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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

Revestive

Teduglutide

Procedure no: EMEA/H/C/002345/P46/015

Note

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

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

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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	01.04.24	01.04.24	☐
☐	CHMP Rapporteur Assessment Report	06.05.24	06.05.24	☐
☐	CHMP members comments	21.05.24	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	23.05.24	n/a	☐
☒	CHMP adoption of conclusions:	30.05.24	30.05.24	☐

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1. Introduction

On 15 of March, the MAH submitted a completed paediatric study for Revestive (teduglutide), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

This study, TAK-633-3008, is a stand-alone study performed in addition to the teduglutide development program in Japan.

The study was an open-label study designed to Japanese pediatric patients aged 4 months of corrected gestational age or older, with short bowel syndrome (SBS). The study was initiated on 18 Jan 2022 (first subject enrolled) as a Phase 3 study, but upon receiving approval from PMDA of the 1.25 mg formulation on 02 Sep 2022, this study was continued as a postmarketing clinical study (Phase 4 study) until each enrolled subject switched to the 1.25 mg commercial formulation.

As the study was conducted in subjects <18 years of age and to comply with the requirements as stipulated in Article 46 of the European Union (EU) Pediatric Regulation (Regulation [EC] No 1901/2006, as amended), the Module 2.5 clinical overview addendum was developed to support the submission.

2.2. Information on the pharmaceutical formulation used in the study

Teduglutide 1,25 mg Powder and solvent for solution for injection.

The dose regimen was 0.05 mg/kg (0.025 mg/kg if moderate or severe renal impairment) subcutaneous injection once daily for 24 weeks per treatment cycle.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted the final report for Study TAK-633-3008 - a Phase 3, open-label study designed to evaluate the administration of the 1.25 mg formulation of teduglutide to Japanese paediatric patients with short bowel syndrome (SBS).

2.3.2. Clinical study

Study TAK-633-3008

Description

Study TAK-633-3008 was a Phase 3, open-label study to evaluate the safety of teduglutide in Japanese pediatric subjects with SBS who were dependent on PS and aged 4 months (corrected gestational age) or older with a body weight of <10 kg (or <20 kg if a subject had moderate or greater renal impairment).

The study was designed to evaluate the use of the 1.25 mg formulation of teduglutide in pediatric and infant subjects with SBS. Upon marketing approval of the teduglutide 1.25 mg formulation on 02 Sep 2022, Study TAK-633-3008 continued as a postmarketing clinical study (Phase 4 study) until all

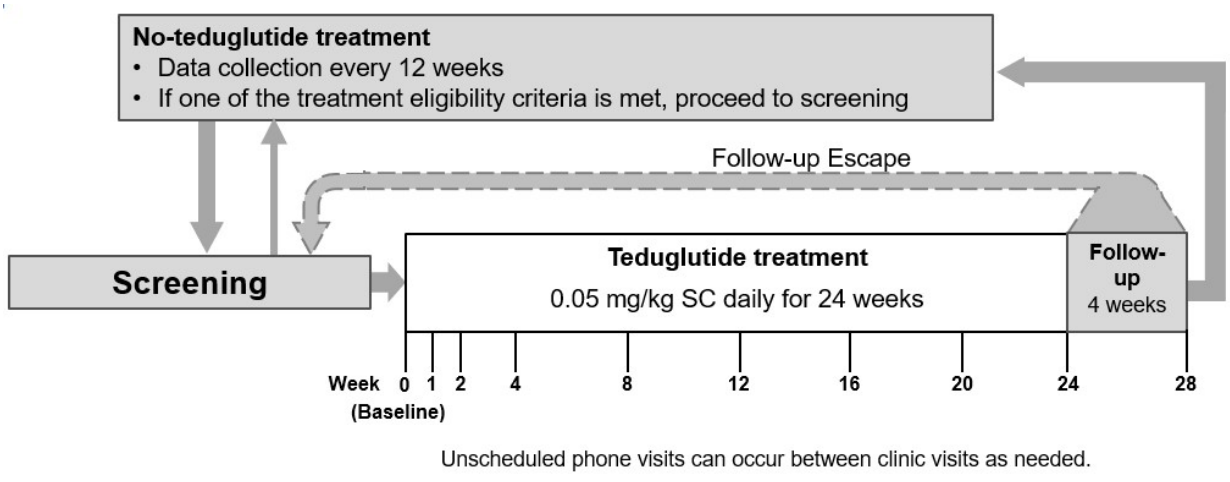
enrolled subject switched to the 1.25 mg commercial formulation. Primary objective was to evaluate the safety of the 1.25 mg formulation of teduglutide in Japanese pediatric patients with SBS who are dependent on PS, aged 4 months (corrected gestational age) or older, and requiring the dosing of 1.25 mg formulation. Secondary objective was to evaluate the efficacy of the 1.25 mg formulation of teduglutide in the same population.

A study design schematic is presented in Figure 1. A 2- to 4-week screening period was used to verify eligibility. After screening, subjects who met the inclusion criteria and none of the exclusion criteria started a 28-week treatment cycle, consisting of 24 weeks of teduglutide treatment at 0.05 mg/kg (0.025 mg/kg for subjects with moderate or greater renal impairment) SC once daily, followed by a 4-week follow-up (no treatment) period. Each subject visited the site at baseline, weekly for the first 2 weeks (Weeks 1 and 2), and every 4 weeks after Week 4 (Weeks 4, 8, 12, 16, 20, 24, and 28). Telephone contact was made as needed during the treatment period. During all site visits and telephone contacts, safety was evaluated, and nutritional support was reviewed and adjusted, as needed.

A subject could "escape" the follow-up period between Week 24 and Week 28 and proceed immediately to another screening visit if the subject met at least 1 of the follow-up period escape criteria. Otherwise, following completion of the 28-week treatment cycle, the subject proceeded to a no-teduglutide treatment (NTT) period. Subjects who escaped the follow-up period and proceeded immediately to another screening visit, started the next cycle of teduglutide treatment when at least 1 of the treatment eligibility criteria and none of the exclusion criteria were met. Similarly, subjects in the NTT period could proceed to another screening visit at any time during this period if at least 1 of the treatment eligibility criteria were met, and they could start the next cycle of teduglutide treatment when at least 1 of the treatment eligibility criteria and none of the exclusion criteria were met.

A subject could participate in multiple treatment cycles and NTT periods depending on their clinical trajectory. The screening period for subsequent treatment cycle following the NTT or follow-up period was -28 to -1 days.

Figure 1. Study Design Schematic



SC=subcutaneous

Source: TAK-633-3008 clinical study report, Figure 1

Methods

Study participants

Japanese pediatric subjects with SBS who were dependent on PS, aged 4 months (corrected gestational age) or older, weighed at least 5 kg and <10 kg for subjects with normal renal function or mild renal impairment or at least 10 kg and <20 kg for subjects with moderate or greater renal impairment.

Treatments

The investigational product was teduglutide 1,25 mg Powder and solvent for solution for injection.

There was no comparator in this study.

Treatment was open-label.

The dose regimen was 0.05 mg/kg (0.025 mg/kg if moderate or severe renal impairment) subcutaneous injection into either thigh or arm or 1 of 4 quadrants of the abdomen (in subjects without a stoma) once daily for 24 weeks per treatment cycle.

Duration of Treatment:

Until subject with ≥15 kg of body weight (or ≥30 kg of body weight if a subject has moderate or greater renal impairment), transition to 1.25 mg formulation when commercially available or subject discontinuation, or study termination. The maximum duration of treatment was expected to be approximately 18 months.

Objective(s)

The study was designed to evaluate the use of the 1.25 mg formulation in pediatric and infant subjects with SBS.

Primary study objective was to evaluate the safety of the 1.25 mg formulation of teduglutide in Japanese pediatric patients with SBS who are dependent on PS, aged 4 months (corrected gestational age) or older, and requiring the dosing of 1.25 mg formulation. Secondary objective was to evaluate the efficacy of the 1.25 mg formulation of teduglutide in the same population.

Outcomes/endpoints

Primary endpoints

The safety of the 1.25 mg formulation of teduglutide in Japanese pediatric patients was evaluated as the primary endpoint of Study TAK-633-3008.

- Incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and adverse events of special interest (AESIs)
- Physical examinations
- Vital signs, including body temperature, respiratory rate, blood pressure, and pulse
- Body weight, height (or length), head circumference and weight-for-length Z-scores (corrected for gestational age)
- Laboratory safety data (biochemistry, hematology, and urinalysis)
- Urine output

- Fecal output

Secondary endpoints

The following efficacy endpoints were analyzed as the secondary objective of Study TAK-633-3008:

- Change from baseline in PS volume by each visit and end-of-treatment (EOT)
- Percent change from baseline in PS volume by each visit and EOT
- Number and percent of subjects achieving at least 20% reduction in PS volume from baseline by each visit and EOT
- Number and percent of subjects achieving enteral autonomy, defined as complete weaning off PS by each visit and EOT
- Change from baseline in days per week of PS by each visit and EOT

Sample size

Approximately 5 subjects were planned; 3 patients were analyzed for safety and efficacy.

The sample size was determined based on enrollment feasibility of this rare population in Japanese children, rather than statistical power calculation.

Randomisation and blinding (masking)

There was no comparator in this study.

Treatment was open-label.

Statistical Methods

Safety analysis

Adverse events were summarized using the safety analysis set. Counts and percentages for subjects with TEAEs and SAEs (any SAE, regardless of relationship to study drug) were summarized descriptively by System Organ Class and Preferred Term using Medical Dictionary for Regulatory Activities terminology. Serious adverse events were also summarized by severity and by relationship to study drug. For clinical laboratory tests, body weight, height (or length), and head circumferences, vital signs, urine, and fecal output, descriptive statistics were used to summarize the absolute values and changes from baseline by visit.

Efficacy Analysis

For the continuous endpoints, the following statistics were presented: non-missing values, mean, median, standard deviation, minimum, maximum, and 95% confidence interval (CI).

For the binary endpoint, the following statistics were presented: count, proportion, and 95% Clopper Pearson CI.

Analyses of PS were based on 2 data sources: the subject diary data (also referred to as actual data) and the investigator prescribed data.

No formal statistical test was performed due to the limited sample size.

Results

Participant flow

A total of 3 subjects were enrolled and completed this study. No subjects prematurely discontinued from any treatment period or from the study.

Overall, the mean (standard deviation [SD]) study treatment compliance was 99.90 (0.171)%. The overall median duration of exposure to teduglutide was 48.14 (range: 47.3 to 51.3) weeks.

Of the 3 subjects, all 3 subjects (100%) completed the study and all 3 subjects had at least 1 protocol deviation. None of the deviations were judged to have impacted evaluation of safety. All 3 subjects were included in All Screened Subjects Analysis Set, Full Analysis Set, and Safety Analysis Set.

Recruitment

Approximately 5 subjects were planned; 3 patients were analyzed for safety and efficacy.

Baseline data

Number analysed

3 patients were analyzed for safety and efficacy.

Efficacy results

The mean (SD) change in PS volume at EOT was −10.99 (27.093) mL/kg/day from baseline of 90.51 (30.166) mL/kg/day, corresponding to a mean percent change of −13.13 (37.259)% for the teduglutide treatment periods. For the NTT periods, data from 1 subject were available. The change in PS volume at the last determination of endpoint or last available measurement during any NTT period

(last NTx) was −3.00 mL/kg/day from baseline of 125.34 mL/kg/day, corresponding to a percent change of −2.39%.

- The mean (SD) change in PS caloric intake at EOT was −25.19 (18.044) kcal/kg/day from baseline of 58.79 (10.435) kcal/kg/day, corresponding to a mean percent change of −46.62 (35.123)% for the teduglutide treatment periods. For the NTT periods, data from 1 subject were available. The change in PS caloric intake at the last NTx was −0.25 kcal/kg/day from baseline of 68.98 kcal/kg/day, corresponding to a percent change of −0.36%.
- For number and percent of subjects achieving at least 20% reduction in PS volume, 1 of the 3 subjects (33.33%) achieved at least 20% reduction in PS volume at EOT, based on diary data during the teduglutide treatment periods.
- None of the subjects were weaned off PS during the study; 3 subjects were dependent on PS, and 2 subjects were dependent on enteral nutrition as well.
- No change from baseline in number of days per week of PS usage at EOT was observed during the teduglutide treatment periods and NTT periods.
- The observed mean reductions of 13.13% in PS volume and 46.6% in PS caloric intake, along with at least a 20% reduction in PS volume in 1 out the 3 subjects, suggest clinically meaningful efficacy results in the use of teduglutide in this patient population.

Safety results

- The overall median duration of exposure to teduglutide and observation were 48.14 (range: 47.3 to 51.3) weeks and 56.14 (range: 50.1 to 76.4) weeks, respectively.
- A total of 26 TEAEs were reported in 3 subjects (100%) during the study. The majority of TEAEs were mild or moderate in intensity. A total of 4 severe TEAEs were reported in 1 subject (33.3%). None of the TEAEs were considered related to the study drug.
- Of the 26 TEAEs reported in the 3 subjects (100%), events reported in 2 subjects (66.7%) each were enterocolitis, COVID-19, device related infection, and respiratory syncytial virus infection. Most TEAEs were single events in single subjects.
- A total of 12 treatment-emergent SAEs (TESAEs) were reported in 3 subjects (100%). Of these, 5 events of device related infection and 4 events of vascular device occlusion were reported in 2 subjects and 1 subject, respectively. Reported events of bacteraemia, catheter site pruritus, and device breakage were single events in single subjects. All TESAEs were resolved. None of the TESAEs were considered related to the study drug.
- There were no deaths, TEAEs leading to treatment discontinuation, or AESIs during the study.
- There were no clinically meaningful changes in hematology and biochemistry measures during the study. No clinically meaningful high or low values were observed from coagulation measures.
- No clinically meaningful changes in any parameters of vital signs, body weight, height (or length), and head circumference were noted.
- No clinically meaningful changes in fecal and urine output were noted.

2.3.3. Discussion on clinical aspects

This study, TAK-633-3008, is a stand-alone study performed in addition to the teduglutide development program in Japan.

The study was an open-label study designed to study the administration of the 1.25 mg formulation of teduglutide to Japanese paediatric patients aged 4 months of corrected gestational age or older, with short bowel syndrome (SBS).

The study was initiated as a Phase 3 study with defined study objectives on safety and efficacy and corresponding endpoints. However, upon receiving approval of the 1.25 mg formulation the study was continued as a post-marketing clinical study (Phase 4 study) until each enrolled subject switched to the 1.25 mg commercial formulation.

The study design is similar to previous phase 3 studies with teduglutide in the paediatric population, including infants aged 4 months (corrected gestational age) or older. The study design is acceptable.

Evaluation of the safety of the 1.25 mg formulation of teduglutide in Japanese paediatric patients was defined as the primary objective of the study, whereas evaluation of efficacy was defined as a secondary objective.

This is supported as the non-comparative open-label study design is best suited to evaluate safety, and less well suited to evaluate efficacy.

Consequently, emphasis of the evaluations should be on the safety endpoints.

The respective lists of safety and efficacy endpoints are similar to previous studies with teduglutide in the paediatric population. These endpoints are accepted.

Approximately 5 subjects were planned; 3 patients were analysed for safety and efficacy. It is accepted to determine the sample size on enrolment feasibility in this study design. It is not clear if any patients were screened, who were subsequently excluded from enrolment. It should have been clarified in the study report. However, it is unlikely to impact the conclusion of the study results. Therefore, this issue will not be pursued further.

The efficacy results in these 3 patients are non-comparative, observational and descriptive only. The results are in line with observations from previous studies in the paediatric population in this age-group, i.e. infants aged 4 months (corrected gestational age) or older.

The safety results in these 3 patients are in line with the observations from previous studies in the paediatric population in this age-group, i.e. infants aged 4 months (corrected gestational age) or older.

There are no reports of deaths or neoplasia.

In conclusion, no new findings on neither safety nor efficacy of teduglutide have been observed in this non-comparative, observational open-label study in 3 infant patients. No regulatory action is warranted.

3. Rapporteur’s overall conclusion and recommendation

☒ Fulfilled