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Human Medicines Development and Evaluation

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/P46/011

Note

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

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Introduction

On 14 January 2021, the MAH submitted a completed paediatric study (SHP633-303) for Revestive, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric study does not influence the benefit risk for Revestive and that no consequential regulatory action is required.

Scientific discussion

Information on the development program

The MAH stated that study SHP633-303 was a Retrospective and Prospective, Open-label, Long-term Safety and Efficacy Study of Teduglutide in Pediatric Subjects with Short Bowel Syndrome Who Completed TED-C13-003. The Study was part of the product development.

Information on the pharmaceutical formulation used in the study(ies)

Teduglutide was provided in 3 mL sterile, single-use, glass vials containing 5 mg or 1.25 mg teduglutide. Sterile water (0.5 mL) was provided in a prefilled syringe. In addition to the active ingredient (teduglutide), each vial of teduglutide contains L-histidine, mannitol, monobasic sodium phosphate monohydrate, and dibasic sodium phosphate as excipients.

Clinical aspects

Introduction

Teduglutide [rDNA origin] is an analog of naturally occurring human glucagon-like peptide-2 (GLP-2), a peptide secreted by L-cells of the distal intestine. Teduglutide under the trade name Revestive® first received marketing authorization in the European Union via centralized procedure for the treatment of short bowel syndrome (SBS) on 30 Aug 2012. On 29 Jun 2016, the European Commission granted an extension of the Market Authorization for teduglutide (Revestive) for the treatment of patients aged 1 year and above with SBS.

Clinical study(ies)

Methods

Study SHP633-303 was a Phase 3, retrospective and prospective, open-label, long-term extension study to evaluate the safety and efficacy of teduglutide in pediatric subjects with SBS who had completed the TED-C13-003 study (hereinafter referred to as the core study). In addition to evaluating the long-term safety and durability of efficacy after 12 weeks of treatment in the core study, the extension study evaluated the need for additional teduglutide treatment in these subjects and allowed for the first-time treatment of teduglutide-naïve subjects who participated in the standard of care treatment arm in the core study.

The primary objective of the study was to evaluate the long-term safety and tolerability of teduglutide treatment in pediatric subjects with SBS who completed the core study. The secondary objective of

this study was to evaluate the long-term efficacy of teduglutide treatment in pediatric subjects with SBS who completed the core study.

Subjects who previously received teduglutide during the core study, as well as subjects who were in the standard of care treatment group, were eligible for the extension study. Subjects might have participated in multiple no-teduglutide treatment (NTT) periods and/or multiple 28-week teduglutide treatment cycles depending on the disease course:

- Subjects not receiving teduglutide treatment (ie, an NTT period) were seen approximately every 12 weeks for collection of safety, parenteral support (PS) requirements, and quality of life data. Visits occurred every 12 weeks, a frequency that is consistent with standard medical practices. At any point during an NTT period, subjects who met at least 1 teduglutide treatment inclusion criteria might have proceeded directly to the pre-treatment visit if the investigator, subject, and parent or legal guardian agreed to proceed with teduglutide therapy.
- Subjects receiving teduglutide treatment participated in treatment cycles, each consisting of 24 weeks of teduglutide treatment followed by a 4-week follow-up period (no treatment). The follow-up period was a mechanism to evaluate whether continued teduglutide was needed. During the teduglutide treatment cycle, visit frequency was similar to that of the core study and other teduglutide studies to ensure sufficient safety monitoring and weaning of PS. Maximum duration of teduglutide treatment was 3 years.

The final clinical results for pediatric subjects with SBS in Study SHP633-303 spans the time from the end of the core study through the end of the extension study. Select data are included from the retrospective period, during which specific safety and efficacy measures were completed in the course of the subject's standard medical care between the end of the core study end of study (EOS) visit and the beginning of the prospective period of this extension study.

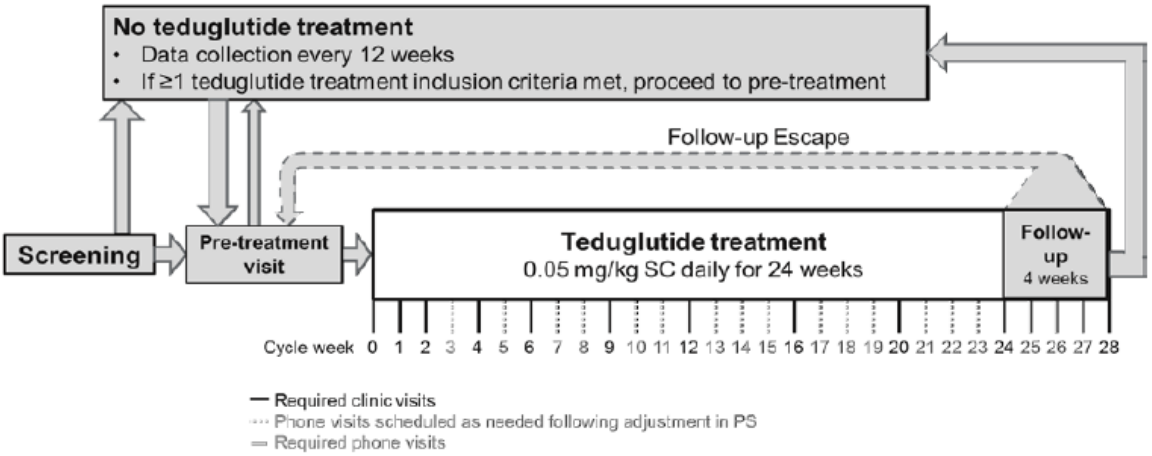
SHP633-303 Study Design

Both retrospective data and prospective data were collected during the extension study, Study SHP633-303, for pediatric subjects with SBS. Data were collected per the reference start dates defined as follows:

- the date of the first teduglutide dose in the core study (for the retrospective data collection, a period of 2.4 to 3.3 years);
- the date of the first teduglutide dose or the date of informed consent for subjects who did not receive any teduglutide during this period (for the prospective period of Study SHP-303)

Prospective data collection occurred at pre-specified visits over 28-week treatment cycle, with clinic visits at Weeks 1, 2, 4, 6, 9, 12, 16, 20, 24, and 28; and phone visits approximately 1 week after adjustments in PS during the teduglutide treatment period (between Weeks 1 and 24) and weekly during the follow-up period (between Weeks 24 and 28). A subject was considered as having completed the study if the subject had not withdrawn early from the study for any reason prior to completing the EOS visit. A schematic representation of the study design for Study SHP633-303 is presented in Figure 1.

Figure 1. Study Design Schematic (Study SHP633-303)



Cross reference: Study SHP633-303 CSR Figure 1.

Note: Safety and efficacy data for subjects not receiving teduglutide treatment were captured approximately every 12 weeks, but subjects might proceed to the pretreatment visit at any time in order to assess eligibility for teduglutide therapy. Eligible subjects entered a 28-week teduglutide cycle. During this cycle, subjects returned to the site for safety and efficacy assessments at Weeks 1, 2, 4, 6, 9, 12, 16, 20, and 24 (solid black lines). Phone visits were required approximately 1 week after adjustments in parenteral support (PS) during the intervening weeks between Weeks 2 and 24 (dashed grey lines). Subjects discontinued teduglutide at Week 24 and entered a 4 week follow-up (no-treatment) period, during which phone visits were performed weekly (solid grey lines). If an escape criterion was met during the follow-up period, subjects might have proceeded directly to another pretreatment visit.

Assessor's comments

Both retrospective data and prospective data were collected during the extension study, Study SHP633-303, for pediatric subjects with SBS. Data were collected per the reference start dates defined as follows:

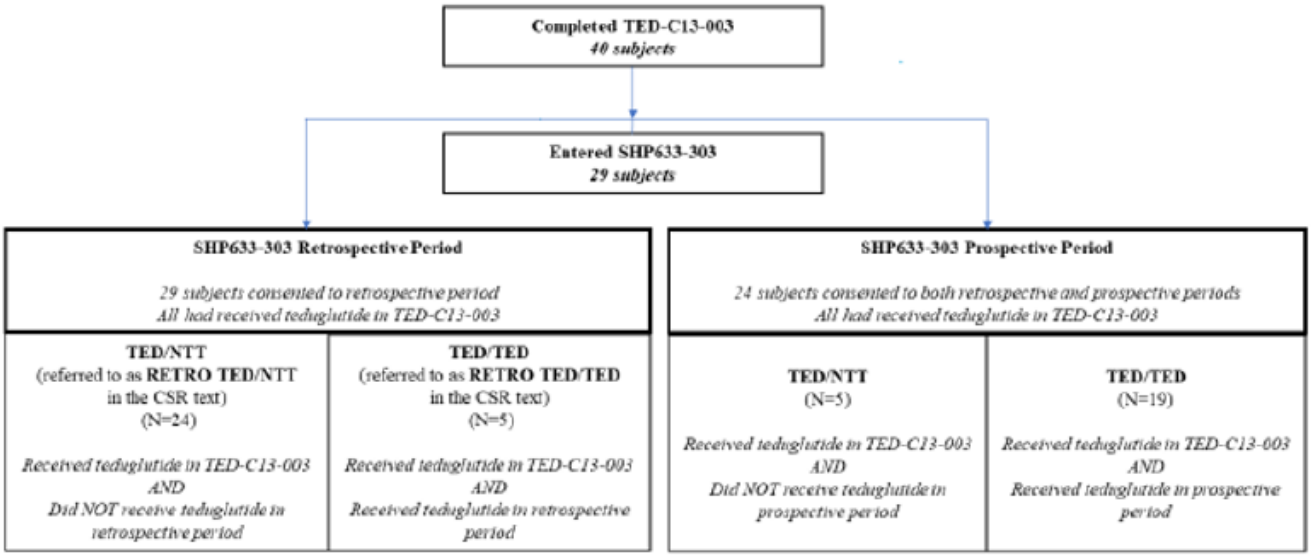
- the date of the first teduglutide dose in the core study (for the retrospective data collection, a period of 2.4 to 3.3 years);
- the date of the first teduglutide dose or the date of informed consent for subjects who did not receive any teduglutide during this period (for the prospective period of Study SHP-303).

Results

- **Disposition of Subjects**

Enrolled into the core study TED-C13-003 were male and female children and adolescents, aged 1 year through 17 years, with SBS as a result of major intestinal resection (eg, due to necrotizing enterocolitis, midgut volvulus, intestinal atresia, or gastroschisis) who had stable PS requirements for at least 3 months prior to screening. A total of 29 subjects who completed the core study, including subjects in the standard of care treatment arm, were screened at 10 sites in the United States and 1 site in the United Kingdom and entered Study SHP633-303. The disposition of subjects in the retrospective and prospective periods is shown in Figure 2. All enrolled subjects in each of the retrospective and prospective study periods were included in the data analyses for that period.

Figure 2. Subject Disposition (Study SHP633-303)



NTT=no teduglutide treatment; RETRO = retrospective; TED=teduglutide treatment
Source: StudyTED-C13-003 CSR Section 14, Table 14.1.2.1; Table 14.1.1.1R; and Table 14.1.1.1.

- **Demographics and Baseline Characteristics**

The mean ages of the 24 subjects in the prospective period at the core study baseline were 5.0 and 5.1 years in the teduglutide (TED)/NTT and TED/TED groups (safety population), respectively. There were 4 subjects (80.0%) in the 1 to less than 12 years of age group and 1 subject (20.0%) 12 to less than 17 years of age in the TED/NTT group, compared with 17 subjects (89.5%) and 2 subjects (10.5%) in those respective age categories in the TED/TED group. Of the 24 subjects in the ANY TED group, most were male (70.8%), white (83.3%), and not Hispanic or Latino (60.9%). Three black subjects (12.5%) and 1 Asian subject (4.2%) were enrolled.

Growth parameters at the core study baseline showed below average weight and height for both groups. Mean body mass index (BMI) and weight and height z-scores were similar in the TED/NTT and TED/TED groups.

Short Bowel Syndrome History

The most common causes of SBS in the safety population were midgut volvulus (7 subjects [29.2%]), intestinal atresia (6 subjects [25.0%]), gastroschisis (6 subjects [25.0%]), and necrotizing enterocolitis (3 subjects [12.5%]). The TED/NTT and TED/TED subjects had similar stoma, colon and intestinal measurement characteristics.

Assessor's comments

Enrolled into the core study TED-C13-003 were children and adolescents, aged 1 year through 17 years, with SBS as a result of major intestinal resection who had stable PS requirements for at least 3 months prior to screening. A total of 29 subjects who completed the core study, including subjects in the standard of care treatment arm. All enrolled subjects in each of the retrospective and prospective study periods were included in the data analyses for that period.

The mean ages of the 24 subjects in the prospective period at the core study baseline were 5.0 and 5.1 years in the teduglutide (TED)/NTT and TED/TED groups (safety population), respectively. There were 4 subjects (80.0%) in the 1 to less than 12 years of age group and 1 subject (20.0%) 12 to less than 17 years of age in the TED/NTT group, compared with 17 subjects (89.5%) and 2 subjects (10.5%) in those respective age categories in the TED/TED group

- **Efficacy Results**

Retrospective Period of Study SHP633-303

Retrospective efficacy data consisted of historical PS prescriptions, as subjects did not complete diaries during the retrospective period. Retrospective PS was captured as the most recent representative PS prescription at 12-week intervals. The 5 subjects in the retrospective (RETRO) TED/TED group did not receive additional teduglutide treatment until 78 to 98 weeks after core study completion. These subjects received treatment for 18 to 67 weeks. Only 3 of the 5 subjects had known prescribed PS parameters at the start and stop dates of treatment.

The efficacy results for the 5 subjects who received TED during the retrospective period (RETRO TED/TED group) showed that long-term administration of teduglutide was temporally associated with reductions in mean prescribed PS volume, caloric intake, and infusion time. In contrast, subjects not treated with teduglutide had minimal long-term changes in prescribed PS parameters. The data collected during the retrospective period. There were no protocol deviations reported during the retrospective data collection.

Prospective Period of Study SHP633-303

During this extension study, all 19 TED/TED subjects completed teduglutide treatment in Cycle 1. But as the study progressed, certain subjects changed to dosing with a commercial product. As such, 17, 14, 13, 8, and 5 subjects completed Cycles 2, 3, 4, 5, and 6, respectively (Study SHP633-303 CSR Table 11). Since Cycle 4 was the last cycle with at least 10 subjects participating and marked the end of 2 years of dosing, the Cycle 1 Day 1 (or C1D1) and Cycle 4 Week 24/end of treatment (EOT), results are preferentially reported in the text discussions of clinical efficacy results.

Efficacy data were collected for 19 subjects in the TED/TED group during the prospective period. Data on PS parameters were captured in subject diaries and investigator prescriptions. Diary data were deemed to be more representative of subject PS intake. Major protocol deviations that occurred during the prospective period are summarized in Study SHP633-303 CSR; all deviations are provided by subject, by type and by COVID-19 relationship in Appendix 16.2, Listing 16.2.1.5. The procedural deviations did affect the scheduled data collection and produced instances of missing data.

All prospective efficacy data are presented in the Study SHP633-303 CSR Section 11.1.2, including data for subjects in the TED/NTT group. The data below focuses on results for the TED/TED group.

Reductions in PS Volume Diary and Prescribed PS Volume

The number and percentage of TED/TED subjects achieving at least 20%, at least 50%, and at least 75% reductions in weight-normalized prescribed PS volume increased over the course of each of the

first 4 to 5 teduglutide treatment cycles at EOT compared with Day 1 (Study SHP633-303 CSR Table 14).

At Cycle 1 Day 1 (C1D1), 8 of 19 subjects (42.1%) achieved at least 20% reduction in diary mean PS volume; at Cycle 4 End of Treatment (C4EOT), this percentage had increased to 9 of 13 subjects (69.2%). This trend was also evident for the 50% and 75% milestones:

- At C1D1, 1 of 19 subjects (5.3%) achieved at least 50% reduction; at C4EOT, this percentage increased to 9 of 13 subjects (69.2%).
- At C1D1, 1 of 19 subjects (5.3%) achieved at least 75% reduction; at C4EOT, this percentage increased to 5 of 13 subjects (38.5%).

A similar trend was observed in number and percentage of subjects achieving reduction in PS volume based on diary data (Study SHP633-303 CSR Table 14).

The mean PS volume required by TED/TED subjects was decreased in the first cycle, and the long-term efficacy of teduglutide resulted in a continuing trend of further decreases over the course of each subsequent treatment cycle. From the mean core study baseline of 64.41 mL/kg/day, the mean diary PS volume was reduced by 11.12 mL/kg/day (11.18%) at C1D1; at C4 EOT the mean volume was decreased by 40.10 mL/kg/day or 62.92% (Study SHP633-303 CSR Table 15).

Change From Baseline in PS Caloric Intake

The mean caloric intake in prescribed PS caloric intake required by TED/TED subjects was decreased by EOT in the first cycle, and the long-term efficacy of teduglutide resulted in a continuing trend of further decreases over the course of each subsequent treatment cycle (Study SHP633-303 CSR Table 16). From the mean core study baseline of 47.27 kcal/kg/day, the mean diary PS caloric intake was increased by 3.60% at C1D1; at C1EOT, the mean PS caloric intake was decreased by 33.50%, and at C4EOT the mean PS caloric intake was reduced by 49.51%. The reduced caloric intake in the diary data were similar to that of the prescribed data.

Enteral Autonomy (no actual or prescribed PS)

Of the 19 TED/TED subjects, 1 (5.3%) achieved enteral autonomy at C1EOT; at C4EOT, 5 of 13 subjects (38.5%) achieved enteral autonomy (Study SHP633-303 CSR Section 14, Table 14.2.4.1).

Change and Percent Change From Baseline in Days per Week of Parenteral Support

Based on diary data, mean PS required by TED/TED subjects at core study baseline ranged from 6.53 to 7.00 days/week. Reductions in PS days/week were as follows (Study SHP633-303 CSR Table 18).

- For the at least 20% reduction group, the mean PS time was reduced from 6.53 to 5.69 days/week (-12.47%) at C1EOT and trended downward to a value of 2.89 days/week (-56.51%) at C4EOT
- For the at least 50% reduction group, the mean PS time was reduced from 7.00 to 4.80 days/week (-31.43%) at C1EOT and trended downward in subsequent cycles to 2.89 days/week (-56.51%) at C4EOT.
- For the at least 75% reduction group, the mean PS time was reduced from 7.00 to 1.50 days/week (-78.57%) at C1EOT and trended downward to 0.00 days/week (-100.00%) at C4EOT.

The reduced PS days/week in the prescribed data were similar to that of the diary data (Study SHP633-303 CSR Section 14, Table 14.2.6.6 and Table 14.2.6.5, respectively).

Change and Percent Change From Baseline in Hours per Day of Parenteral Support

Based on diary data, PS required by TED/TED subjects at core study baseline ranged from 10.00 to 14.59 hours/day. Reductions in PS hours/day were as follows (Study SHP633-303 CSR Table 17):

- For the at least 20% reduction group, the mean PS time was reduced from 12.50 to 7.86 hours/day (-36.21%) at C1EOT and trended downward to 4.19 hours/day (-65.60%) at C4EOT.
- For the at least 50% reduction group, the mean PS time was reduced from 14.59 to 6.14 hours/day (-62.28%) at C1EOT and trended downward to 4.19 hours/day (-65.60%) at C4EOT.
- For the at least 75% reduction group, the mean PS time was reduced from 10.00 to 2.36 hours/day (-80.36%) at C1EOT and trended downward to 0.00 hours/day (-100.00%) at C4EOT.

The reduced PS time (hours/day) in the prescribed data were similar to that of the diary data (Study SHP633-303 CSR Section 14, Table 14.2.5.6 and Table 14.2.5.5, respectively).

Based on diary data, reductions in PS infusion hours/day (Study SHP633-303 CSR Table 17) and days/week (Study SHP633-303 CSR Table 18) were observed among subjects who achieved reductions in diary PS volume at C4EOT (or C1D1) (Study SHP633-303 CSR Table 14):

• For the 9 TED/TED subjects (69.2%) who achieved at least a 20% reduction in diary PS volume at C4EOT, the mean change from baseline in PS infusion hours/day was -65.60% and -56.51% days/week.

• For the 9 TED/TED subjects (69.2%) who achieved at least a 50% reduction in diary PS volume at C4EOT, the mean change from baseline in PS infusion hours/day was -65.60% and -56.51% days/week.

• For the 5 TED/TED subjects (38.5%) who achieved at least a 75% reduction in diary PS volume at C4EOT, the mean change from baseline in PS infusion time was -100.00% for both hours/day and days/week.

The relative reductions in prescribed hours per day and days per week (Study SHP633-303 CSR Section 14, Table 14.2.5.6 and Table 14.2.6.6) were similar to that of the diary data.

Quality of Life Findings

Most of the Pediatric Quality of Life (PedsQL) Generic Core subscale scores, PedsQL Family Impact Module subscale scores, and the PedsQL Gastrointestinal Symptoms Module subscale scores showed little change for the teduglutide cycles over the course of the study (SHP633-303 CSR Section 11.2). However, scores that showed a trend toward higher scores (improvement) to Cycle 4 Week 24 for the TED/TED group included school functioning, with a 13.57-point mean improvement (Study SHP633-303 CSR Table 19), and a 4.4-point improvement in cognitive functioning.

Assessor's comments

Efficacy data were collected for 19 subjects in the TED/TED group during the prospective period. During the extension study, all 19 TED/TED subjects completed teduglutide treatment in Cycle 1. But as the study progressed, certain subjects changed to dosing with a commercial product. As such, 17, 14, 13, 8, and 5 subjects completed Cycles 2, 3, 4, 5, and 6, respectively (Study SHP633-303 CSR Table 11). Since Cycle 4 was the last cycle with at least 10 subjects participating and marked the end of 2 years of dosing, the Cycle 1 Day 1 (or C1D1) and Cycle 4 Week 24/end of treatment (EOT), results are reported.

Reductions in PS Volume Diary and Prescribed PS Volume

The number and percentage of TED/TED subjects achieving at least 20%, at least 50%, and at least 75% reductions in weight-normalized prescribed PS volume increased over the course of each of the first 4 to 5 teduglutide treatment cycles at EOT compared with Day 1.

At Cycle 1 Day 1 (C1D1), 8 of 19 subjects (42.1%) achieved at least 20% reduction in diary mean PS volume; at Cycle 4 End of Treatment (C4EOT), this percentage had increased to 9 of 13 subjects (69.2%). This trend was also evident for the 50% and 75% milestones:

- At C1D1, 1 of 19 subjects (5.3%) achieved at least 50% reduction; at C4EOT, this percentage increased to 9 of 13 subjects (69.2%).
- At C1D1, 1 of 19 subjects (5.3%) achieved at least 75% reduction; at C4EOT, this percentage increased to 5 of 13 subjects (38.5%).

A similar trend was observed in number and percentage of subjects achieving reduction in PS volume based on diary data.

Change From Baseline in PS Caloric Intake

From the mean core study baseline of 47.27 kcal/kg/day, the mean diary PS caloric intake was increased by 3.60% at C1D1; at C1EOT, the mean PS caloric intake was decreased by 33.50%, and at C4EOT the mean PS caloric intake was reduced by 49.51%. The reduced caloric intake in the diary data were similar to that of the prescribed data.

Enteral Autonomy

Of the 19 TED/TED subjects, 1 (5.3%) achieved enteral autonomy at C1EOT; at C4EOT, 5 of 13 subjects (38.5%) achieved enteral autonomy.

- **Safety Results**

Extent of Exposure in Pediatric Subjects

Mean exposure to 0.05 mg/kg/day teduglutide during the retrospective period was 42.9±17.92 weeks for the 5 subjects in the RETRO TED/TED group (Study SHP633-303 CSR Section 12.1.1). These subjects started treatment between Week 78 and Week 96 after completion of the core study and received teduglutide treatment for 18 to 67 weeks. Safety data for these subjects is presented in the Study SHP633-303 CSR and discussed only briefly in this section.

Mean exposure to 0.05/mg/kg/day teduglutide during the prospective period was 94.269±40.2928 weeks for the 19 subjects in the TED/TED group. All subjects had at least 24 weeks of exposure; 8 (42.1%) had 120 to less than 144 weeks of exposure and 4 (21.1%) had less than 48 weeks of exposure (Study SHP633-303 CSR Table 21).

Safety Results

Retrospective Period

The retrospective data encompassed observations of subjects for a period of 2.4 to 3.3 years after completion of the core study. Only adverse events (AEs) related to teduglutide, adverse events of special interest (AESIs), and serious adverse events (SAEs) were reported for the retrospective data collection. The AE data for the retrospective period are presented in the Study SHP633-303 CSR, Section 12.2.1 through Section 12.2.1.4. No laboratory data were collected during the retrospective period of the study.

Of the 23 AEs reported in 4 subjects (80.0%) in the RETRO TED/TED group (Study SHP633-303 CSR Table 22), 2 AEs (abdominal pain and constipation) were assessed as study drug related in 1 subject and led to interruption of teduglutide treatment (Study SHP633-303 CSR, Section 12.2.1.2 and Section 12.2.1.3).

No deaths were reported (Study SHP633-303 CSR Section 12.3.1.1). A total of 21 SAEs were reported in 4 of the 5 subjects receiving teduglutide (RETRO TED/TED group [80.0%]; Study SHP633-303 CSR Table 28). The most frequently reported SAEs were pyrexia in 2 subjects and device-related infection in 2 subjects. All device-related events were related to the central venous catheters used to administer PS, not to the teduglutide injection device. No SAEs were assessed as related to teduglutide.

Prospective Period

All reported AEs are listed in Study SHP633-303 Appendix 16.2, Listing 16.2.7.1.

Adverse Events

Data for 24 subjects who provided informed consent for the prospective period and met all study eligibility criteria are included in the safety population.

A total of 503 TEAEs in 23 subjects (95.8%) were reported in the safety population, which includes 454 TEAEs in 19 subjects in the TED/TED group and 503 TEAEs in 24 subjects in the ANY TED group (Table 1). The majority of TEAEs were mild or moderate in severity. Two subjects (8.3%) in the ANY TED group had 3 treatment-emergent serious adverse events (TESAEs) that were considered study drug-related. No TEAEs led to teduglutide discontinuation or study discontinuation. No AESIs were reported. No deaths occurred during the study.

Table 1. Overall Summary of Treatment-Emergent Adverse Events - Safety Population

Category	TED/NTT (N=5) n (%)	E	TED/TED (N=19) n (%)	E	ANY TED (N=24) n (%)	E
Any TEAE (prospective study period)	**4 (80.0)**	**49**	**19 (100)**	**454**	**23 (95.8)**	**503**
TEAE Highest Severity[a]						
Mild	1 (20.0)		2 (10.5)		3 (12.5)	
Moderate	2 (40.0)		9 (47.4)		11 (45.8)	
Severe	1 (20.0)		8 (42.1)		9 (37.5)	
TEAE Relationship						
Not related	4 (80.0)	47	19 (100)	444	23 (95.8)	491
Related	1 (20.0)	2	6 (31.6)	10	7 (29.2)	12
Any TESAE	**3 (60.0)**	**8**	**17 (89.5)**	**85**	**20 (83.3)**	**93**
TESAE Relationship						
Not related	2 (40.0)	6	17 (89.5)	84	19 (79.2)	90
Related	1 (20.0)	2	1 (5.3)	1	2 (8.3)	3
TEAE Leading to Treatment Discontinuation	**0**		**0**		**0**	
TEAE Leading to Study Discontinuation	**0**		**0**		**0**	
TEAE Leading to Death	**0**		**0**		**0**	
Any AESI	**0**		**0**		**0**	

Table 1. Overall Summary of Treatment-Emergent Adverse Events - Safety Population

Category	TED/NTT (N=5) n (%)	E	TED/TED (N=19) n (%)	E	ANY TED (N=24) n (%)	E

AESI=adverse events of special interest; E=event(s); TEAE=treatment-emergent nonserious adverse event; TESAE=treatment-emergent serious adverse event

[a] Only highest severity per subject is counted for incidence and percentage.

Notes:

- TED/NTT - subjects who received teduglutide in the core study but not during the prospective period of this study; TED/TED - subjects who received teduglutide in the core study and during the prospective period of this study; ANY TED - subjects who received any teduglutide in either core study or during the prospective period of this study.
- TEAEs are defined as AEs that started or worsened on or after the first dose of teduglutide treatment in the core study. Subjects are counted no more than once for incidence, but could be counted multiple times for the number of events.
- Any TEAEs with missing severity were classified as severe. Any TEAE with a missing relationship to Investigational Product was classified as related.

Source: Study SHP633-303 CSR Section 14, Table 14.3.2.1.

In the TED/TED and ANY TED groups, the highest percentages of TEAEs (≥50% of subjects) occurred in the system organ classes (SOCs) of Infections and infestations, Gastrointestinal disorders, General disorders and administration site conditions, Investigations, and Respiratory, thoracic and mediastinal disorders. The most frequently reported (>35% of subjects) TEAEs in each group were preferred terms of vomiting, pyrexia, upper respiratory tract infection, device-related infection, and abdominal pain (Study SHP633-303 CSR Table 25). In the TED/TED group, 6 subjects (31.6%) had 10 TEAEs that

were considered related to teduglutide; in the ANY TED group, 7 subjects (29.2%) reported 12 TEAEs that were considered related (Study SHP633-303 CSR Table 26).

Deaths, Other Serious Events and Other Significant Events

For subjects in the ANY TED group, there were no deaths (Study SHP633-303 CSR Section 12.3.2.1), AESIs including polyps of the colon or neoplasia (Study SHP633-303 CSR Section 12.3.2.3), or TEAEs leading to treatment discontinuation or study discontinuation (Study SHP633-303 CSR Section 12.3.2.3). Overall, 93 TESAEs were reported in 20 subjects in the ANY TED group, with 85 TESAEs being reported in 17 subjects in the TED/TED group (Table 2). In the ANY TED group, 2 subjects (8.3%) reported 3 TESAEs that were related to teduglutide (Table 1).

Thirty-seven of 85 TESAEs reported in the TED/TED group and 5 of the 8 TESAEs reported in the TED/NTT group belonged to the SOC of Infections and infestations. The TESAEs occurring in more than 2 subjects were device-related infection, which occurred in 9 subjects in the TED/TED group and 1 in the TED/NTT group, pyrexia in 7 subjects in the TED/TED group, and influenza in 4 subjects in the TED/TED group. All SAEs are listed in Study SHP633-303 CSR Section 14, Table 14.3.4.3).

Table 2. Treatment-Emergent Serious Adverse Events By System Organ Class and Preferred Term-Prospective Data - Safety Population

	TED/NTT (N=5)		TED/TED (N=19)		ANY TED (N=24)	
Category	**n (%)**	**E**	**n (%)**	**E**	**n (%)**	**E**
Any TESAE	**3 (60.0)**	**8**	**17 (89.5)**	**85**	**20 (83.3)**	**93**
Blood and lymphatic system disorders	**0**		**4 (21.1)**	**4**	**4 (16.7)**	**4**
Haemorrhagic anaemia	0		2 (10.5)	2	2 (8.3)	2
Febrile neutropenia	0		1 (5.3)	1	1 (4.2)	1
Microcytic anaemia	0		1 (5.3)	1	1 (4.2)	1
Congenital, familial and genetic disorders	**0**		**1 (5.3)**	**1**	**1 (4.2)**	**1**
Congenital megacolon	0		1 (5.3)	1	1 (4.2)	1
Gastrointestinal disorders	**1 (20.0)**	**2**	**6 (31.6)**	**15**	**7 (29.2)**	**17**
Gastrointestinal haemorrhage	0		2 (10.5)	6	2 (8.3)	6
FIleus	0		2 (10.5)	2	2 (8.3)	2
Short-bowel syndrome	0		2 (10.5)	2	2 (8.3)	2
Abdominal adhesions	1 (20.0)	1	0		1 (4.2)	1
Diarrhoea	0		1 (5.3)	2	1 (4.2)	2
Duodenal ulcer	0		1 (5.3)	1	1 (4.2)	1
Intestinal obstruction	1 (20.0)	1	0		1 (4.2)	1
Vomiting	0		1 (5.3)	2	1 (4.2)	2
General disorders and administration site conditions	**0**		**8 (42.1)**	**14**	**8 (33.3)**	**14**
Pyrexia	0		7 (36.8)	12	7 (29.2)	12
Face oedema	0		1 (5.3)	1	1 (4.2)	1
Oedema peripheral	0		1 (5.3)	1	1 (4.2)	1
Infections and infestations	**1 (20.0)**	**5**	**15 (78.9)**	**37**	**16 (66.7)**	**42**
Device related infection	1 (20.0)	1	9 (47.4)	13	10 (41.7)	14
Influenza	0		4 (21.1)	4	4 (16.7)	4
Gastroenteritis viral	1 (20.0)	1	2 (10.5)	3	3 (12.5)	4
Cellulitis	1 (20.0)	1	1 (5.3)	1	2 (8.3)	2
Device related sepsis	1 (20.0)	1	1 (5.3)	1	2 (8.3)	2
Gastroenteritis	0		2 (10.5)	2	2 (8.3)	2
Upper respiratory tract infection	0		2 (10.5)	2	2 (8.3)	2
Viral infection	0		2 (10.5)	2	2 (8.3)	2
Bacteraemia	0		1 (5.3)	1	1 (4.2)	1

Table 2. Treatment-Emergent Serious Adverse Events By System Organ Class and Preferred Term-Prospective Data - Safety Population

	TED/NTT (N=5)		TED/TED (N=19)		ANY TED (N=24)	
Category	**n (%)**	**E**	**n (%)**	**E**	**n (%)**	**E**
Bacterial infection	0		1 (5.3)	2	1 (4.2)	2
Cystitis	1 (20.0)	1	0		1 (4.2)	1
Fungal infection	0		1 (5.3)	1	1 (4.2)	1
Sepsis	0		1 (5.3)	3	1 (4.2)	3
Staphylococcal sepsis	0		1 (5.3)	1	1 (4.2)	1
Infections and infestations (cont'd)	**1 (20.0)**	**5**	**15 (78.9)**	**37**	**16 (66.7)**	**42**
Viral upper respiratory tract infection	0		1 (5.3)	1	1 (4.2)	1
Injury, poisoning and procedural complications	**0**		**1 (5.3)**	**2**	**1 (4.2)**	**2**
Anastomotic ulcer	0		1 (5.3)	2	1 (4.2)	2
Investigations	**0**		**1 (5.3)**	**1**	**1 (4.2)**	**1**
Influenza A virus test positive	0		1 (5.3)	1	1 (4.2)	1
Metabolism and nutrition disorders	**1 (20.0)**	**1**	**4 (21.1)**	**10**	**5 (20.8)**	**11**
Metabolic acidosis	1 (20.0)	1	1 (5.3)	1	2 (8.3)	2
Electrolyte imbalance	0		1 (5.3)	4	1 (4.2)	4
Hypoalbuminaemia	0		1 (5.3)	1	1 (4.2)	1
Hyponatraemia	0		1 (5.3)	1	1 (4.2)	1
Lactic acidosis	0		1 (5.3)	1	1 (4.2)	1
Weight gain poor	0		1 (5.3)	2	1 (4.2)	2
Vascular disorders	**0**		**1 (5.3)**	**1**	**1 (4.2)**	**1**
Superior vena cava occlusion	0		1 (5.3)	1	1 (4.2)	1

Table 2. Treatment-Emergent Serious Adverse Events By System Organ Class and Preferred Term-Prospective Data - Safety Population

	TED/NTT (N=5)		TED/TED (N=19)		ANY TED (N=24)	
Category	n (%)	E	n (%)	E	n (%)	E

AE=nonserious adverse event; E = event; SOC=system organ class; TEAE=treatment-emergent AE; TESAE=treatment-emergent serious adverse event

Notes:

- TED/NTT – subjects who received teduglutide in the core study but not during the prospective period of this study; TED/TED - subjects who received teduglutide in the core study and during the prospective period of this study; ANY TED – subjects who received any teduglutide in either core study or during the prospective period of this study.
- Percentages are based on the number of subjects in the safety population for the defined treatment groups.
- TEAEs are defined as AEs that started or worsened on or after the first dose of teduglutide treatment in the core study.
- Subjects are counted no more than once for incidence, but can be counted multiple times for the number of events.
- Adverse events were coded to primary SOC and preferred term using Medical Dictionary for Medical Activities (MedDRA) version 19.1.
- SOCs are sorted alphabetically and preferred terms are sorted by the descending order of frequency in the ANY TED treatment group.

Source: Study SHP633-303 CSR Section 14, Table 14.3.4.1.

AE Summary

In the prospective period, there were no deaths (Study SHP633-303 CSR Section 14, Table 14.3.4.6) or discontinuations due to TEAEs. No AESIs were reported.

There were a total of 93 TESAEs reported in 20 subjects during the prospective period, with 8 TESAEs reported in 3 subjects (60.0%) in the TED/NTT group and 85 TESAEs in 17 subjects (89.5%) in the TED/TED group (Table 1). Two subjects reported 3 SAEs that were related to teduglutide (Study SHP633-303 Section 14, Table 14.3.4.3).

Clinical Laboratory Evaluations in Pediatric Subjects

In clinical laboratory measures, 3 subjects (15.8%) in the TED/TED group experienced an isolated alanine transaminase (ALT) level greater than 8 × upper limit of normal (ULN) (Study SHP633-303 Section 12.4.2.3); all had elevated ALT levels at core study baseline. No TEAEs related to these liver laboratory abnormalities were reported in these 3 subjects. An additional subject had nonserious ALT values at multiple timepoints throughout the study and an isolated ALT value greater than 8 × ULN value at Cycle 1 Week 16; a TEAE of ALT increased was reported. Few subjects had markedly abnormal values for other serum chemistry laboratory measures, which included 2 subjects (10.5%) in the TED/TED group who experienced an amylase level greater than 3 × ULN (Study SHP633-303 Section 14, Table 14.3.5.13). Subjects with markedly abnormal hematology values included 1 subject (5.3%) in the TED/TED group who had both leukocyte and neutrophil counts below the lab reference range (considered markedly abnormal) at multiple timepoints (Study SHP633-303 Section 14, Table 14.3.5.15) and 1 subject in the TED/NTT group who had a markedly abnormal high platelet count (>700 × 109/L) and for whom an AE of platelet count increased was reported (Study SHP633-303 Section 14, Table 14.3.5.16 and Table 14.3.2.2).

Gastrointestinal-Specific Testing

Three subjects in the TED/TED group had clinically significant findings for colonoscopy, and 10 subjects had clinically significant findings for fetal occult blood testing (Study SHP633-303 CSR Table 32). No polyps or neoplastic lesions were identified in any subject.

No clinically meaningful changes in stool output, stool consistency, or urine output were observed, despite the reductions in PS, indicating that the adjustments in PS and enteral support were appropriately titrated to match the changes in intestinal absorptive capacity.

Vital Signs and Other Observations Related to Safety

There were no clinically significant vital sign results (Study SHP633-303 CSR Appendix 16.2, Listing 16.2.8.9).

Body Weight and Body Mass Index

No clinically meaningful changes in weight, height, or BMI z-scores were noted, indicating that the reductions in PS in the teduglutide arm were appropriately titrated to match nutritional needs (Study SHP633-303 CSR Section 14, Table 14.3.8.1).

Assessor's comments

Retrospective Period

Of the 23 AEs reported in 4 subjects (80.0%) in the RETRO TED/TED group (Study SHP633-303 CSR Table 22), 2 AEs (abdominal pain and constipation) were assessed as study drug related in 1 subject and led to interruption of teduglutide treatment (Study SHP633-303 CSR).

No deaths were reported (Study SHP633-303 CSR Section 12.3.1.1). A total of 21 SAEs were reported in 4 of the 5 subjects receiving teduglutide (RETRO TED/TED group [80.0%]; Study SHP633-303 CSR). The most frequently reported SAEs were pyrexia in 2 subjects and device-related infection in 2 subjects. All device-related events were related to the central venous catheters used to administer PS, not to the teduglutide injection device. No SAEs were assessed as related to teduglutide

Prospective Period

A total of 503 TEAEs in 23 subjects (95.8%) were reported in the safety population, which includes 454 TEAEs in 19 subjects in the TED/TED group and 503 TEAEs in 24 subjects in the ANY TED group (Table 1). The majority of TEAEs were mild or moderate in severity. Two subjects (8.3%) in the ANY TED group had 3 treatment-emergent serious adverse events (TESAEs) that were considered study drug-related. No TEAEs led to teduglutide discontinuation or study discontinuation. No AESIs were reported. No deaths occurred during the study.

Deaths, Other Serious Events and Other Significant Events

For subjects in the ANY TED group, there were no deaths, AESIs including polyps of the colon or neoplasia, or TEAEs leading to treatment discontinuation or study discontinuation. Overall, 93 TESAEs were reported in 20 subjects in the ANY TED group, with 85 TESAEs being reported in 17 subjects in the TED/TED group. In the ANY TED group, 2 subjects (8.3%) reported 3 TESAEs that were related to teduglutide.

The two subjects in the ANY TED group had 3 treatment-emergent serious adverse events (TESAEs) that were considered study drug-related. The MAH should describe the TESAEs in narratives **(OC)**.

Clinical Laboratory Evaluations in Pediatric Subjects

The MAH became aware that some Clinical Laboratory Samples had been missed in the Study SHP633-303 Clinical Study Report (CSR). The finding required a post-lock rerun of the data files. The MAH does not anticipate any change to the overall interpretations of efficacy and safety for the study, however a CSR Addendum should be prepared and submit it for CHMP Review within 2 months **(OC)**.

Benefits and Risk Conclusions as presented by MAH

Long-term data for teduglutide treatment in Study SHP633-303 has provided additional information beyond the core study (Study TED-C13-003) supporting the beneficial effects of teduglutide in children with SBS, as well as continued evidence for the maintenance and durability of the response.

The efficacy results of Study SHP633-303 in pediatric subjects with SBS demonstrated the clinical benefits of teduglutide treatment, including reductions in PS and increases in patients weaning off PS.

The long-term safety outcomes for subjects receiving teduglutide in this extension study are consistent with the known safety profile of the product. The safety results for subjects in the teduglutide development program was consistent with the known characteristics of the SBS subject population, PS infusions, or the pharmacologic effect of teduglutide. There appears to be no difference in the frequency or severity of the TEAEs observed in the overall evaluation of safety in children with SBS who are 1 to 17 years of age. The frequency and severity of TEAEs reported in Study SHP633-303 were similar to those observed in the overall evaluation of the safety of teduglutide in adult subjects with SBS. The observed AEs and SAEs are consistent with previously reported safety data for teduglutide. No occurrences of polyps or neoplastic lesions were identified with over 141 weeks of exposure to 0.5 mg/kg/day teduglutide. No new safety signals have been identified.

Teduglutide is approved for pediatric use in the European Union, at a dose of 0.05 mg/kg SC once daily. Population pharmacokinetic modeling and simulations were previously conducted to determine the effective dose to be used in pediatric subjects using data from 8 adult clinical studies, including adult Phase 1 studies and Phase 2/3 studies as well the completed TED-C13-003 study (the core study) and suggested that the dose in pediatric subjects was likely to be same as the dose in adults. This completed pediatric extension study (Study SHP633-303) has demonstrated that teduglutide dosing at 0.05 mg/kg/day has a favorable benefit/risk profile in children with SBS.

The overall benefit-risk balance for teduglutide remains favorable.

No updates to the product information are required.

Assessor's comments

The long-term safety outcomes for subjects receiving teduglutide in this extension study appears to be consistent with the known safety profile of the product.

There appears to be no difference in the frequency or severity of the TEAEs observed in the overall evaluation of safety in children with SBS who are 1 to 17 years of age.

No occurrences of polyps or neoplastic lesions were identified with over 141 weeks of exposure to 0.5 mg/kg/day teduglutide. No new safety signals have been identified.

The two subjects in the ANY TED group had 3 treatment-emergent serious adverse events (TESAEs) that were considered study drug-related. The MAH should describe the TESAEs in narratives **(OC)**.

Discussion on clinical aspects

On 14 January 2021, the MAH submitted a completed paediatric study (SHP633-303) for Revestive, in accordance with Article 46 of Regulation (EC) No1901/2006.

Study SHP633-303 was a Phase 3, retrospective and prospective, open-label, long-term extension study to evaluate the safety and efficacy of teduglutide in pediatric subjects with SBS who had completed the TED-C13-003 study.

Efficacy data were collected for 19 subjects in the TED/TED group during the prospective period.

The primary objective of the study was to evaluate the long-term safety and tolerability of teduglutide. treatment in pediatric subjects with SBS who completed the core study.

The long-term safety outcomes for subjects receiving teduglutide in this extension study appears to be consistent with the known safety profile of the product.

No occurrences of polyps or neoplastic lesions were identified with over 141 weeks of exposure to 0.5 mg/kg/day teduglutide. No new safety signals have been identified.

The two subjects in the ANY TED group had 3 treatment-emergent serious adverse events (TESAEs) that were considered study drug-related. The MAH should describe the TESAEs in narratives **(OC)**.

The MAH became aware that some Clinical Laboratory Samples had been missed in the Study SHP633-303 Clinical Study Report (CSR). The finding required a post-lock rerun of the data files. The MAH does not anticipate any change to the overall interpretations of efficacy and safety for the study, however a CSR Addendum should be prepared and submit it for CHMP Review within 2 months **(OC)**.

Rapporteur's overall conclusion and recommendation

Overall conclusion

The long-term safety outcomes for subjects receiving teduglutide in this extension study appears to be consistent with the known safety profile of the product, and no new safety signals have been identified. However, two subjects in the ANY TED group had 3 treatment-emergent serious adverse events (TESAEs) that were considered study drug-related. The MAH should describe these TESAEs in narratives. In addition, a CSR Addendum including the missing Clinical Laboratory Samples should be prepared and submitted This should be clarified before it can be concluded that no changes are required in the PI.

Recommendation

☒ **Not fulfilled**:

Based on the data submitted, the MAH should provide additional clarifications (see section "Additional clarifications requested")

Additional clarifications requested

1. Two subjects in the ANY TED group had 3 treatment-emergent serious adverse events (TESAEs) that were considered study drug-related. The MAH should describe these TESAEs in narratives.
2. The MAH became aware that some Clinical Laboratory Samples had been missed in the Study SHP633-303 Clinical Study Report (CSR). The finding required a post-lock rerun of the data files. The MAH does not anticipate any change to the overall interpretations of efficacy and safety for the study, however a CSR Addendum should be prepared and submit it for CHMP Review within 2 months.

The timetable as proposed by the Rapporteur is as follows:

- 30 day response timetable without clock stop will apply.

Rapporteur's Assessment of response to RSI

Question 1

Two subjects in the ANY TED group had 3 treatment-emergent serious adverse events (TESAEs) that were considered study drug-related. The MAH should describe these TESAEs in narratives.

Response

The MAH acknowledges the comment and would like to clarify that the narratives related to the 3 study drug-related TESAEs were included in the initial CSR submission, please refer to CSR Section 14.3.3. These events are noted repeatedly in the CSR, with details regarding the study day that the event began provided in CSR Section 12.3.2.4 and a citation to the narratives provided in Section 14.3.3.

The MAH initially decided not to provide subject numbers in the CSR to ensure the security of subject identification; the events can be located referring to the study day that the event began, as discussed in Section 12.3.2.4 of the CSR. Relevant details are also provided below.

Two of the 3 teduglutide-related SAEs (abdominal adhesions and intestinal obstruction) were reported by one Subject (TED/NTT group). The SAEs were considered by the investigator to be possibly related to the investigational product.

The company pharmacovigilance physician assessed that the SAEs were not related to the investigational product since the subject was in the non-treatment arm of the study (as noted by the investigator). All the narratives are provided for that subject on pages 41-45, including the 2 related SAEs.

The third SAE (ileus) was reported by one Subject (TED/TED group). The SAE was considered by the investigator to be possibly related to the investigational product. The company pharmacovigilance physician assessed that the event was not related to the investigational product but was more likely associated with the disease under study. All the narratives are provided for that subject on pages 47-55, including the related SAE.

While these narratives are provided and are noted in the CSR sections and tables as teduglutide-related, the MAH would like to highlight that some discrepancy exists in the CIOMS accounts and opinions cited in the narrative reports as to whether they were teduglutide-related or not. The 2 SAEs of one Subject were noted in the CIOMS as related; in the abdominal adhesion/intestinal obstruction narrative, the investigator noted the SAEs as possibly related but the company pharmacovigilance physician noted them as not related. The ileus SAE of one Subject was noted in the CIOMS as not related; in the narrative the investigator noted the SAE as possibly related but the company pharmacovigilance physician noted it as not related.

Rapporteur's assessment

The Applicant has clarified the occurrence of TESAEs that were considered study drug related. Two of the 3 teduglutide-related SAEs (abdominal adhesions and intestinal obstruction) were reported by one Subject (TED/NTT group). The SAEs were considered by the investigator to be possibly related to the investigational product. The company pharmacovigilance physician assessed that the SAEs were not related to the investigational product since the subject was in the non-treatment arm of the study.

The third SAE (ileus) was reported by one Subject (TED/TED group). The SAE was considered by the investigator to be possibly related to the investigational product. The company pharmacovigilance physician assessed that the event was not related to the investigational product but was more likely associated with the disease under study.

In addition, the Applicant refers to the initial CSR submission, section 14.3.3, for narratives related to the 3 study drug-related TESAEs. This is accepted.

Conclusion

Issue solved

Question 2

The MAH became aware that some Clinical Laboratory Samples had been missed in the Study SHP633-303 Clinical Study Report (CSR). The finding required a post-lock rerun of the data files. The MAH does not anticipate any change to the overall interpretations of efficacy and safety for the study, however a CSR Addendum should be prepared and submit it for CHMP Review within 2 months.

Response

While performing vendor reconciliations for the SHP633-304 final database lock, 3 accession numbers that were logged to the incorrect study SHP633-304, rather than the correct study SHP633-303, were identified.

As a corrective action plan, the results were transferred to the correct study databases under new accession numbers and new transfer files were provided for reconciliation.

For study SHP633-303, a post-lock rerun of the data files was performed, as needed to complete the CSR addendum. At the time of the rerun, a revised protocol deviation listing, comprised of 5 previously undocumented protocol deviations discovered at site during closeout visits, was also included. The details of the CSR revisions required for the antibody samples, protocol deviations, and clinical laboratory sample changes are provided in the SHP633-303 CSR Addendum. A complete set of tables and listings is provided in this addendum, which includes the revisions of affected tables and listings.

The Clinical Study Report (CSR) Addendum is provided as part of this Responses to Question in relevant Module 5.3.5.2 Study Reports of Uncontrolled Clinical Studies.

As anticipated, none of the data corrections shown in the CSR Addendum have changed the overall interpretations of efficacy and safety for the study SHP633-303, or its conclusions.

As a note, the MAH would like to clarify that data relevant to study SHP633-304 was revised accordingly before the database lock date.

Rapporteur's assessment

The MAH has provided the CSR Addendum as part of this Responses to Question in Module 5.3.5.2 Study Reports of Uncontrolled Clinical Studies as requested.

The MAH states that none of the data corrections shown in the CSR Addendum have changed the overall interpretations of efficacy and safety for the study SHP633-303, or its conclusions.

This is accepted.

Conclusion

Issue solved

Rapporteur's updated overall conclusion and recommendation

The long-term safety outcomes for subjects receiving teduglutide in this extension study appears to be consistent with the known safety profile of the product, and no new safety signals have been identified. Two subjects in the ANY TED group had 3 treatment-emergent serious adverse events (TESAEs) that were considered study drug-related by the study investigator. Two of the 3 teduglutide-related SAEs (abdominal adhesions and intestinal obstruction) were reported by one subject. In a subsequent review by the sponsor pharmacovigilance physician it was found that the SAEs were not related to the investigational product since the subject was in the non-treatment arm of the study. The third SAE (ileus) was reported by one subject. The sponsor physician found that the SAE was not related to study drug but more likely to the disease under study.

The MAH has provided a CSR Addendum including the missing laboratory samples as requested. None of the data corrections shown in the CSR Addendum have changed the overall interpretations of efficacy and safety for the study SHP633-303.

Recommendation

☒ **Fulfilled**

No regulatory action required