Amsterdam, 24 February 2022
EMA/199172/2022
Committee for Medicinal Products for Human Use (CHMP)

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/P46/017

Note

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

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1. Introduction

On 19-10-2021, the MAH submitted a completed paediatric study, LIN-MD-67, for Constella (linaclotide), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has not been provided with this submission.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study LIN-MD-67 is part of the agreed PIP (EMEA-000927-PIP01-10-M03). 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.

The applicant also states that they have taken the opportunity to correct editorial errors in the tabular listing of the clinical studies in Module 5.2 for study LIN-MD-62. This correction is not part of the assessment.

2.2. Information on the pharmaceutical formulation used in the study

The investigational product used in study LIN-MD-67 refers to a capsule formulation with different strengths compared to the marketed formulation, which contains 290 µg active substance. The strength of the capsules used were 290 µg, 145 µg, 72 µg, and 36 µg.

However, the administration was not by swallowing whole capsules, but contents were to be sprinkled into 20 mL of bottled water, and 5 mL of this solution is dosed to the participant using an oral syringe. The following scheme was used:

- 36 µg capsules, were used to prepare the 9 µg dose

- 72 µg capsules, were used to prepare the 18 µg dose

- 145 µg capsules, were used to prepare the 36 µg dose

- 290 µg capsules, were used to prepare the 72 µg dose

- Placebo preparation is identical for all dose cohorts

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study LIN-MD-67, A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Sequential, Ascending, Multidose Study to Evaluate the Safety and Efficacy of Linaclotide in Pediatric Participants (Age 2 to 5 Years) with Functional Constipation.

The study is submitted with a complete study report, protocol, and necessary appendices and documents. However, the study report contains mainly raw data tables only (usually divided by the treatment cohorts, see below), which are not very convenient for reading.

2.3.2. Clinical study LIN-MD-67

Description

Study LIN-MD-67 was a A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Sequential, Ascending, Multidose Study to Evaluate the Safety and Efficacy of Linaclotide in Pediatric Participants (Age 2 to 5 Years) with Functional Constipation

The study was initiated (first patient in) 14 October 2019, and finalised (last subject visit) 27 April 2021. The study was conducted as a multi-centre study in the USA.

Methods

Study participants

The targeted population for this study were male and female participants aged 2 to 5 years. The main inclusion criterion refers to the presence of functional constipation (FC) according to the Rome III criteria:

According to these criteria, a participant must suffer from FC, for at least 2 months before Screening (Visit 1) (for participants aged ≥ 4 years old), or for at least 1 month before Screening (Visit 1) (for participants aged < 4 years old), the participant has had 2 or fewer defecations (with each defecation occurring in the absence of any laxative, suppository, or enema use during the preceding 24 hours) per week.

In addition, at least once per week, the participant must meet 1 or more of the following:

a. History of retentive posturing or excessive volitional stool retention

b. History of painful or hard bowel movements (BMs)

c. Presence of a large fecal mass in the rectum

d. History of large diameter stools that may obstruct the toilet

e. At least one episode of fecal incontinence per week after the acquisition of toileting skills

In addition, participants were required to have an average of fewer than 3 spontaneous bowel movement (SBMs) per week during the 14 days before the randomization day and up to the randomization (including the clinic eDiary assessments reported before administration of the first dose of double-blind study intervention on the randomization day). An SBM is defined as a BM that occurs in the absence of laxative, enema, or suppository use on the calendar day of the BM or the calendar day before the BM.

All concomitant medication potentially influencing GI motility (not only laxatives) were to be washed out before intake of the trial medication, and was forbidden throughout the trial duration.

Assessor's comment:

It appears somewhat surprising that Rome III instead of Rome IV is used for this study, however, the differences are considered marginal. For comparison, the (short) definition of Rome IV for childhood FC is as follows: Must include one month of at least two of the following in infants up to 4 years of age:

- Two or fewer defecations per week, - History of excessive stool retention, - History of painful or hard bowel movements, - History of large diameter stools, - Presence of a large fecal mass in the rectum

- In toilet-trained children, the following additional criteria may be used: -At least one episode/week of incontinence after the acquisition of toileting skills, - History of large diameter stools which may obstruct the toilet

The inclusion criteria adequately defined a childhood FC population.

Treatments

The study was to consist of up to 4 Cohorts, each of which were to be 9 to 12 weeks in duration: 2- to 4-week Screening Period, a 2- to 3-week Preintervention Period, followed by a 4-week double-blind Study Intervention Period, and a 1-week Postintervention Period.

Cohort 1 was to receive 18 µg (or matching placebo), cohort 2 36 µg, Cohort 3 72 µg. These cohorts were to consist of 8 participants randomised in 3:1 ratio. A DSMB was to evaluate safety after completion of the previous cohorts and to determine the dose of the upcoming cohort (could recommend dose proposed, or lowering of the dose) Cohort 4 planned to consist of 6 participants (termed "Final Cohort") was to be treated with the highest dose determined to be safe during the previous cohort treatments, depending on the recommendation of the DSMB with a 5:1 randomisation.

In consequence, 30 patients maximum were to be recruited for the study.

Objective(s)

The purpose of this Phase 2 study was to investigate the potential therapeutic dose(s) of linaclotide in the target pediatric subset of participants, 2 to 5 years of age, with FC.

According to the protocol, the objectives were defined as follows: To evaluate the dose response, safety, and efficacy of 4 weeks of study intervention with linaclotide compared with placebo in pediatric participants, 2 to 5 years of age, with FC.

Given the lack of clinical data in this younger age group, a sequential, ascending multidose escalation design was selected.

Assessor's comment:

The applicant also states that there is a contraindication for the product for patients lower than 6 years of age, which, however, is not true for the EU licensed product, where only a recommendation against the treatment of adolescents, and children is included. It may also refer to a potential license (in the US) for FC in adults as well as children (older than 6 years), which is, however, currently unclear. Irrespective of the licensing status in the US, it also needs to be reminded upon the fact that the license in the EU if for IBS-C only.

Outcomes/endpoints

The following endpoints were defined for this study:

- Change from baseline in 4-week overall spontaneous bowel movement (SBM) frequency rate (SBMs/week) during the Study Intervention Period of each cohort
- Change from Baseline in 4-Week Stool Consistency Reported by the Caregiver During the Intervention Period of Each Cohort (reported according to the paediatricBristol Stool Form Scale (BSFS).
- Change from Baseline in 4-Week Straining Reported by the Caregiver During Study Intervention Period for Each Cohort

- Proportion of days with fecal incontinence during study intervention period (for participants who have acquired toileting skills during daytime and nighttime or acquired toileting skills during daytime only) within each cohort

The study objectives also included the determination of PK and whether PK was similar in children compared to adults, or whether systemic exposure was higher in children. Sparse PK sampling was therefore also included in the study.

The safety objective was addressed by AE monitoring, clinical laboratory assessments, vital signs, ECG, height and weight, as well as physical examinations.

Sample size

This was an explorative study, and no sample size calculation was undertaken. The study was designed to enrol a sufficient population in order to "observe the clinical response trends and monitor safety".

Randomisation and blinding (masking)+

After a parent/LAR/caregiver signed the permission/consent at Screening (Visit 1), the participant was assigned a randomization number.

The randomization number encodes the participant's assignment to 1 of the 2 study intervention groups of the study, according to the randomization schedule generated prior to the study by the statistics department at the sponsor. Each participant was dispensed blinded study intervention, labelled with his/her unique PID number, throughout the study.

No unblinding – except for the DSMB purposes – was to take place unless in case of emergency.

Statistical Methods

All efficacy analyses were to be performed on the mITT population defined as all randomized patients who have received at least one dose of intervention, and who had at least 1 post-baseline entry on BMs.

SBM frequency, stool consistency, straining, and incontinence were to be based on entries during the respective evaluation period in the eDiary.

Descriptive statistics (mean, median, SD, standard error of mean, minimum, and maximum) were to be provided by study intervention group for each cohort as main analysis approach.

Assessor's comment:

The use of descriptive statistics is fully acceptable considering the context of the trial

Results

Participant flow

A total of 95 potential participants were screened. Of these, 10 were discontinued from screening due to COVID-19 disease, and 8 were screen failures. Of the 68 remaining patients, 35 completed the pre-treatment phase, and 33 were discontinued, mostly due to screen failure.

Of the 35 remaining participants, 9 were randomised to Cohort 1, 9 to Cohort 2, 8 to Cohort 3 and 9 to the Final Cohort.

For those participants randomized to receive linaclotide, participants in Cohort 1 received an 18 µg dose, in Cohort 2 received a 36 µg dose, and in Cohort 3 and the Final, Cohort received a 72 µg dose.

1 patient in the pooled final cohort/cohort 3 (dosed with 72 µg) discontinued double-blind treatment. All other participants completed the four-week treatment course.

Baseline data

Due to the mode of reporting (per cohort) no overview on overall demographics is available. The cohort 1 had a mean age of 4.0 years ranging from 2 to 5. Cohort 2 had a mean age of 3.2 years, with a similar range as cohort 1. Cohort 3 had a mean age of 3.9 years ranging from 3-5, and Final Cohort had a mean age of 3.6 years ranging from 2 to 5. The pooled cohort [cohort 3+final cohort] had a mean age of 3.5 with a range from 3-4 years. Sex was quite equally distributed in all cohorts, and the proportion of black/African American patients was overall higher than the proportion of Whites, with some discrepancy in the 3 cohorts.

The mean weight in the cohorts 1, 2, 3, final and pooled placebo was 18.42 kg, 15.62 kg, 20.48 kg, 19.59 kg, 16.85 kg, the height was 104.53 cm, 98.72 cm, 105.58 cm, 104.58 cm, 100.00 cm and the BMI was 16.75 kg/m^2, 15.99 kg/m^2, 18.31 kg/m^2 17.88 kg/m^2 , 16.65 kg/m^2 respectively. The mean weight for the pooled cohort [cohort 3+final chort was 16.85 kg, the height was 100.00, and the BMI was 16.65 kg/m^2. While therefore, the cohorts overall were quite similar, for the small placebo groups in the four cohorts, some relevant deviations from the active treatment cohorts can be detected.

The baseline overall SBM frequency rate as given by the caregiver in cohorts 1, 2, 3, final and pooled placebo was 1.502, 0.590, 1.026, 0.966, 1.267, the SBM frequency as given by all observers was 1.609, 0.751, 1.026, 1.126, 1.388, stool consistency was 1.643, 1.667, 2.707, 2.017, 2.024 the frequency of straining was 2.436, 2.667, 2.427, 2.556, 2.548 and the proportion of days with fecal incontinence was 0.0, 0.019, 0.020, 0.013 and 0.0. Similar to the data on weight, BMI and height there were also relevant discrepancies between placebo cohorts and active cohorts within the cohorts 1, 2, and pooled cohort.

Assessor's comment:

The study was obviously burdened with some inconsistencies with regard to the severity of constipation within and between the treatment cohorts evaluated.

Number analysed

Efficacy results are reported for the mITT population consisting of all randomised patients. As reported above, 1 patient in the "pooled cohort" discontinued treatment early.

Efficacy results

Efficacy results are reported only very briefly by the applicant in the study report, which is reproduced below:

- For the 4-week overall SBM frequency rate (SBMs/week) observed by the caregiver, the mean change from Baseline was numerically higher in the linaclotide 18 µg and 72 µg groups compared to the placebo group, and similar in the linaclotide 36 µg group compared to the placebo group.
- The mean change from Baseline in the 4-week stool consistency (based on BSFS) reported by caregivers was numerically lower in the linaclotide 18 µg group compared to the placebo group

and numerically higher in the linaclotide 36 µg and 72 µg groups compared to the placebo groups.

- The mean change (decrease) from Baseline in the 4-week straining reported by caregivers was similar in the linaclotide 18 µg and 36 µg groups versus placebo and numerically higher in the linaclotide 72 µg group versus placebo.
- The proportion of days with fecal incontinence during the study treatment period was low for both the linaclotide treatment groups and the placebo groups.

In the following, a summary table trying to provide the data in a synoptic manner is presented and is restricted to include the three endpoints for which some changes could be detected. For ease of comparison, the pooled placebo group only is included.

Table 1: Summary of efficacy results; change from baseline to EOT; Study LIN-MD-67.

Change from Baseline (parameter)	Linaclotide 18 µg n=7	Linaclotide 36 µg n=7	Linaclotide 72 µg (pooled) n= 13	Placebo (pooled) n=8
SBM (caregiver)	**3.1**	**0.032**	**2.511**	**0.482**
BSFS stool consistency	**0.917**	**1.60**	**1.707**	**0.596**
Straining	**-0.370**	**-0.320**	**-0.928**	**-0.334**

PK evaluation:

Participants in Cohorts 1-3 were to be randomized on Study Day 1 (Visit 3) at a 1:3 ratio to either a pre-dose or post-dose PK sample and the 6 participants in the Final Cohort were to be randomized at a 1:2 ratio to either a pre-dose or post-dose PK sample, respectively, to be completed before or after the last dose of study intervention at Visit 5 (Week 4) for determination of linaclotide and active metabolite (MM-419447) concentrations in plasma. One blood sample was to be collected from each participant at Visit 5 (Week 4) before or after the last dose of study intervention, along with all laboratory blood samples at same time. Postintervention PK sample were to be collected at 1 to 8 hours post-dose.

The plasma concentrations of linaclotide and its active metabolite MM-419447 were below the limit of quantitation in all the pediatric participants enrolled in this study. Thus, no PK parameters were calculated.

Safety results

For the reporting of safety, and AE was considered as treatment-emergent (TEAE) if the AE began on or after the date of the first dose of study intervention or the AE was present before the data of the first dose of study intervention, but increased in severity of became serious on or after the data of the first dose of study intervention.

Most participants did not experience AEs. Two participants (28.6%) in Cohort 1 and 2 participants in the pooled Cohort 3 and the Final Cohort (15.4%) experienced TEAEs, one of which was treatment-related (mild diarrhea).

There were no serious adverse events (SAE) experienced by any participants in this study. In addition, two participants in Cohort 1 experienced TEAEs, including otitis media, increased blood creatinine, and cough. Two participants in the pooled Cohort 3 and the Final Cohort experienced TEAEs, including upper abdominal pain, diarrhea, and an ear infection.

All AEs were mild or moderate in severity. Only one event (mild diarrhoea) was considered treatment related.

There were no deaths, SAEs, or AESIs (defined as significant volume depletion, and/or significant electrolyte abnormality, and/or ECG abnormality considered related to diarrhoea) during the study.

There were no unexpected or clinically relevant changes to either vital signs or ECG measurements.

Assessor's comment:

Obviously, only 1 diarrhoea event was treatment-emergent, which means that two participants had a diarrhoea event before intake of the study medication, which is remarkable in a cohort of patients with FC. While cough and otitis media appear to be common AEs in a paediatric cohort, the GI AEs appear to be similar to what is observed in adults (what is known from the IBS population). The conclusion of the applicant that the safety profile was consistent with prior pediatric linaclotide FC study in patients 6-17 years and prior adult linaclotide studies can, however, not be fully assessed, since there was no full evaluation of paediatric data in the EU up to now. However, the consistency with the adult safety profile can be agreed with.

2.3.3. Discussion on clinical aspects

The applicant has filed a completed study (LIN-MD-67) conducted in paediatric patients aged 2-5 suffering from chronic constipation as defined by the Rome III criteria. The study was an explorative, combined safety, and dose-exploration trial which included 35 patients divided into four cohorts, which were subsequently recruited and randomised to increasing doses of linaclotide. A DSMB was installed for the conduct of the study, which evaluated unblinded safety data from the lower preceding dose cohorts before the following cohort using higher doses was to be treated.

The study design and preliminary objectives of the trial are considered fully adequate, and the cautious proceeding with staggered randomisation into the three different dose-cohorts was welcomed. The trial was addressing multiple objectives with dose exploration, overall safety, as well as the determination of PK.

The small sizes of the cohorts, as well as finally also partly of the treatment groups created some imbalances with regard to the baseline characteristics, especially for the baseline disease severity, which may have influenced the overall trial results, and has made efficacy evaluation difficult and partly inconsistent.

Nevertheless, the following conclusions can be drawn from the study:

- The PK of the compound is obviously not different from what is known from the adult population, with none of the participants developing measurable plasma concentrations during the course of the study, based on sparse PK sampling, and up to doses of 72 µg daily in the paediatric population aged 2-5 years.
- The safety profile of the compound appears to be similar to what is known from the adult population (in EU restricted to the IBS-C population), which is mainly the development of

rather mild AEs related to the PD action of the compound (diarrhoea). Relevant concerns with regard to the treatment of 2-5 year old children with doses up to 72 µg cannot be derived.

- Although the applicant does not conclude on the efficacy results, it appears that some effects can be detected which might warrant further evaluation in this population, especially showing consistently superior results above placebo in the highest dose evaluated.

The applicant has neither displayed consistently the overall context of the trial – with regard to the overall development plans in the indication functional constipation – nor with regard to their final assessment of the trial, and whether it is considered encouraging (or de-couraging) with regard to the further development and conduct of confirmatory trials in the younger paediatric population.

The applicant has stated in their submission that there are currently no regulatory consequences with regard to the finalisation of this trial, and that there is no intent for further changes (e.g. for the PI) in Europe. This is agreed with, as far as the immediate consequences of the trial are concerned.

However, in order to fully understand the context of the filing of the trial, as well as the trial results, the applicant is requested to answer a couple of additional questions.

3. Rapporteur's overall conclusion and recommendation

☒ Not Fulfilled:

No further action is required, however, a request for supplementary information is brought forward, and the applicant should provide statements as requested below, to enable a full assessment of the context of the trial. (See 4.)

Based on the data submitted, the MAH should provide statements as requested below, to enable a full assessment of the context of the trial as part of this procedure. (see section 4.0 "Request for supplementary information").

4. Request for supplementary information

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

1. The MAH is requested to display the history of the development of linaclotide in the paediatric indication referring to both the fact that the compound is licensed in the EU for IBS-C only, and referring to the agreed PIP.
2. The MAH is requested to display their assessment of the trial data more clearly, and whether the partly inconclusive results of the trial has led to any conclusions with regard to the continuation of exploring (and confirming) the efficacy and safety of the compound in FC in small children. In case a further development is planned, these plans should be displayed.
3. Although marketing the compound in indications other than (adult) IBS-C is the decision of the MAH, the MAH is asked to display their further regulatory strategy with regard to marketing of the compound in the EU for the indication of functional constipation, including children.

The timetable is a 30-day response timetable without a clock stop.

MAH responses to Request for supplementary information

1. The MAH is requested to display the history of the development of linaclotide in the paediatric indication referring to both the fact that the compound is licensed in the EU for IBS-C only andreferring to the agreed PIP.

MAH Response:

The initial Constella PIP EMEA-00927-PIP01-10 was approved by PDCO on 6th May 2011 for the indication functional constipation. Following the initial approval, five PIP modifications have been submitted to align the paediatric plan globally in paediatric patients. Currently the MAH does not intend to register the IBS-C indication in the EU Constella marketing authorisation for children. The MAH will continue to submit final CSRs for paediatric studies for Linaclotide regardless of the studied indication in accordance with Article 46 of Regulation (EC) No 1901/2006, however currently does not plan to register this indication for the EU licence.

Assessment of the MAHs response.
The applicant only makes a short statement about the approved PIP, which was, right from the initial approval, referring to a different indication than the one approved for adults in the EU. The intention not to register the IBS-C indication for children is noted, as well as the intention to submit the results of all paediatric studies in accordance with Article 46 of Reg (EC) 1901/2006.

Overall Conclusion:
Issue resolved.

2. The MAH is requested to display their assessment of the trial data more clearly, and whetherthe partly inconclusive results of the trial has led to any conclusions with regard to the continuation of exploring (and confirming) the efficacy and safety of the compound in FC in small children. In case a further development is planned, these plans should be displayed.

MAH Response:

With the limitations of the exploratory nature of the phase 2 study LIN-MD-67, there is a numerical improvement in 3 out of the 4 efficacy endpoints for the highest dose of linaclotide used in this trial in 2–5-year-old patients (spontaneous bowel movement, straining and consistency). This finding warrants further evaluation in a phase 3 study which is planned to confirm the efficacy and safety of linaclotide versus placebo. The global study will consist of a phase 3 component (part 1) and a long-term safety component (part 2) and is projected to start in 2022. Consequently, any updates to the proposed paediatric studies will be submittedto PDCO as a PIP modification in Q3 2022.

Assessment of the MAHs response.
The MAH has displayed their intent for further develop the CC-indication in children, including young children of 2-5 years of age, and have displayed their plans to conduc a subsequent phase 3 study, starting this year. This is welcomed. A subsequent PIP modification is planned to be submitted in Q3. The answer is satisfactory.

Overall Conclusion:
Issue resolved.

3. Although marketing the compound in indications other than (adult) IBS-C is the decision of theMAH, the MAH is asked to display their further regulatory strategy with regard to marketing

ofthe compound in the EU for the indication of functional constipation, including children.

MAH Response:

The MAH currently does not plan to initiate clinical trials in adults with functional constipation and does not plan to seek the registration of functional constipation in children as an EU indication. The MAH will review the data once the development program is finalised. The clinical trial studies that are currently ongoing and planned will be completed as per the current agreed PIP EMEA-00927-PIP01-M06 and final study results will be submitted to the EMA in accordance with Article 46 of Regulation (EC) No 1901/2006.

Assessment of the MAHs response.
The applicant has stated that the functional constipation indication for children is not intended for registration in the EU. This is noted, and not regarded to be of concern considering the wide availability of treatment alternatives for this indication, even for young children. The applicant has renewed their intention to adhere to the agreed PIP. The answer is satisfactory.

Overall Conclusion:
Issue resolved.

5. Rapporteur's revised overall conclusion and recommendation

☒ Fulfilled:

The applicant has presented study LIN-MD-67 completed. This study was part of the agreed PIP (EMEA-000927-PIP01-10-M03) conducted in paediatric patients aged 2-5 suffering from chronic constipation as defined by the Rome III criteria. The applicant has stated that the functional constipation indication for children is not intended for registration in the EU. This was not regarded to be of concern considering the wide availability of treatment alternatives for this indication. No regulatory consequences were identified with this study which was agreed by the CHMP. However, a request for supplementary information was brought forward, to enable a full assessment of the context of the trial. All the points requested for clarification have been resolved.

Furthermore, there were no new data that change or result in a new benefit/risk evaluation and, consequently, no changes were proposed to be made to the PI.

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

The studies should be listed by chronological date of completion:

Clinical study submitted

Product Name: Constella Active substance: Linaclotide

Study title	Study number	Date of completion	Date of submission of final study report
Phase 2, Randomized, Double-Blind, Placebo-Controlled, Sequential, Ascending, Multidose Study to Evaluate the Safety and Efficacy of Linaclotide in Pediatric Participants (Age 2 to 5 Years) with Functional Constipation	LIN-MD-67	27 April 2021	19-10-2021