29 May 2019
EMA/260767/2019
Human Medicines Evaluation Division

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

Constella

linaclotide

Procedure no: EMEA/H/C/002490/P46/013

Note

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

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

Table of contents

1. Introduction 3

2. Scientific discussion 3

2.1. Information on the development program 3
2.2. Information on the pharmaceutical formulation used in the study.....3
2.3. Clinical aspects 3
2.3.1. Introduction.....3
2.3.2. Clinical study LIN-MD-62 4
2.3.3. Discussion on clinical aspects 19

3. Rapporteur's overall conclusion and recommendation 19

Fulfilled: 20

4. Additional clarification requested 20

Annex. Line listing of all the studies included in the development program 21

1. Introduction

On 13th March, 2019, the MAH submitted one completed paediatric study for Constella, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview, dated 26th February 2019 has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that LIN-MD-62 (A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Safety and Efficacy Study of a Range of Linaclotide Doses Administered Orally to Children, Ages 6 to 17 Years, Who Fulfill Modified Rome III Criteria for Child/Adolescent Functional Constipation is a standalone study.

LIN-MD-62 is Measure 3 of the agreed PIP EMEA-000927-PIP01-10-M03. The PIP consists of 9 measures in total, of which 7 concern clinical measures. The measure 3 is the first step mentioned in the PIP.

2.2. Information on the pharmaceutical formulation used in the study

The pharmaceutical formulation used in the study were either capsules for oral administration which contain 28, 36, 72, or 145 µg linaclotide or oral solution containing 9 or 36 µg linaclotide per ml, used in doses of 9, 18, 72, or 145 µg linaclotide (=doses up to 4 ml).

2.3. Clinical aspects

2.3.1. Introduction

Marketing authorization for Constella was granted by the EMA on 26 Nov 2012 for the treatment of moderate to severe IBS-C in adults. The indication functional constipation is licensed in other regions of the world, but not in the EU. The only pharmaceutical form and strength available are capsules with a content of 290 µg linaclotide.

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 were made to the PI.

Assessor's comment:

The submitted report appears to have limited importance for the current license of the substance of the product Constella, which is licensed for a different indication (IBS-C instead of FC), as well as a higher dose (290 µg instead of 145 µg, as licensed for FC in other regions of the world).

The PIP EMEA-000927-PIP01-10-M03 did indeed only include measures and studies to develop the compound in the treatment of FC for children, but not in IBS. Consequences with regard to labelling the product currently licensed in the EU would therefore be rather guided by results on the safety, but not by results on efficacy. This AR therefore includes only the most important features and results of the study.

The conclusion of the applicant is therefore agreed with from a formal point of view, pending the evaluation of safety from the submitted study (see below).

The MAH submitted one final report(s) for:

- LIN-MD-62: A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Safety and Efficacy Study of a Range of Linaclotide Doses Administered Orally to Children, Ages 6 to 17 Years, Who Fulfill Modified Rome III Criteria for Child/Adolescent Functional Constipation.

2.3.2. Clinical study LIN-MD-62

Clinical study number and title

Study LIN-MD-62 is termed: A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Safety and Efficacy Study of a Range of Linaclotide Doses Administered Orally to Children, Ages 6 to 17 Years, Who Fulfill Modified Rome III Criteria for Child/Adolescent Functional Constipation (FC).

Description

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, safety and efficacy dose-ranging study in pediatric participants with chronic constipation.

Methods

Objective(s)

The objectives of this study were to evaluate the dose response, safety, and efficacy of 4 weeks of treatment with 1 of 3 linaclotide doses (A, B, or C) or 145 µg (as an exploratory objective in adolescent participants 12 to 17 years of age using the approved adult dose) compared with placebo in pediatric participants 6 to 17 years of age who fulfill modified Rome III criteria for pediatric FC.

Assessor's comment:

No specific comment on objectives, which appear adequate. This is obviously an explorative study, and a treatment duration of 4 weeks in children with FC can thus be considered adequate.

Study design

This clinical study was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, safety and efficacy study comparing 1 of 3 linaclotide doses (A, B, and C) or linaclotide 145 µg (only participants 12 to 17 years of age) with placebo in pediatric participants 6 to 17 years of age with a diagnosis of FC based on modified Rome III Child/Adolescent Criteria (ie, who fulfill modified Rome III criteria for pediatric FC). The study was to include a total of 6 visits and was approximately 9 to 12 weeks in duration.

The study included a 2-week screening period, which tested evavluated the eligibility criteria, and tested the ability of the potential participants (those in the age 12-17 years) to swallow the capsule formulation. During the screening period, the participants and all caregivers also received information about lifestyle modifications (increased water and fiber intake, increased physical activity, and consistent toileting habits). A minimum of a 2-week interval between discussing the lifestyle modifications during the Screening Period and the participant's entry into the Pretreatment Period was required. The following pre-treatment period of 1 week mainly consisted of making participants and cargivers familiar with the use and handling of the e-diary (including clarification if the patient or the

caregiver would handle the device). Additionally, caregivers of participants 6 to 11 years of age were trained on completing the observer-completed global items once weekly on the e-diary. Participants and caregivers were provided instructions regarding fasting to ensure the participants had fasted for at least 2 hours before receiving their first dose of study treatment at the study site during the Randomization Visit (Visit 3/Day 1).

The double blind treatment period was of 3 weeks duration and included 3 study visits (one visit at first drug intake, one after two weeks, and one after the end of treatment).

A post-treatment period of at least 1 week duration followed with the fainal end-of-study visit scheduled at least 7 days after the week 4 visit.

Randomization was stratified by age group (6 to 11 or 12 to 17 years of age) with a minimum of 40% of participants within each age group. Participants 6 to 11 years of age were randomized to linaclotide doses (A, B, or C) or placebo in a 1:1:1:1 allocation. Participants 12 to 17 years of age were randomized to linaclotide doses (A, B, or C, or the approved adult dose, 145 µg) or placebo in a 1:1:1:1:1 allocation.

Dosages were given as follows:

- Participants 6 to 11 years of age (weight 18 to < 35 kg)

o Dose A: 9 µg
o Dose B: 18 µg
o Dose C: 36 µg

- Participants 6 to 11 years of age (weight ≥ 35 kg) or 12 to 17 years of age

o Dose A: 18 µg
o Dose B: 36 µg
o Dose C: 72 µg

- Approved adult dose: 145 µg (for participants 12 to 17 years of age only)

Study population /Sample size

Approximately 160 participants were planned to be enrolled with a minimum of 40% of participants per age group (6 to 11 years and 12 to 17 years). A total of 173 were enrolled and randomized to receive 1 of the 3 linaclotide doses. All were included in the intent-to-treat (ITT) and safety populations. The following table shows the distribution of the patients in the different dosing groups:

Table 1: Number of participants (planned and enrolled) in the dose-groups:

	Placebo	Dose A	Dose B	Dose C	145 µg (12 to 17 years of age only)
Planned	35	35	35	35	14 - 19
Enrolled	41	36	41	39	16

Treatments

Patients received identically appearing bottles containing 18 µg, 26 µg, 72 µg, or 145 µg capsules, and 9µg/ml or 36 µg/ml oral solution or matching placebo capsules or oral solution. For the doses administered: See above.

Rescue medication was provided with senna or bisacodyl (oral or rectal). The dosing scheme is again shown in the following table:

Table 2: Double-blind dosing regimen:

		4-Week Treatment Period			
Age Group	Weight	Linaclotide Dose A	Linaclotide Dose B	Linaclotide Dose C	Approved Adult Dose
Participants 6 -11 years[a]					
	18 to < 35 kg	9 µg	18 µg	36 µg	—
		placebo	placebo	placebo	—
	≥ 35 kg	18 µg	36 µg	72 µg	—
		placebo	placebo	placebo	—
Participants 12 -17 years[b]					
		18 µg	36 µg	72 µg	145 µg[c]
		placebo	placebo	placebo	placebo

Outcomes / endpoints

The primary efficacy assessments used to determine the change from baseline in 4-week overall SBM frequency rate during the Treatment Period (primary efficacy endpoint) were the occurrences of "Satisfactory Bowel Movements" (SBMs) based on the assessment of overall BM frequency and rescue medication use as recorded in the e-diary. A SBM was defined as a BM that occurred in the absence of laxative, suppository, or enema use on the calendar day of the BM or the calendar day before the BM. Participants reported their BM frequency (the number of BMs during the corresponding e-diary interval period) and their use of rescue medication by responding to corresponding questions in the morning and evening e-diary. The submitted study report also states that the e-diary was developed and validity for content validity in the anticipated age group.

The following 6 secondary endpoints were evaluated:

1. Abdominal Pain - Daytime: Participants rated their abdominal pain in the evening eDiary.

2. Stool Consistency (Pediatric Bristol Stool Form Scale [p-BSFS]): Stool consistency of each BM was based on the p-BSFS. Participants used the p-BSFS 7-point ordinal scale to rate their stool consistency for each BM in the morning and evening eDiary.

3. Straining With Bowel Movement: Participants assessed the degree of straining for each BM in the morning and evening eDiary .

4. Abdominal bloating - Daytime: Participants recorded their assessment of abdominal bloating in the evening eDiary.

5. CSBM/Incomplete Evacuation: A CSBM was an SBM that was associated with a sense of complete evacuation. Participants recorded their assessment of the sensation of incomplete evacuation for each BM in the morning and evening eDiary .

6. Fecal Incontinence - Daytime: Participants recorded their episodes of fecal incontinence in the evening eDiary following the implementation of Protocol Amendment 3.

A number of additional efficacy assessments were also included, assessing night-time abdominal pain, abdominal bloating, Quality of Life, global assessments (caregiver and patients), and responders.

The study also included the collection of blood samples at the randomisation visit (3 blood draws at 1-2 hours post-dose, at 3-4 hours post-dose, and at 6-8 hours post-dose) and at the two-week visit (one blood draw 8-24 hours post-dose).

Assessor's comment:

No further statements on the validation of the e-diary and the endpoint used (especially for the smaller children) are included. Usually, it would be expected that validation data on the methods used to assess the primary endpoint would be fully submitted. However, due to the limited relevance with regard to the current EU MA of the trial submitted, this is considered a minor issue.

Overall, the primary and secondary endpoints used appear to be adequate for the population envisaged.

Statistical Methods

For the primary efficacy endpoint, comparison between each linaclotide dose (Dose A, B, and C) and placebo was performed using an ANCOVA model with treatment and age group (6 to 11 or 12 to 17 years of age) as factors and baseline value as a covariate. Least squares means (LSMs) for each treatment group, differences in LSMs between each linaclotide treatment group (Dose A, B, and C) versus placebo, associated 2-sided 95% CIs) for these differences in LSMs, and the corresponding statistical test p-values were reported. Treatment-by-age group interaction was investigated as an exploratory analysis to assess the homogeneity of treatment effects across age groups. Sensitivity analyses (missing at random, not missing at random, imputing worse response for postbaseline missing response, and excluding participants impacted by e-diary malfunction issue to assess robustness of the primary analysis ANCOVA in the presence of missing data were performed

To understand the dose-response relationship, a test for linear dose-response trend was explored for the primary efficacy endpoint based on the ordinal dosing for the placebo and linaclotide Dose A, B, and C groups using orthogonal polynomial contrast. Further, dose-response trend (eg, quadratic trend) was explored if the linear trend was not clearly indicated. Cumulative distribution function plots were provided for primary efficacy endpoint by treatment group

The primary efficacy endpoint was also summarized descriptively within each age group by treatment group. For the summaries of the 6 to 11 years of age group, linaclotide doses (A, B, and C) and placebo were included. For the summaries of the 12 to 17 years of age group, linaclotide doses (A, B, and C), the adult approved dose 145 µg, and placebo were included.

The planned sample size was designed for the overall analysis of the placebo and the linaclotide A, B, and C dose groups, with 35 participants per treatment group (140 participants in total for the overall analysis). With inclusion of 14 to 19 participants who were 12 to 17 years of age for the linaclotide approved adult dose (145 µg), the planned sample size was approximately 160 participants. Based on the analyses of each previous linaclotide adult study (ie, including the 72, 145, and 290 µg doses in MCP-103-201, 145 and 290 µg in LIN-MD-01 and MCP-103-303, and 145 and 290 µg in LIN-MD-04) in CIC with the change from baseline in 4-week overall SBM frequency rate during the Treatment Period as the efficacy endpoint, the range of mean treatment differences between pooled linaclotide doses and placebo was 1.7 to 2.6 (approximately). The standard deviations were between 3.0 and 3.5 in those studies. Assuming the SBM response in the 6- to 17-year-old population was to be similar to the adult population, it was assumed that the treatment effect in this study would fall around the middle of the range (approximately 2.2) observed in the adult population. With a standard deviation of 3.2, the planned sample size of 35 participants per treatment group in this study would have had 80% power to detect treatment difference of 2.2 in the primary efficacy endpoint at the 5% level of significance (2-sided). With the observed common standard deviation of 3.2, the minimum observed treatment difference to achieve statistical significance would be about 1.5 (at 2-sided 5% level of significance with 35 participants per treatment group).

There were 4 populations used for analyses of data from this study as follows:

- The screened population included all participants who underwent the Screening visit (Visit 1) and received a participant identification number.

- The randomized population included all participants in the screened population who were randomized to a treatment group in the study.

- The safety population included all participants in the randomized population who took at least 1 dose of doubleblind study treatment.

- The ITT population consisted of all participants in the safety population who had at least 1 postbaseline entry on BM characteristic assessments that determined occurrences of SBMs (ie, BM frequency and rescue medication use).

Assessor's comment:

The analysis was appropriate to compare the three dose groups to placebo. However, no multiplicity adjustment was used. In any case, this appears irrelevant since no significant difference to placebo could be found. Furthermore, and this may be seen as more relevant in a pure dose finding study, a linear trend test based on the ordinal dosing was performed, with further testing of an additional quadratic term which investigates a potential deviation from the linear model. Another dose response model or the suitability on a linear model based on the ordinal dosing was not investigated or discussed. Although due to the results of the trend test and that on the quadratic term a different conclusion does not appear to be likely, the use of a different dose-response model (e.g. incorporating the age and weight group and other functional dose response relationship) may have been suited for further investigation. None of the secondary endpoint were investigated with respect to a linear dose response, which also does not appear to be relevant due the lack of a significant trend in the primary endpoint.

Results

Recruitment / Number analysed

471 participants were screened at 52 study centres (all in the United States). 97.7% of these entered the pre-treatment period after completion of the scrrening. Of the participants who entered the pre-treatment period, over 50% discontinued during the pre-treatment period. The most frequent reason for discontinuation during the pre-treatment period was screen failure (214 participants (45.4%)). The following table shows the numbers of patients screened, included in pre-treatment and reasons for exclusion, according to age range:

Table 3: Screening and pre-treatment completion and discontinuation

Period Disposition	6 to 11 Years (N = 276) n (%)	12 to 17 Years (N = 195) n (%)	Total (N = 471) n (%)
Screening			
Completed phase	251 (90.9)	162 (83.1)	413 (87.7)
Discontinued phase	25 (9.1)	33 (16.9)	58 (12.3)
Reason for phase discontinuation			
Screen failure	20 (7.2)	22 (11.3)	42 (8.9)
Adverse event	1 (0.4)	1 (0.5)	2 (0.4)
Withdrawal of consent	1 (0.4)	7 (3.6)	8 (1.7)
Lost to follow-up	1 (0.4)	3 (1.5)	4 (0.8)
Other	2 (0.7)	0	2 (0.4)
Pretreatment			
Completed phase	90 (32.6)	83 (42.6)	173 (36.7)
Discontinued phase	161 (58.3)	79 (40.5)	240 (51.0)
Reason for phase discontinuation			
Screen failure	147 (53.3)	67 (34.4)	214 (45.4)
Adverse event	0	1 (0.5)	1 (0.2)
Withdrawal of consent	7 (2.5)	5 (2.6)	12 (2.5)
Lost to follow-up	4 (1.4)	3 (1.5)	7 (1.5)
Site terminated by sponsor	1 (0.4)	0	1 (0.2)
Other	2 (0.7)	3 (1.5)	5 (1.1)

The overall recruitment and conduct of the trial was taking place between 3rd Novfembrer 2015 (first patient screened) and 29th May 2018 (last patietn completed).

As already displayed above, 173 participants were finally included, of which 93.6% completed thet traetment period. The most frequent reason for discontinuation durign the treatment period was withdrawal of consent (2.3%). 3 participants discontinued due to AEs. The overview on subject dispostions is shown in the following table:

Table 4: Participant Completion and discontinuation (randomised population):

Period Disposition	Placebo (N = 41) n (%)	LIN Dose A (N = 36) n (%)	LIN Dose B (N = 41) n (%)	LIN Dose C (N = 39) n (%)	LIN 145 µg (N = 16) n (%)	Total (N = 173) n (%)
Treatment Period						
Completed phase	39 (95.1)	34 (94.4)	39 (95.1)	36 (92.3)	14 (87.5)	162 (93.6)
Discontinued phase	2 (4.9)	2 (5.6)	2 (4.9)	3 (7.7)	2 (12.5)	11 (6.4)
Reason for phase discontinuation						
Adverse event	0	2 (5.6)	0	1 (2.6)	0	3 (1.7)
Withdrawal of consent	0	0	1 (2.4)	2 (5.1)	1 (6.3)	4 (2.3)
Lost to follow-up	1 (2.4)	0	0	0	0	1 (0.6)
Protocol violation	1 (2.4)	0	0	0	1 (6.3)	2 (1.2)
Other	0	0	1 (2.4)	0	0	1 (0.6)
Post-treatment Period						
Completed phase	40 (97.6)	35 (97.2)	39 (95.1)	37 (94.9)	15 (93.8)	166 (96.0)
Discontinued phase	0	1 (2.8)	0	0	0	1 (0.6)
Reason for phase discontinuation						
Withdrawal of consent	0	1 (2.8)	0	0	0	1 (0.6)

Baseline data

Across the placebo and linaclotide Dose A, B, and C treatment groups in the safety population, the mean age was 11.0 years. Overall (not including linaclotide dose 145 µg), 54.1% of participants were female and 45.9% of participants were male, and the majority were white (76.4%) and not Hispanic or Latino (77.1%). Mean body weight was 50.32 kg and mean BMI was 22.40 kg/m2.

In the 6 to 11 years of age group, mean weight was 37.01 kg and mean BMI was 20.03 kg/m2, with 57.8% of participants weighing between 18 to < 35 kg and 42.2% of participants weighing ≥ 35 kg at the Randomization visit (Visit 3). In the 12 to 17 years of age group, mean weight was 68.97 kg and mean BMI was 25.81 kg/m2 (Table 10–7). In both age subgroups, the other baseline characteristics (sex, race, and ethnicity) were similar to that observed for the overall safety population.

The baseline demographics in the different dose groups (with the exception o fthe 145 µg dose group) are displayed in the following table:

Table 5: Baseline demographics

Characteristic	Placebo (N = 41)	LIN Dose A (N = 36)	LIN Dose B (N = 41)	LIN Dose C (N = 39)	Total (N = 157)
Age (years)[a]					
Mean (SD)	10.7 (3.8)	10.9 (3.0)	11.0 (3.2)	11.3 (3.7)	11.0 (3.5)
Median	11.0	10.5	10.0	11.0	11.0
Min, Max	6, 17	6, 16	6, 17	6, 17	6, 17
Age group, n (%)					
6 to 11 years	23 (56.1)	21 (58.3)	26 (63.4)	20 (51.3)	90 (57.3)
12 to 17 years	18 (43.9)	15 (41.7)	15 (36.6)	19 (48.7)	67 (42.7)
Sex, n (%)					
Female	20 (48.8)	17 (47.2)	25 (61.0)	23 (59.0)	85 (54.1)
Male	21 (51.2)	19 (52.8)	16 (39.0)	16 (41.0)	72 (45.9)
Race, n (%)					
White	30 (73.2)	29 (80.6)	32 (78.0)	29 (74.4)	120 (76.4)
Other	11 (26.8)	7 (19.4)	9 (22.0)	10 (25.6)	37 (23.6)
Black or African American	10 (24.4)	7 (19.4)	9 (22.0)	8 (20.5)	34 (21.7)
American Indian or Alaska Native	0	0	0	1 (2.6)	1 (0.6)
Multiple[b]	1 (2.4)	0	0	1 (2.6)	2 (1.3)
Ethnicity, n (%)					
Hispanic or Latino	8 (19.5)	7 (19.4)	12 (29.3)	9 (23.1)	36 (22.9)
Not Hispanic or Latino	33 (80.5)	29 (80.6)	29 (70.7)	30 (76.9)	121 (77.1)
Weight (kg)					
Mean (SD)	47.66 (25.79)	52.92 (24.79)	49.64 (25.07)	51.44 (19.83)	50.32 (23.86)
Median	36.30	49.45	42.00	50.80	45.00
Min, Max	21.1, 136.5	21.7, 126.8	21.0, 132.0	18.4, 84.9	18.4, 136.5
Body mass index (kg/m^2)					
Mean (SD)	21.69 (6.84)	23.13 (7.24)	21.87 (7.02)	23.01 (4.89)	22.40 (6.53)
Median	19.04	21.23	19.98	23.31	20.51
Min, Max	14.6, 43.8	14.8, 45.8	14.6, 43.6	14.6, 32.5	14.6, 45.8

The 16 patients included into the 145 µg dose group had a mean age of 14.7 years, of which 6 were aged 12-13, and 10 aged 15-17. Both genders were represented by 50% of the participants, and the majority of the patients were white (68.8%), and "not Hispanic or latino" (75%). The mean weight was 72.2 kg, and the mean BMI 26.8 Kg/m2. No relevant difference could be detected in comparison to the other dose groups when restricting these to those aged 12-17 (data not shown separately).

Across all of the treatment groups, mean study treatment compliance was ≥ 96.46% during the4-week Treatment Period. Results were similar across the treatment groups in the 6 to 11 and 12 to 17 years of age groups within the safety population.

Across all of the treatment groups, mean compliance with completing the e-diary was ≥ 83.91% during the pre-treatment period, ≥ 72.62% in the Treatment Period, and ≥ 65.50% during the post-treatment Period. There was an issue with the e-diary malfunction at a certain time-point during the trial: A total of 14 randomized participants who had eligibility reports were impacted by this issue. Participants who were impacted by the e-diary malfunction issues and were not able to complete the evening eDiary during the affected period were considered noncompliant for the days that were impacted.

A second issue with the e-diary malfunction was due to incorrect programming by e-diary vendor. wherein weekly participant-completed questions were not available for 51 participants in the 6 to 11 years of age group if the sites selected the interviewer administered format mode of e-diary administration. In addition, interviewer-completed weekly questions were made available to 5 participants in the 12 to 17 years of age group, which was inconsistent with the protocol.

Efficacy results

For the primary and key secondary endpoints, none of the 3 linaclotide doses indicated clear improvement over placebo (p-value ≥ 0.1502) based on the ITT population. However, a numerical trend toward efficacy at the higher doses was observed for the primary endpoint of change from

baseline in 4-week overall SBM frequency rate (SBMs/week). The main results of the study are displayed in the following table:

Table 6: Key efficacy results (ITT population)

Parameter Timepoint	Statistic	Placebo N = 41	LIN Dose A (Low) N = 36	LIN Dose B (Medium) N = 41	LIN Dose C (High) N = 39
Primary: CFB in 4-week overall SBM frequency rate[a]					
	n	41	36	41	39
Baseline	Mean (SD)	1.248 (0.850)	1.462 (0.852)	1.307 (0.734)	1.324 (0.789)
	Median	1.448	1.448	1.448	1.448
	Min, Max	0.00, 2.90	0.00, 2.90	0.00, 2.90	0.00, 2.90
Change from baseline	Mean (SD)	2.048 (3.273)	1.317 (1.813)	1.816 (2.359)	2.367 (2.469)
	Median	0.917	0.724	1.207	2.517
	Min, Max	-1.74, 14.32	-1.93, 6.75	-2.41, 7.78	-2.41, 7.61
Secondary: CFB in 4-week stool consistency (adult derivation)[b]					
	n	34	32	34	34
Baseline	Mean (SD)	2.900 (1.089)	2.446 (0.847)	2.463 (1.064)	2.431 (1.103)
	Median	3.000	2.333	2.000	2.225
	Min, Max	1.00, 5.50	1.00, 4.00	1.00, 5.00	1.00, 5.00
Change from baseline	Mean (SD)	0.397 (1.509)	0.736 (1.039)	0.727 (1.181)	1.155 (1.510)
	Median	0.292	0.472	0.606	1.165
	Min, Max	-3.33, 5.17	-1.00, 3.19	-2.14, 3.34	-2.50, 4.00
Secondary: CFB in 4-week stool consistency (based on observed weighted average)[c]					
	n	34	32	34	34
Baseline	Mean (SD)	2.887 (1.071)	2.433 (0.834)	2.463 (1.063)	2.429 (1.111)
	Median	3.000	2.333	2.000	2.225
	Min, Max	1.00, 5.50	1.00, 4.00	1.00, 5.00	1.00, 5.00
Change from baseline	Mean (SD)	0.383 (1.458)	0.706 (0.974)	0.663 (1.182)	1.034 (1.463)
	Median	0.188	0.386	0.476	0.854
	Min, Max	-3.33, 5.11	-1.00, 3.04	-2.14, 3.29	-2.50, 4.23
Secondary: CFB in 4-week overall CSBM frequency rate[d]					
	n	41	36	41	39
Baseline	Mean (SD)	0.553 (0.737)	0.764 (0.889)	0.742 (0.764)	0.706 (0.725)
	Median	0.000	0.241	0.483	0.483
	Min, Max	0.00, 2.41	0.00, 2.90	0.00, 2.41	0.00, 1.93
Change from baseline	Mean (SD)	1.305 (2.365)	0.813 (1.804)	1.025 (1.667)	1.318 (1.955)
	Median	0.241	0.302	0.500	0.724
	Min, Max	-0.91, 10.30	-1.93, 7.23	-1.48, 5.00	-1.93, 7.31
Secondary: CFB in 4-week daytime abdominal pain[e]					
	n	41	36	41	39
Baseline	Mean (SD)	1.362 (1.257)	0.903 (1.061)	1.047 (1.074)	0.935 (1.118)
	Median	1.000	0.439	0.636	0.357
	Min, Max	0.00, 4.00	0.00, 3.85	0.00, 3.38	0.00, 4.00
Change from baseline	Mean (SD)	-0.434 (0.847)	-0.278 (0.663)	-0.310 (0.848)	-0.115 (0.879)
	Median	-0.154	-0.050	-0.154	0.000
	Min, Max	-3.12, 1.32	-2.50, 0.74	-2.73, 1.40	-3.41, 1.36

In the linaclotide 145 µg group (which only included participants 12 to 17 years of age), change from baseline in 4-week overall SBM frequency rate was 2.623 SBMs/week (SD = 4.108) compared to 1.788 SBMs/week (SD = 2.891) for participants 12 to 17 years of age in the placebo group.

The treatment effects in the difernt age groups was not relevantly different based on exploratory analysis of treatment-by-age group interaction.

Similar results for the change from baseline in 4-week overall SBM frequency rate were observed in 4 sensitivity analyses using different methods of missing data imputation (missing at random, not missing at random, imputing based on worst response, and excluding participants impacted by e-diary malfunction issue). Similar results for the change from baseline in 4-week overall SBM frequency rate were also observed in an analysis using an alternative SBM definition (defined as a BM that occurred in the absence of laxative, enema, or suppository use in the current and previous 4 scheduled e-diary intervals) based on the ITT population.

The results of further secondary endpoints are shown in the following table:

Table 7: Summary of secondary endpoints related to severity of straining, daytime abdominal bloating, and daytime faecal incontinence (ITT population).

Endpoint Timepoint	Statistic	Placebo N = 41	LIN Dose A (Low) N = 36	LIN Dose B (Medium) N = 41	LIN Dose C (High) N = 39
CFB in 4-week severity of straining (adult derivation)[a]					
	n[a]	34	32	34	34
Baseline	Mean (SD)	2.284 (1.141)	2.110 (1.135)	2.629 (0.965)	2.475 (1.168)
	Median	2.250	2.083	2.417	3.000
	Min, Max	0.33, 4.00	0.00. 4.00	0.80, 4.00	0.00, 4.00
Change from baseline	Mean (SD)	-0.610 (1.045)	-0.575 (1.134)	-0.926 (0.932)	-0.950 (0.961)
	Median	-0.363	-0.278	-0.801	-0.823
	Min, Max	-3.68, 1.67	-3.10, 2.00	-3.14, 0.61	-2.66, 0.60
CFB in 4-week severity of straining (weighted average)[b]					
	n[a]	34	32	34	34
Baseline	Mean (SD)	2.296 (1.164)	2.108 (1.125)	2.627 (0.969)	2.478 (1.167)
	Median	2.196	2.083	2.375	3.000
	Min, Max	0.33, 4.00	0.00, 4.00	0.80, 4.00	0.00, 4.00
Change from baseline	Mean (SD)	-0.614 (1.033)	-0.571 (1.134)	-0.914 (0.956)	-0.912 (0.929)
	Median	-0.396	-0.225	-0.780	-0.847
	Min, Max	-3.58, 1.67	-3.09, 1.86	-3.00, 0.56	-2.65, 0.57
CFB in 4-week daytime abdominal bloating[c]					
	n[a]	41	36	41	39
Baseline	Mean (SD)	1.273 (1.252)	0.808 (1.021)	0.917 (1.029)	0.882 (1.145)
	Median	0.857	0.374	0.400	0.333
	Min, Max	0.00, 4.00	0.00, 3.92	0.00, 3.15	0.00, 4.00
Change from baseline	Mean (SD)	-0.477 (0.753)	-0.211 (0.623)	-0.301 (0.964)	-0.234 (1.005)
	Median	-0.261	0.000	-0.119	0.000
	Min, Max	-2.88, 0.48	-2.25, 1.18	-3.15, 2.35	-3.85, 2.73
CFB in 4-week daytime fecal incontinence[d]					
	n[a,b]	11	9	13	10
Baseline	Mean (SD)	0.144 (0.311)	0.042 (0.102)	0.059 (0.099)	0.067 (0.138)
	Median	0.000	0.000	0.000	0.000
	Min, Max	0.00, 1.00	0.00, 0.31	0.00, 0.29	0.00, 0.43
Change from baseline	Mean (SD)	-0.028 (0.081)	-0.025 (0.083)	-0.009 (0.067)	0.170 (0.298)
	Median	0.000	0.000	0.000	0.000
	Min, Max	-0.21, 0.07	-0.23, 0.04	-0.15, 0.12	0.00, 0.89

Responder analysis with "weekly SBM+1 response" (a weekly SBM + 1 responder was a participant who had a SBM increase ≥ 1 in the SBM weekly rate from baseline for that week. If a participant did not complete at least 4 morning and evening assessments on the same day in the eDiary for a particular Treatment Period week, the participant was not considered a weekly SBM + 1 responder for that week) are shown in the following table:

Table 8: Weekly SBM+1 responder during the treatment period (ITT population).

Timepoint	Statistic	Placebo (N = 41)	LIN Dose A (N = 36)	LIN Dose B (N = 41)	LIN Dose C (N = 39)
Week 1	N1	41	36	41	39
	Responder n (%)	18 (43.9)	17 (47.2)	20 (48.8)	24 (61.5)
	Nonresponder, n (%)	23 (56.1)	19 (52.8)	21 (51.2)	15 (38.5)
	Treatment difference, 95% CI		3.3 (-19.0, 25.6)	4.9 (-16.7, 26.4)	17.6 (-3.9, 39.2)
	Odds ratio[a], 95% CI		1.1 (0.5, 2.8)	1.3 (0.5, 3.0)	2.0 (0.8, 5.0)
	P-value[b]		0.7879	0.5934	0.1213
Week 2	N1	41	36	40	39
	Responder n (%)	20 (48.8)	16 (44.4)	24 (60.0)	18 (46.2)
	Nonresponder, n (%)	21 (51.2)	20 (55.6)	16 (40.0)	21 (53.8)
	Treatment difference, 95% CI		-4.3 (-26.6, 18.0)	11.2 (-10.3, 32.8)	-2.6 (-24.5, 19.3)
	Odds ratio[a], 95% CI		0.8 (0.3, 2.0)	1.5 (0.6, 3.7)	0.9 (0.4, 2.2)
	P-value[b]		0.6863	0.3419	0.8581
Week 3	N1	41	35	40	38
	Responder n (%)	19 (46.3)	19 (54.3)	23 (57.5)	16 (42.1)
	Nonresponder, n (%)	22 (53.7)	16 (45.7)	17 (42.5)	22 (57.9)
	Treatment difference, 95% CI		7.9 (-14.5, 30.4)	11.2 (-10.5, 32.8)	-4.2 (-26.1, 17.7)
	Odds ratio[a], 95% CI		1.4 (0.5, 3.4)	1.5 (0.6, 3.7)	0.8 (0.3, 2.1)
	P-value[b]		0.5161	0.3502	0.7191
Week 4	N1	40	35	39	36
	Responder n (%)	16 (40.0)	11 (31.4)	17 (43.6)	18 (50.0)
	Nonresponder, n (%)	24 (60.0)	24 (68.6)	22 (56.4)	18 (50.0)
	Treatment difference, 95% CI		-8.6 (-30.2, 13.0)	3.6 (-18.2, 25.3)	10.0 (-12.3, 32.3)
	Odds ratio[a], 95% CI		0.7 (0.3, 1.8)	1.1 (0.5, 2.8)	1.5 (0.6, 3.8)
	P-value[b]		0.4370	0.7945	0.3718

The evaluation of the number of patients with such a response in 3 of the 4 weeks of treatment resulted in responder rates of 36.6% for placebo, and 30.6%, 43.9%, and 38.5% for the dose groups A,B, and C.

Overall, the proportion of participants in the ITT population who reported using per-protocol rescue medicines or any other laxative, suppositories, or enemas during the 4-week treatment period was numerically lower in each linaclotide dose groups (A, B, and C) than in the placebo group.

Further analyses are not included in this AR, due to missing relevance.

Assessor's comment:

No evaluation has done within the EU of the efficacy of linaclotide in the adult population for the treatment of FC. However, from the data known in the literature (e.g. Lembo et al NEJM 2011; reporting results of two studies), where a clear difference was shown in relatively "hard endpoints" (response based on "at least 3 CSBMs per week with an increase of at least 1 CSBM from baseline for 9 of the 12 weeks treatment", which showed rates of 21% and 16% for the 145 µg dose, and 19.4% and 21.3% for the 290 µg dose; while placebo response rates were 3.3% and 6.0%), the results reported

here for the paediatric population appear disappointing. In consequence, it would appear reasonable to analyse the reasons for the failure of this study to show relevant effects. However, the applicant has not included any reasoning, neither in the study report, nor in the clinical overview. Questions to be answered could be, whether the trial setting, with potentially insufficient inclusion criteria, could have favoured the inclusion of a less severely diseased population, favouring a lower response in active treatment, and a higher response in placebo-treated patients. Also, the effectiveness of the instructions for life-style modifications could play a role here. Furthermore, the appropriateness of the doses could be debated: A adult person with a weight of 75 kg receives approx. 1.9 µg/kg b.w. when given the adult dose for the treatment of FC. The dose groups in this study received in dose group A of 9 or 18 µg depending on weight and age, which results in a b.w.-related dose of 0.36 µg/kg (assuming a mean weight of 25 kg in the younger age group with a weight below 35 kg, and a weight of 50 kg in the young age group with a weight of >35 kg, and adolescents). This would mean a dose of 0.72 µg/kg in group B, and 1.44 µg/kg in group C, which is below the "usual" adult dose. Therefore, the cautious dosing could also play a role for these results, although the overall results in those receiving the adult dose did also not clearly show efficacy. However, the analysis of the causes for the failure of the study to show effects (including the explorative application of another dose-response model) could help to modify the further paediatric studies to be conducted.

The statistical evaluation of the dose-response was not discussed in the main body of final study report, but displayed in tables in the appendix showing that a significant dose-response could not be seen, when applying a linear trend test. Also, a test on an additional quadratic term investigating a deviation from the linear model was not significant. Other dose response models were not discussed or applied. Hence, using the pre-specified methods no significant dose response could be shown.

However, study LIN-MD-63 for FC in the paediatric population aged 6-17 is already ongoing at the time of submission of study LIN-MD-62 using similar doses as LIN-MD-62.

For the currently EU license, however, the results of the efficacy analysis do not have any consequences.

PK analysis:

Similar to adult data, due to limited absorption, the plasma concentrations of linaclotide and its active metabolite MM-419447 were below the limit of quantitation in most of the pediatric participants enrolled in this studyThus, no PK parameters were calculated. However, 4 participants in the 6 to 11 years of age group had quantifiable plasma concentrations of linaclotide and/or its active metabolite (1 each in dose groups A and B, and 2 in dose group C). The concentrations determined were between 0.107 ng/ml and 1.26 ng/ml, with the exception of a value of 300 ng/ml in one patient in dose group A. This is considered "theoretically impossible" by the applicant (even if the dose would have given intravenously, the calculated plasma concentration would be 4.79 ng/ml), and a suspicion on contamination of the plasma sample was brought forward by the applicant.

Assessor's comment:

These results are in line with the results from adult PK studies, although the number of samples with measurable concentration appears somewhat higher than in adult PK studies, where usually for none of the participants any measurable concentration was detected. The exceptionally high value of 300 ng/ml remains somewhat obscure, because, although the study report ascribes this to potential contamination, the analytical report rather considers this to be highly unlikely. Of note, is the fact that the LLoQ has been set to 0.1 ng/ml, and this has previously (in the adult PK programme been at 0.2 ng/ml. There were – in addition – a couple of issues reported in the validation report, which should

give rise to caution when looking at the PK results. However, the overall conclusion that linaclotide is minimally or not at all absorbed in children and adolescents aged 6-17 is clearly supported.

Safety results

Exposure:

There were 21 patients receiving the 9/18 µg dose in the two weight groups (10 between 18 and 35 kg, and 11 above 35 kg), and 26 receiving 18/36 µg with 13 and 13 in the two weight groups, ans finally 20 patients receiving 36/72 µg with 12 and 8 in the higher and lower weight groups. There were 16 patients receiving the 145 µg dose. All patients 6-11 years of age received the oral liquid formulation, and 90% of the older age group received the capsule formulation.

The final treatment durations are shown in the following table:

Table 8: Treatment duration (safety population)

Treatment Duration (Days)[a]	Placebo (N = 41)	LIN Dose A (N = 36)	LIN Dose B (N = 41)	LIN Dose C (N = 39)	LIN 145 µg (N = 16)[b]
Distribution duration interval, n (%)					
1 day	0	0	0	0	0
> 1 to ≤ 14 days	0	1 (2.8)	1 (2.4)	2 (5.1)	1 (6.3)
> 14 to ≤ 28 days	14 (34.1)	18 (50.0)	19 (46.3)	14 (35.9)	7 (43.8)
> 28 to ≤ 30 days	23 (56.1)	14 (38.9)	17 (41.5)	19 (48.7)	7 (43.8)
> 30 days	4 (9.8)	3 (8.3)	4 (9.8)	4 (10.3)	1 (6.3)
Mean (SD)	29.3 (3.9)	28.1 (3.7)	28.3 (5.7)	28.0 (4.4)	27.2 (6.3)
Median	29.0	28.0	29.0	29.0	28.5
Min, Max	16, 47	8, 32	3, 49	11, 35	4, 31
N	41	36	41	39	16
Participant-years[c]	3.3	2.8	3.2	3.0	1.2

Adverse events:

The overall number of treatment emergent adverse events (TEAEs) in the different dose groups, as well as the number of treatment-related TEAEs, SAEs, and AEs ledaing to discontinuation are shown in the following table:

Table 9: Overall Summary of Adverse events:

Participants with Adverse Events	Placebo (N = 41) n (%)	LIN Dose A (N = 36) n (%)	LIN Dose B (N = 41) n (%)	LIN Dose C (N = 39) n (%)	LIN 145 µg (N = 16)[a] n (%)
Any TEAEs	9 (22.0)	6 (16.7)	12 (29.3)	15 (38.5)	4 (25.0)
Any treatment-related TEAEs	0	1 (2.8)	3 (7.3)	6 (15.4)	2 (12.5)
Any SAEs	0	1 (2.8)	0	0	1 (6.3)
Any AEs leading to discontinuation	0	2 (5.6)	0	1 (2.6)	0

The most common adverse events according to SOC and PT are shown in the following table

Table 10: Summary of treatment-emergent adverse events (safety population) in more than 5% of the participants:

System Organ Class Preferred Term	Placebo (N = 41) n (%)	LIN Dose A (N = 36) n (%)	LIN Dose B (N = 41) n (%)	LIN Dose C (N = 39) n (%)	LIN 145 µg (N = 16)[a] n (%)
Gastrointestinal disorders	3 (7.3)	2 (5.6)	6 (14.6)	8 (20.5)	2 (12.5)
Diarrhoea	0	1 (2.8)	3 (7.3)	4 (10.3)	2 (12.5)
Faecaloma	0	0	0	2 (5.1)	0
Vomiting	1 (2.4)	1 (2.8)	0	0	1 (6.3)
Infections and infestations	4 (9.8)	2 (5.6)	6 (14.6)	7 (17.9)	1 (6.3)
Viral sinusitis	0	0	0	0	1 (6.3)
Investigations	1 (2.4)	0	1 (2.4)	1 (2.6)	1 (6.3)
ALT increased	1 (2.4)	0	0	0	1 (6.3)
AST increased	1 (2.4)	0	0	0	1 (6.3)
Nervous system disorders	1 (2.4)	1 (2.8)	0	5 (12.8)	0
Headache	1 (2.4)	1 (2.8)	0	4 (10.3)	0

There were no AEs of special interest (ie, significant volume depletion and/or significant electrolyte abnormalities and/or ECG abnormalities that were considered by the investigator orsponsor to be related to diarrhea) or deaths reported.

The majority of treatment-emergent AEs reported were considered mild or moderate in severity. One participant in the placebo group and one participant in the linaclotide Dose A group experienced severe TEAEs during the study.

Severe TEAEs of tooth impacted, toothache, post-procedural swelling, ALT increased, and AST increased were reported in the placebo participant. Severe TEAE of suicidal ideation was reported in the linaclotide Dose A group participant. None of these events were considered by the investigator to be related to the study drug.

The majority of the TEAEs of diarrhea among participants 6 to 17 years of age, across all doses, were mild, and none were severe

Serious events and deaths:

There were not deaths in the study.

Overall, a total of 2 participants (both in the 12 to 17 years of age group) experienced SAEs, neither of which were considered related to study drug (suicidal ideation in the linaclotide Dose A group and vomiting in the linaclotide 145 µg group).

Laboratory values and vital signs:

There were no unexpected changes of clinical relevance in the study. The most frequent potentially clinically (PCS) significant values were observed for albumin (> 1.1 × ULN) and BUN (> 1.2 × ULN), neither of which was associated with concomitant reports of diarrhea. The overall evaluation of PCS cases in laboratory values are shown in the following table:

Table 11: Number of participants with PCS postbseoline values of laboratory investigations during the double-blind treatment period (safety population)

Parameter PCS Criterion	Placebo (N = 41) n/N1 (%)	LIN Dose A (N = 36) n/N1 (%)	LIN Dose B (N = 41) n/N1 (%)	LIN Dose C (N = 39) n/N1 (%)	LIN 145 µg (N = 16)[a] n/N1 (%)
Hematology					
Hematocrit (ratio)					
> 1.1 × ULN	0/38	0/33	1/38 (2.6)	0/36	0/14
Hemoglobin (g/L)					
> 1.1 × ULN	0/38	0/33	1/38 (2.6)	0/36	0/14
Neutrophils absolute cell count (109/L)					
< 0.8 × LLN	0/37	0/32	0/38	1/36 (2.8)	0/14
White blood cell count (109/L)					
< 0.7 × LLN	0/38	0/32	0/38	1/36 (2.8)	0/14
Chemistry					
ALT (U/L)					
≥ 3 × ULN	1/38 (2.6)	0/33	1/38 (2.6)	0/36	1/14 (7.1)
Albumin (g/L)					
> 1.1 × ULN	1/29 (3.4)	1/26 (3.8)	6/33 (18.2)	2/29 (6.9)	1/10 (10.0)
Alkaline phosphatase (U/L)					
Age 6-12 (inclusive) male and female: ≥ 1.2 × ULN	1/22 (4.5)	0/20	0/27	2/18 (11.1)	0/2
AST (U/L)					
≥ 3 × ULN	1/38 (2.6)	0/33	0/38	0/36	0/14
BUN (mmol/L)					
> 1.2 × ULN	1/36 (2.8)	4/33 (12.1)	1/36 (2.8)	1/35 (2.9)	0/14
Potassium (mmol/L)					
> 1.1 × ULN	0/33	0/30	2/37 (5.4)	0/32	0/14
Urinalysis					
pH					
> 1.1 × ULN	1/38 (2.6)	0/32	4/34 (11.8)	1/33 (3.0)	0/11

The incidences of all vital sign parameters (supine and standing blood pressure, supine and standing pulse rate, temperature, respiratory rate, and weight) that were identified as PCS based on the criteria defined in the SAP are presented in the following table. There were no unexpected changes of clinical relevance.

Table 12: Number of participants with PCS post-baseline vital sign parameters (safety population):

Parameter PCS Criterion	Placebo (N = 41) n/N1 (%)	LIN Dose A (N = 36) n/N1 (%)	LIN Dose B (N = 41) n/N1 (%)	LIN Dose C (N = 39) n/N1 (%)	LIN 145 µg (N = 16)[a] n/N1 (%)
Standing – supine diastolic blood pressure (mm Hg)					
≤ -10 and decrease ≥ 10	1/40 (2.5)	0/36	1/40 (2.5)	1/38 (2.6)	1/16 (6.3)
Pulse rate (bpm) – supine					
Age 12-17 (inclusive): ≥ 120 and increase of ≥ 15	1/18 (5.6)	0/15	0/14	0/18	1/16 (6.3)
Standing – supine pulse rate (bpm)					
≥ 20 and increase of ≥ 10	5/40 (12.5)	5/36 (13.9)	3/40 (7.5)	1/38 (2.6)	2/16 (12.5)
Weight (kg)					
Decrease of ≥ 5%	2/40 (5.0)	0/36	2/40 (5.0)	1/38 (2.6)	0/16
Increase of ≥ 5%	4/40 (10.0)	4/36 (11.1)	4/40 (10.0)	1/38 (2.6)	0/16

Assessor's comment:

The overall conclusions on safety are of course hampered by the fact that the numbers in the different dose groups are small, and the treatment duration was limited. However, as an overall conclusions, it appears that the adverse effects to be deduced from the study are clearly related to the pharmacodynamics activity of the compound, with diarrhea being the only events occurring in clearly higher rates, and in dose dependent manner in the active treatment groups. The further analysis could not reveal any clinically relevant consequences of the diarrhea events (e.g. related to electrolyte, blood pressure, occurrence of syncope, etc.).

It is concluded that the known safety profile of the compound in adults is confirmed in children and adolescents aged 6-17 years. There appears to be no obvious increased risk of adverse effects in the paediatric population down to the age of 6 as compared to an adult population.

2.3.3. Discussion on clinical aspects

The applicant has presented the first study which was part of the agreed PIP, in this Article 46 procedure. Whereas all studies agreed in the PIP will be conducted in the indication functional constipation, the product is currently licensed in the indication IBS only. The results of any of these studies will therefore be of limited relevance for the product licensed in the EU.

The study LIN-MD-62 was an explorative PK- dose-finding, and safety study in patients aged 6-17 in patients with functional constipation. Whereas – as an overall result – the known properties of the substance with regard to PK and safety can be considered to have been confirmed with this study, the results with regard to efficacy do not show clinically relevant differences in comparison to the placebo treatment in any of the dose levels studied.

However, due to the different patient population, the different indication, and the potential use of relatively low doses in the trial, the results with regard to efficacy are not considered to have any repercussion on the existing license for adults with IBS-C.

3. Rapporteur's overall conclusion and recommendation

The applicant has submitted the results of study LIN-MD-62 being the first of a series of studies to be conducted in the paediatric population. However, this study was conducted in patients suffering from functional constipation, an indication for which the compound is currently not licensed in the EU. While

the results with regard to efficacy are therefore not relevant, the results with regard to safety do confirm the known safety profile of linaclotide, with the majority of effects restricted to the gastrointestinal effect and the “laxative” effects induced.

Therefore, the proposal of the applicant, that no changes to the PI should be implemented, and that the trial has no impact on the overall conclusion on benefit risk, is supported.

☒ **Fulfilled:**

No regulatory action required.

4. Additional clarification requested

None

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

The studies should be listed by chronological date of completion:

Non clinical studies

N/A

Clinical studies

Product Name: Constella Active substance: Linaclotide

Study title	Study number	Date of completion	Date of submission of final study report
	LIN-MD-62	29 May 2018	26 February 2019