C according to modified Rome-III criteria.

The character of the study can be considered to be overall exploratory in nature, although it is obviously intended to form the basis of approval for the extension of the IBS-C indication to the paediatric population in the US. However, several elements of the approach used, including the selection of the patient population, the comparator groups, the Bayesian approach to statistics, as well as the results achieved question the suitability of the study to form the basis of such a claim.

However, the MAH has stated that they do clearly not intend to change any details of the current licensing status. This is acceptable with regard to not claiming a paediatric indication. However, the EU PI does usually also include information on paediatric data in case incomplete, or unsuccessful development programmes in children have been conducted and can be considered relevant to the prescriber. Usually, a few sentences are included in the Chapter 5.1 and 5.2 to characterise the results of clinical studies, and the PK and PD properties in children (and their difference to adults) even if the treatment of children is (still) not recommended.

It is understood that the mainstay of the paediatric development programme has been conducted in children with FC, and the Applicant is currently in the process of re-considering the strategy for marketing of the product for CC/FC both in adults as well as in children. While therefore, the non-inclusion of any data on FC in children in a product's PI which is licensed for IBS-C only can be considered acceptable, this might not be the case when results are available in children for the licensed indication in adults.

At request, the MAH has declared that a proposal will be forwarded to the EMA in 2026 to include information on paediatric patients with IBS into the EU Product Information with the justification that the planned labelling changes for the US product are intended to be awaited before a proposal can be put forward to EMA. While this is overall a rather weak justification, the one year delay is finally be accepted considering the overall (long) history of the generation of the paediatric data.

☒ Fulfilled:

No further action required, however further data are expected in the context of a variation.

The MAH has stated that a variation submission will be done in 2026. While this date appears relatively late, the proposal is finally accepted. The MAH is reminded that the legal requirement for submitting a variation is 18 months after presentation of the data. Since submission of 002490-P46-020 was dated 12-11-2024, the latest submission date will be 11-05-2026.

4. Request for supplementary information

Based on the data submitted, the MAH should address the following questions as part of this procedure:

The MAH is requested to elaborate on the possibility and need to include information on the use of the compound in the paediatric population in the SmPC, referring to data collected with regard to PK, PD, and clinical efficacy (as submitted in study LIN-MD64). A proposal should be brought forward for a

future variation with potential changes in the Chapters 4.2 (and potentially the corresponding chapter in the PL), 5.1 and 5.2 of the SmPC.

In case the MAH has no intent to include this information in the PI, a thorough justification for not doing so should be provided.

MAH responses to Request for supplementary information

AbbVie agrees to include information on the use of the compound in the paediatric population in the EU Summary of Product Characteristics (and the corresponding sections in the package leaflet, as applicable), referring to data collected regarding pharmacokinetics, pharmacodynamics, and clinical efficacy (as submitted in study LIN-MD-64) but proposes to defer the variation submission to update the EU Product Information to 2026.

At the time of this response, AbbVie is in the process of submitting the results of studies (including Study LIN-MD-64) conducted in paediatric patients with irritable bowel syndrome with Constipation (ages 7-17 years) to FDA as a Supplemental New Drug Application (sNDA), with a targeted submission in 2025. The sNDA will contain the proposed United States Prescribing Information (USPI) based on data available from Study LIN-MD-64. Given the planned labelling communication with the FDA, AbbVie proposes deferring submission of the EU variation application to update the EU Product Information, addressing the EMA's comment until we receive the final sNDA and USPI approval.

Assessment of the MAH response:

The MAH has principally agreed to include information on the use of the compound in the paediatric population into the Product Information based on the data submitted with the study LIN-MD-64. However, it is proposed to defer the submission of such a proposal until 2026.

This appears to be a rather long time to elapse between the availability of the data and the time of making the results visible to prescribers in Europe.

It is, on the other hand, understood that the labelling communication with the FDA may have influence on the proposal to be made in the EU, and that the final US label (USPI) is intended to be awaited before a submission in the EU should take place.

The generation of data in the paediatric IBS population was not part of the EU PIP and is therefore outside the legal obligations of the MAH. Considering the proposal of the MAH and its justification, and the fact that anyhow the submission of the data took 12 years already from the date of licensing of the compound, the proposal of the MAH to submit a proposal for including the paediatric IBS data into the EU Product Information can be accepted.

Overall conclusion:

Issue resolved. The MAH is requested to submit a proposal for including information on paediatric patients with IBS into the EU PI in 2026.

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Nonclinical studies

None

Clinical studies

Product Name: Constella Active substance: Linaclotide

Study title	Study number	Date of completion	Date of submission of final study report
Phase 3, Multicenter, Randomized, Double-blind, Parallel-group, Safety and Efficacy Study of Linaclotide in Pediatric Participants, Ages 6 to 17 Years, with Irritable Bowel Syndrome with Constipation (IBS-C) and of Linaclotide versus Placebo in Pediatric Participants with Functional Constipation (FC).	LIN-MD-64	29.05.2024 (lplv)	12 November 2024