11 November 2021
EMA/717241/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Revestive

International non-proprietary name: teduglutide

Procedure No. EMEA/H/C/002345/II/0053

Note

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

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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	26 Apr 2021	26 Apr 2021	☐
☐	CHMP Rapporteur Assessment Report	31 May 2021	15 Jun 2021	☐
☐	CHMP members comments	14 Jun 2021	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	17 Jun 2021	n/a	☐
☐	RSI	24 Jun 2021	24 Jun 2021	☐
☐	Submission	13 Aug 2021		☐
☐	CHMP Rapporteur Assessment Report	20 Sep 2021	21 Sep 2021	☐
☐	CHMP members comments	04 Oct 2021	04 Oct 2021	☐
☐	Updated CHMP Rapporteur Assessment Report	07 Oct 2021	12 Oct 2021	☐
☐	2nd RSI	14 Oct 2021	14 Oct 2021	☐
☐	Submission	19 Oct 2021	19 Oct 2021	☐
☐	CHMP Rapporteur Assessment Report	27 Oct 2021	28 Oct 2021	☐
☐	CHMP members comments	03 Nov 2021	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	05 Nov 2021	n/a	☐
☒	Opinion	11 Nov 2021	11 Nov 2021	☐

Procedure resources	
Rapporteur:	Kirstine Moll Harboe

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Shire Pharmaceuticals Ireland Limited submitted to the European Medicines Agency on 24 March 2021 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

Update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC in order to update the Product information with results from two studies included in the paediatric investigation plan (PIP). Study SHP633-301 was performed to evaluate the safety, efficacy/pharmacodynamics (PD), and pharmacokinetics (PK) of teduglutide in infants 4 to 12 months gestational age with SBS and who are dependent on parenteral support. The second study is a paediatric population PK model including data from study SHP633-301. The Package Leaflet was updated accordingly. In addition, the MAH took the opportunity to make editorial changes to section 4.5 of the SmPC.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

2. Overall conclusion and impact on the benefit/risk balance

This variation proposed changes to Product information, updating SmPC sections 4.2, 4.8 and 5.1 to include results from two paediatric studies with "Revestive 1.25 mg powder and solvent for solution for injection". In addition, editorial changes were made to section 4.5 of SmPC.

SHP633-301 was a randomized, open-label study, conducted in 10 paediatric subjects from 4 to 12 months of gestational age with short bowel syndrome (SBS) dependent on parenteral support (PS) to evaluate safety, efficacy/pharmacodynamics and pharmacokinetics of teduglutide. The study consisted of a 2- to 4-week screening period, a 24-week treatment period, and a 4-week follow-up period. Randomization was stratified according to the presence of a small bowel ostomy. During the 24-week treatment period, subjects in the SOC arm (n=5) received standard medical therapy for SBS while those in the teduglutide (TED) arm (n=5) received 0.05 mg/kg/day subcutaneously in addition to standard medical therapy.

Based on subject diary data for the 3 individuals in the TED arm that completed the study, a reduction in the PS volume was reported, with a mean change in PS volume at end of treatment (EOT) from baseline of -21.5±28.91 mL/kg/day, corresponding to a mean percentage change of -24.8±34.72%. Furthermore, a mean reduction in PS caloric intake (-27.0±29.47%), daily infusion time (-28.9±30.61%) and number of days per week in PS usage (-28.5±30.05%) was observed at EOT from baseline. No subject achieved enteral autonomy.

Adverse events reported in the study were consistent with the safety profile seen in the previous paediatric studies and no new safety issues were identified. Overall, there were a total of 87 treatment-emergent adverse events (TEAEs) reported in 10 (100%) subjects. TEAEs were mostly mild in severity and deemed not related to study drug by the investigators. No TESAEs were deemed related to study drug by the investigator. There were no TEAEs leading to death. There were no AESIs (events of polyps of the colon, benign neoplasia of the gastrointestinal tract, or tumor-promoting ability) reported during the study.

Changes in body weight, length, and weight/length ratio Z-scores were within the expected range for the subjects' age group and comparable between the teduglutide treatment arm and the SOC arm. Head circumference Z-scores observed in the SOC arm seemed to drop further over time compared with the teduglutide treatment arm.

In order to justify dosing in the paediatric population, population pharmacokinetics (PK), PK/PD modelling and simulation of teduglutide were conducted based on data from 18 clinical studies, including Study SHP633-301. The relationship between teduglutide exposure (C_{max} and AUC) and PS volume was evaluated using a time and exposure-response model. The analysis included a total of 251 subjects with SBS with both exposure and values of prescribed PS volume at both baseline and the end of each study. The population included 5 subjects from 4 months to <1 year with a total of 19 PK samples collected via a sparse sample collection approach. The MAH states that C_{max} similarity was observed across age groups supporting 0.05 mg daily dosing in paediatric subjects who are 4 months to less than 1 year of age. The mean CL/F values in subjects with moderate, severe renal impairment, and end-stage renal disease (ESRD) were approximately 32%, 44%, and 57% lower than those in subjects with normal renal function, respectively. Based on the above results, a 50% dosage reduction is recommended in paediatric patients with moderate to severe renal impairment and ESRD as adult patients with same degrees of renal impairment.

The exposure-safety analysis results showed a statistically significant relationship between steady state teduglutide exposure C_{max} or AUC versus nausea or abdominal pain.

There is no change in the indication and Revestive remain indicated from 1 year of age.

CHMP agrees that current data do not support a recommendation on posology nor indication for children below 1 year of age. This has been implemented in section 4.2 of SmPC. Section 5.1 and 5.2 have been amended to briefly describe results of study SHP633-301.

The benefit-risk balance of Revestive, remains positive in the current indication.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0479/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0479/2020 was completed. The PDCO issued an opinion on compliance for the PIP P/0479/2020.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

Update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC in order to update the Product information with results from two studies included in the paediatric investigation plan (PIP). Study SHP633-301 was performed to evaluate the safety, efficacy/pharmacodynamics (PD), and pharmacokinetics (PK) of teduglutide in infants 4 to 12 months gestational age with short bowel syndrome (SBS) and who are

dependent on parenteral support. The second study is a paediatric population PK model including data from study SHP633-301. The Package Leaflet was updated accordingly. In addition, the MAH took the opportunity to make editorial changes to section 4.5 of the SmPC.

☒is recommended for approval

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0479/2020 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB are recommended.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion 'Revestive-H-C-002345-II-0053'

In a completed clinical trial (SHP633-301) in paediatric subjects aged 4 to 12 months corrected gestational age with short bowel syndrome (SBS) dependent on parenteral support (PS), a total of 10 subjects were randomized to the teduglutide arm (n=5) and Standard of Care arm (SOC, n=5), of which 8 subjects completed the study. Overall, results showed a relatively higher number of subjects achieving clinically meaningful reductions in PS nutrition volume, caloric intake and a higher percentage of the average reductions in PS calories, daily infusion time an number of days per week in PS usage within the teduglutide arm than the SOC arm. No subject achieved enteral autonomy during the study. Adverse events reported in the study were consistent with the safety profile seen in the previous paediatric studies and no new safety issues were identified.

Population pharmacokinetics (PK) and PK/PD modelling and simulation of teduglutide demonstrated C_{max} similarity across age groups (4 months to 17 years) supporting 0.05 mg daily dosing in pediatric subjects who are 4 months to less than 1 year of age. A 50% dosage reduction is recommended in paediatric patients with moderate to severe renal impairment and end stage renal disease (ESRD) as adult patients with same degrees of renal impairment.

Currently available data in children below 1 year are described in section 5.1 and 5.2, but no recommendation on a posology can be made. Long-term safety data are not yet available for the paediatric population.

For more information, please refer to the Summary of Product Characteristics.

Annex: Rapporteur's assessment comments on the type II variation

5. Introduction

Teduglutide (rDNA origin) is an analog of naturally occurring human glucagon-like peptide-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.

The MAH proposes to update the Summary of Clinical Pharmacology with the results of

- The pharmacokinetics (PK) results of Study SHP633-301, a randomized, open-label study to evaluate the safety, efficacy/pharmacodynamics (PD), and PK of teduglutide in infants 4 to 12 months corrected gestational age (a premature baby's chronological age minus the number of weeks or months he/she was born early) with SBS who are dependent on parenteral support (PS).
- A population PK analysis of teduglutide based on data from 18 clinical studies including the recently completed Phase 3 Study SHP633-301 in pediatric subjects 4 months to <1 year corrected gestational age (SHIR-CSC-129_PKglobal).
- An exposure-response analysis (SHIR-CSC-129_ERglobal) to assess the relationship between
    - teduglutide exposure and the change from baseline in PS volume in pediatric subjects (4 months and older) with SBS.
    - teduglutide exposure and safety endpoints of interest (ie, vomiting, abdominal pain, nausea and diarrhea) in subjects (4 months and older) with SBS

6. Clinical Pharmacology aspects

6.1. Methods – analysis of data submitted

Study SHP633-301

SHP633-301 was a randomized, open-label study consisting of a 2- to 4-week screening period, a 24 week treatment period, and 4-week follow-up period. All subjects were screened prior to start of treatment to verify the requirements for nutritional support for each subject and to ensure adherence to eligibility parameters. Subjects were randomized (1:1 ratio) to the teduglutide or standard of care (SOC) treatment arm. Randomization was stratified according to the presence of a small bowel ostomy (eg, end jejunostomy or ileostomy). During the 24-week treatment period, subjects in the SOC arm received standard medical therapy for SBS while those in the teduglutide arm received 0.05 mg/kg/day subcutaneously in addition to standard medical therapy. At each site visit during the treatment phase, efficacy (adjustments to PS) and safety were monitored.

Sparse blood samples for PK analysis were collected in subjects enrolled in the teduglutide arm at predose, and 1 hour (±10 minutes) and 4 hours (±10 minutes) postdose at baseline (Visit 0). Samples were also collected 2 hours (±10 minutes) postdose at Week 7 (Visit 7) or Week 12 (Visit 12) of the

treatment period. Originally, there was an option to collect postbaseline PK samples at Week 7 or Week 12; however, this option was removed in protocol Amendment 4 and thereafter all postbaseline PK samples were to be collected at Week 7.

At the end of the treatment period (Week 24/EOT), all subjects entered a 4-week follow-up period until the end of study (Week 28) during which time subjects received standard medical therapy, but no investigational product was administered. At the end of the treatment period, some subjects who completed the study had the opportunity to participate in a long-term extension study, SHP633 304, in which eligible subjects would continue to receive teduglutide. The follow-up period for subjects in the teduglutide treatment arm may have been truncated and the subjects could have proceeded immediately to the end of study visit if at least 1 "escape" criteria was met.

Assessor´s comments

SHP633-301 was a randomized, open-label study consisting of a 2- to 4-week screening period, a 24 week treatment period, and 4-week follow-up period. Randomization was stratified according to the presence of a small bowel ostomy (e.g., end jejunostomy or ileostomy). During the 24-week treatment period, subjects in the SOC arm received standard medical therapy for SBS while those in the teduglutide arm received 0.05 mg/kg/day subcutaneously in addition to standard medical therapy.

Sparse blood samples for PK analysis were collected in subjects enrolled in the teduglutide arm at predose, and 1 hour and 4 hours postdose at baseline (Visit 0). Samples were also collected 2 hours postdose at Week 7 (Visit 7) or Week 12 (Visit 12) of the treatment period. Originally, there was an option to collect postbaseline PK samples at Week 7 or Week 12; however, this option was removed in protocol Amendment 4 and thereafter all postbaseline PK samples were to be collected at Week 7.

The MAH is asked to present the number of plasma samples collected and used for analysis in study SHP633-301 **(OC)**.

At the end of the treatment period, some subjects who completed the study had the opportunity to participate in a long-term extension study, SHP633 304, in which eligible subjects would continue to receive teduglutide.

6.2. Results

A total of 10 subjects were randomized in the study, 5 subjects in each treatment arm and analyzed for safety and efficacy/PD.

Eight subjects completed the study. Two subjects discontinued from the study: 1 subject in the teduglutide arm met escape criteria during the follow-up period and 1 subject in the SOC arm discontinued early from the study during the treatment period. In addition, 1 subject interrupted teduglutide treatment following the parents' decision to stop teduglutide administration as they thought several adverse events were caused by the study drug; teduglutide treatment never resumed and the subject completed the study.

The PK set contains all subjects who received at least 1 dose of teduglutide and had at least 1 evaluable and interpretable postdose PK concentration value. All 5 subjects randomized in the teduglutide arm were included in the PK set; 1 subject missed the Week 7 postdose sample collection due to the COVID 19 pandemic. The mean ±standard deviation (SD) teduglutide plasma concentrations over time are presented in the SHP633-301 clinical study report (CSR) Section 14, Figure 14.2.3.18 in both linear and semi-log scales.

The exposure to teduglutide, as presented by serum teduglutide concentrations measured in the samples collected at different times post once daily subcutaneous (SC) administration and at different

days over the treatment period, was demonstrated over the study duration in infant subjects receiving teduglutide.

The summary of mean, median, minimum, and maximum teduglutide plasma concentrations by timepoint is presented in Table 1. The median postdose teduglutide plasma concentrations were 16.30 ng/mL at 1 hour, 16.95 ng/mL and 25.65 ng/mL at 2 hours (Week 7 and Week 12 visits, respectively), and 8.39 ng/mL at 4 hours. The minimum and maximum postdose teduglutide plasma concentrations were 2.21 ng/mL and 29.00 ng/mL over the sample collection time during the treatment, respectively.

Table 1 Summary of Mean Teduglutide Plasma Concentrations by Subject and Timepoint (Pharmacokinetic Set) - Study SHP633-301

		Teduglutide Concentrations (ng/mL)			
		Scheduled Timepoint (hours)			
Visit		**Predose**	**1**	**2**	**4**
Baseline	n	4	3	NA	4
	Mean (SD)	0.00 (0.000)	16.417 (9.226)		10.783 (8.315)
	Median	0.00	16.300		8.385
	Min/Max	0.00/0.00	7.25/25.70		3.86/22.50
Week 7	n	NA	NA	2	NA
	Mean (SD)			16.950 (3.041)	
	Median			16.950	
	Min/Max			14.80/19.10	
Week 12	n	NA	NA	4	NA
	Mean (SD)			20.628 (12.415)	
	Median			25.650	
	Min/Max			2.21/29.00	

Min=minimum; Max=maximum; NA=not applicable
Source: SHP633-301 CSR; Table 14.2.2.15

The plasma concentrations of teduglutide for individual subjects are listed in SHP633-301 CSR Appendix 16.2.5, Listing 16.2.5.4. All subjects tested presented teduglutide concentrations that were below the limit of quantification (<1.0 ng/mL) at the predose timepoint (baseline visit) and measurable teduglutide plasma concentrations postdose at least at 1 visit. One subject presented teduglutide concentrations that were below limit of quantification at the 1-hour and 4-hour postdose timepoints at the baseline visit but presented concentrations of 19.1 ng/mL and 26.8 ng/mL at the 2-hour postdose timepoint at Week 7 and Week 12 visits, respectively.

Assessor´s comments

A total of 10 subjects were randomized in the study, 5 subjects in each treatment arm and analyzed for safety and efficacy/PD.

Eight subjects completed the study. Two subjects discontinued from the study: 1 subject in the teduglutide arm met escape criteria during the follow-up period and 1 subject in the SOC arm discontinued early from the study during the treatment period. In addition, 1 subject interrupted teduglutide treatment following the parents' decision to stop teduglutide administration.

The PK set contains all subjects who received at least 1 dose of teduglutide and had at least 1 evaluable and interpretable postdose PK concentration value. All 5 subjects randomized in the teduglutide arm were included in the PK set; 1 subject missed the Week 7 postdose sample collection.

The median postdose teduglutide plasma concentrations were 16.30 ng/mL at 1 hour, 16.95 ng/mL and 25.65 ng/mL at 2 hours (Week 7 and Week 12 visits, respectively), and 8.39 ng/mL at 4 hours. The minimum and maximum postdose teduglutide plasma concentrations were 2.21 ng/mL and 29.00 ng/mL over the sample collection time during the treatment, respectively.

6.3. Discussion

SHP633-301 was a randomized, open-label study consisting of a 2- to 4-week screening period, a 24 week treatment period, and 4-week follow-up period. During the 24-week treatment period, subjects in the SOC arm received standard medical therapy for SBS while those in the teduglutide arm received 0.05 mg/kg/day subcutaneously in addition to standard medical therapy.

Sparse blood samples for PK analysis were collected in subjects enrolled in the teduglutide arm at baseline, at Week 7 or Week 12 of the treatment period.

A total of 10 subjects were randomized in the study, 5 subjects in each treatment arm and analyzed for safety and efficacy/PD.

Eight subjects completed the study. Two subjects discontinued from the study: 1 subject in the teduglutide arm met escape criteria during the follow-up period and 1 subject in the SOC arm discontinued early from the study during the treatment period. In addition, 1 subject interrupted teduglutide treatment.

The PK set contains all subjects who received at least 1 dose of teduglutide and had at least 1 evaluable and interpretable postdose PK concentration value. All 5 subjects randomized in the teduglutide arm were included in the PK set; 1 subject missed the Week 7 postdose sample collection. The MAH is asked to present and describe the number of plasma samples collected and used for analysis in study SHP633-301 (OC).

The median postdose teduglutide plasma concentrations were 16.30 ng/mL at 1 hour, 16.95 ng/mL and 25.65 ng/mL at 2 hours (Week 7 and Week 12 visits, respectively), and 8.39 ng/mL at 4 hours. The minimum and maximum postdose teduglutide plasma concentrations were 2.21 ng/mL and 29.00 ng/mL over the sample collection time during the treatment, respectively.

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Eight subjects completed the study. Two subjects discontinued from the study: 1 subject in the teduglutide arm met escape criteria during the follow-up period and 1 subject in the SOC arm discontinued early from the study during the treatment period. In addition, 1 subject interrupted teduglutide treatment following the parents' decision to stop teduglutide administration.

The PK set contains all subjects who received at least 1 dose of teduglutide and had at least 1 evaluable and interpretable postdose PK concentration value. All 5 subjects randomized in the teduglutide arm were included in the PK set; 1 subject missed the Week 7 postdose sample collection.

The median postdose teduglutide plasma concentrations were 16.30 ng/mL at 1 hour, 16.95 ng/mL and 25.65 ng/mL at 2 hours (Week 7 and Week 12 visits, respectively), and 8.39 ng/mL at 4 hours. The minimum and maximum postdose teduglutide plasma concentrations were 2.21 ng/mL and 29.00 ng/mL over the sample collection time during the treatment, respectively.

6.4. Pharmacodynamic Studies

Study SHP633-301

Methods – analysis of data submitted

Comparison and Analyses of Results Across Studies

Further population PK and PK/PD modeling and simulation to support Type II submission for pediatrics 4 months to <1 year were conducted including data from Study SHP633-301, following the Japanese submission for adult and pediatric patients with SBS. A total of 7 pediatrics subjects 4 months to <1 year of age with SBS who are dependent on PS are included, 5 subjects from Study SHP633-301 and 2 subjects from Study SHP633-302.

Pharmacokinetics in PS-dependent Pediatric Subjects with SBS

Results from a population PK analysis of teduglutide is presented using data from 18 clinical trials, including data of 101 pediatric subjects 4 months and older collected in studies TED-C13-003, TED-C14-006, SHP633-302, and SHP633-301.

Methodology

The population PK modeling analysis included a total of 7 pediatric subjects 4 months to <1 year of age, 5 subjects from Study SHP633-301 and 2 subjects from Study SHP633-302; this PK information was available after the completion of study SHP633-301. Overall, a total of 480 subjects were included in the population PK analysis. The PK population included a total of 101 pediatric and 379 adult subjects. The population consisted of 304 (63.3%) male and 176 (36.7%) female subjects. Most subjects were of white origin (81.5%). The population included a total of 7 pediatric subjects from 4 months to <1 year, 86 pediatric subjects 1 to <12 years, 8 pediatric subjects 12 to <18 years, and 379 adult subjects (≥18 years). A total of 349 (72.7%) subjects had normal renal function. A total of 78 (16.2%), 40 (8.3%), and 7 (1.5%) subjects presented mild, moderate, severe renal impairment, respectively. A total of 6 (1.2%) subjects were at end-stage renal disease (ESRD).

A one-compartment disposition model with a first-order rate constant of absorption (Ka) and lag time (ALAG) was previously used to describe the concentration-time profiles of teduglutide based on data collected in 478 subjects (18 clinical studies). The population PK model included allometric functions accounting for the effect of body weight on PK parameters (Ka, apparent clearance [CL/F], and apparent central volume of distribution [Vc/F]). The above population PK model was updated by including pediatric subjects 4 months to <1 year with SBS enrolled in Studies SHP633-301 and SHP633-302. In addition, source of variability on PK parameters of teduglutide, including intrinsic factors (body weight, age, renal function, race, sex, and disease status) and extrinsic factors (dose, formulation strength, and site injection) were performed to improve the population PK model. The model evaluation was based on standard model diagnostics and goodness-of-fit criteria and by looking

at pertinent graphical representations of goodness-of-fit. Finally, the simulation was performed to estimate the PK parameters using the final population PK model and the PK parameters were summarized for pediatric (across age groups) and adult subjects with SBS (SHIR-CSC-129_PKglobal).

Assessor´s comments

Further population PK and PK/PD modeling and simulation were conducted to support the proposed type II variation in pediatrics 4 months to <1 year A total of 7 pediatrics subjects 4 months to <1 year of age with SBS who are dependent on PS are included, 5 subjects from Study SHP633-301 and 2 subjects from Study SHP633-302. The model evaluation was based on standard model diagnostics and goodness-of-fit criteria and by looking at pertinent graphical representations of goodness-of-fit.

The population PK modeling analysis included a total of 7 pediatric subjects 4 months to <1 year of age, 5 subjects from Study SHP633-301 and 2 subjects from Study SHP633-302; this PK information was available after the completion of study SHP633-301. Overall, a total of 480 subjects were included in the population PK analysis. The PK population included a total of 101 pediatric and 379 adult subjects. The population included a total of 7 pediatric subjects from 4 months to <1 year, 86 pediatric subjects 1 to <12 years, 8 pediatric subjects 12 to <18 years, and 379 adult subjects (≥18 years)

A one-compartment disposition model with a first-order rate constant of absorption (Ka) and lag time (ALAG) was previously used to describe the concentration-time profiles of teduglutide based on data collected in 478 subjects (18 clinical studies). The population PK model included allometric functions accounting for the effect of body weight on PK parameters (Ka, apparent clearance [CL/F], and apparent central volume of distribution [Vc/F]). The above population PK model was updated by including pediatric subjects 4 months to <1 year with SBS enrolled in Studies SHP633-301 and SHP633-302

Finally, the simulation was performed to estimate the PK parameters using the final population PK model and the PK parameters were summarized for pediatric (across age groups) and adult subjects with SBS.

Results

Population PK parameters of teduglutide derived with the final model (run009) are presented. Body weight, age, baseline creatinine clearance (CrCL), injection site, and disease status were identified as significant covariates affecting PK parameters including CL/F, Vc/F, and Ka. Sensitivity analyses did not show any differences in population PK model improvement between with and without including the kidney maturation. Overall, data collected in pediatric subjects 4 months to <1 year did not impact the population PK estimates as compared with the previous population PK for the Japanese submission.

Table 2 Population PK Analysis of Teduglutide: Final Parameter Estimates

PK Parameters	Typical Values	RSE (%)	BSV (%)	Shrinkage (%)
CL/F (L/h)	**16.0** × (Body Weight/70)$^{0.493}$ × (CRCLT/99.35)$^{0.341}$ × 0.667 if non-SBS patients × 0.933 if Female	**114.4**	**22.3**	**16.2**
Vc/F (L)	**33.9** × (Body Weight/70)$^{1.36}$ × (Age/34.0)$^{-0.316}$	**6.2**	**31.1**	**9.9**
Ka (h^{-1})	**0.330** × (Body Weight/70)$^{-0.790}$ × 0.767 for SC administration other than abdomen	**5.6**	**23.3**	**13.2**
ALAG (h)	**0.299** × 1.457 for SC administration other than abdomen × 0.476 for Formulation strength ≥10 mg/vial × 1.784 for Supra-therapeutic dose level	**34.9**	**NA**	**NA**
F1	**1, Fixed** × 0.936 for SC administration other than abdomen	**NA**	**NA**	**NA**
Error Model				
Additive Error (ng/mL)	6.50	31.7	NA	NA
Proportional Error (%)	24.3	6.0	NA	NA

ALAG=Lag time; BSV=between-subjects variability; CL/F=apparent clearance; CRCLT=baseline creatinine clearance capped to 150 mL/min; F1=relative bioavailability; Ka=first-order rate constant of absorption; NA=Not applicable; PK=Pharmacokinetic; RSE=relative standard error; SBS=short bowel syndrome; Vc/F=apparent central volume of distribution

Note: the reference subject is a 34 year, 70-kg male subject with SBS, with a typical CRCL of 99.35 mL/min who received a therapeutic dose of teduglutide in abdomen (formulation strength <10 mg/vial). Additional PK parameters estimates are presented in SHIR-CSC-129_PKglobal, Appendix 2, Section 12.2.

Source: SHIR-CSC-129_PKglobal, Table 4

Descriptive Statistics of PK Parameters

Rich concentration-time profiles were simulated with the final population PK model and actually observed subjects to derive PK parameters such as CL/F, Vc/F, Ka, area under the curve under steady state (AUC_{ss}), maximum concentration ($C_{max,ss}$), and elimination half-life ($t_{1/2}$). Descriptive statistics of PK parameters in pediatric subjects with SBS (4 months to <18 years) and adult subjects (≥18 years) with SBS and descriptive statistics of PK parameters by age groups in pediatric and adult subjects with SBS (0.05 mg/kg).

Table 3 Descriptive Statistics of PK and Exposure Parameters of Teduglutide in Pediatric (4 months to <18 years) and Adult Subjects with SBS (0.05 mg/kg)

Pediatric Subjects with SBS (0.05 mg/kg)	
AUC_{ss} (ng•h/mL)	$C_{max,ss}$ (ng/mL)
56	56
120	33.9
48.4	12.3
40.3	36.4
115	32.0
58.7	20.7
409	84.9

AUC_{ss}=area under the curve over the dosing interval at steady state; CL/F=apparent clearance; $C_{max,ss}$=maximum concentration at steady state; CV=coefficient of variation; Ka=rate constant of absorption; Max=maximum; Min=minimum; n=number of subjects; SD=standard deviation; $t_{1/2}$=terminal elimination half-life; Vc/F=apparent volume of distribution

Source: SHIR-CSC-129_PKglobal, Table 5

Table 4 Descriptive Statistics of PK and Exposure Parameters of Teduglutide in Pediatric Subjects with SBS (0.05 mg/kg)

Age Groups	Descriptive Statistics	Age (years)	Body Weight (kg)	CL/F (L/h)	Vc/F (L)	AUC_{ss} (ng•h/mL)	$C_{max,ss}$ (ng/mL)	$t_{1/2}$ (h)
4 months to <1 year	n	7	7	7	7	7	7	7
	Mean	0.741	7.51	4.91	5.93	78.6	33.5	0.813
	SD	0.222	1.61	0.952	2.57	22.4	13.8	0.240
	CV%	30.0	21.4	19.4	43.3	28.5	41.1	29.6
	Median	0.807	7.51	5.36	6.19	70.0	30.4	0.801
	Min	PPD	5.15	3.04	2.98	58.7	23.0	0.484
	Max	PPD	10.3	5.76	9.40	123	62.7	1.13
≥1 to <2 years	n	1	1	1	1	1	1	1
	Mean	PPD	10.5	4.92	6.95	102	33.0	0.979
	SD	NA	NA	NA	NA	NA	NA	NA
	CV%	NA	NA	NA	NA	NA	NA	NA
	Median	PPD	10.5	4.92	6.95	102	33.0	0.979
	Min	PPD	10.5	4.92	6.95	102	33.0	0.979
	Max	PPD	10.5	4.92	6.95	102	33.0	0.979
≥2 to <4 years	n	14	14	14	14	14	14	14
	Mean	2.74	13.6	6.39	9.03	125	35.4	1.01
	SD	0.698	1.77	2.14	2.91	84.5	17.1	0.207
	CV%	25.5	13.0	33.5	32.2	67.3	48.2	20.4
	Median	2.97	13.6	6.71	9.18	107	28.9	0.970
	Min	2.00	11.1	1.69	3.61	65.0	21.8	0.714
	Max	3.71	16.8	9.83	13.0	409	84.9	1.49
≥4 to <6 years	n	13	13	13	13	13	13	13
	Mean	4.66	16.3	7.07	10.1	113	31.8	0.979
	SD	0.565	2.28	1.06	2.48	14.9	6.44	0.162
	CV%	12.1	14.0	15.0	24.7	13.2	20.2	16.6
	Median	5.00	16.5	7.04	10.3	109	32.1	0.953
	Min	4.00	10.9	5.56	6.48	94.5	24.0	0.769
	Max	5.60	18.8	9.39	13.4	149	45.1	1.26
≥6 to <8 years	n	5	5	5	5	5	5	5
	Mean	6.35	20.3	7.39	9.15	138	43.0	0.873
	SD	0.490	3.62	1.16	2.30	32.1	17.4	0.250
	CV%	7.7	17.9	15.7	25.2	23.3	40.6	28.6
	Median	6.00	20.9	7.04	9.97	142	37.4	0.852

Table 4 Descriptive Statistics of PK and Exposure Parameters of Teduglutide in Pediatric Subjects with SBS (0.05 mg/kg)

Age Groups	Descriptive Statistics	Age (years)	Body Weight (kg)	CL/F (L/h)	Vc/F (L)	AUC_{ss} (ng•h/mL)	$C_{max,ss}$ (ng/mL)	$t_{1/2}$ (h)
	Min	PPD	16.4	6.37	5.98	86.5	25.6	0.538
	Max	PPD	25.4	9.25	11.4	165	71.3	1.15
≥8 to <12 years	n	12	12	12	12	12	12	12
	Mean	9.04	24.8	9.46	14.0	130	32.4	1.01
	SD	1.10	4.21	1.49	4.51	23.3	9.11	0.221
	CV%	12.2	17.0	15.7	32.2	17.9	28.1	21.9
	Median	9.00	24.8	9.75	15.1	131	32.5	1.06
	Min	8.00	18.5	6.42	6.49	88.8	20.7	0.567
	Max	11.0	34.9	11.5	21.5	180	51.9	1.30
≥12 to <18 years	n	4	4	4	4	4	4	4
	Mean	15.0	44.4	14.9	25.9	149	28.5	1.17
	SD	0.777	9.36	3.21	11.0	13.8	7.50	0.242
	CV%	5.2	21.1	21.5	42.6	9.2	26.3	20.7
	Median	15.0	40.8	14.7	23.1	148	26.7	1.09
	Min	PPD	38.0	11.4	16.1	135	22.3	0.979
	Max	PPD	58.0	18.9	41.1	166	38.0	1.51
Adults (≥18 years)	n	68	68	68	68	68	68	68
	Mean	46.9	58.2	13.8	24.2	223	39.6	1.22
	SD	12.7	10.1	3.58	8.68	58.3	12.4	0.298
	CV%	27.0	17.3	25.9	35.8	26.1	31.2	24.4
	Median	48.0	57.6	13.7	23.6	209	38.6	1.25
	Min	20.0	40.7	7.36	11.5	119	19.5	0.691
	Max	80.0	87.9	23.2	49.9	381	75.3	2.08

AUC_{ss}=area under the curve over the dosing interval at steady state; CL/F=apparent clearance; $C_{max,ss}$=maximum concentration at steady state; CV=coefficient of variation; Max=maximum; Min=minimum; n=number of subjects; NA=not applicable; SD=standard deviation; $t_{1/2}$=terminal elimination half-life; Vc/F=apparent volume of distribution

Source: SHIR-CSC-129_PKglobal, Table 6

Mean and median $C_{max,ss}$ values of teduglutide in pediatric subjects with SBS across age groups (mean range: 28.5 ng/mL to 43.0 ng/mL and median range: 26.7 ng/mL to 37.4 ng/mL) were consistent with that observed in adult subjects with SBS (mean: 39.6 ng/mL) when receiving 0.05 mg/kg daily. Moreover, the range of individual $C_{max,ss}$ values of teduglutide in pediatric subjects with SBS across age groups (20.7 to 84.9 ng/mL) was similar to that observed in adult subjects with SBS (19.5 ng/mL to 75.3 ng/mL). In addition, mean $t_{1/2}$ values of teduglutide in pediatric subjects with SBS across age groups (mean range: 0.813 h to 1.17 h) were consistent with that observed in adult subjects with SBS (mean: 1.22 h).

Mean AUCss values were age-dependent and gradually decreased with age from a mean of 223 ng•h/mL in adults to 78.6 ng•h/mL in pediatric subjects 4 months to <1 year when receiving 0.05 mg/kg teduglutide daily.

It is to be noted that a 87% decrease in body weight (from 57.9 kg in adults to 7.51 kg in the 4 months to <1 year) resulted in a 65% decrease in AUC_{ss} (from 223 ng•h/mL in adults to 78.6 ng•h/mL in the 4 months to <1 year).

Overall, results confirmed that pediatric patients 4 months to <18 years are expected to present similar $C_{max,ss}$ values of teduglutide as observed in adults. On the other hand, the AUC_{ss} of teduglutide was age-dependent and gradually decreased from adults to pediatric subjects between 4 months and <1 year of age. Clinical PS response data in conjunction with $C_{max,ss}$ were demonstrated to support

teduglutide dose selection since AUC_{ss} was previously shown not to correlate with efficacy. Thus, as a response marker, C_{max} of teduglutide has been targeted across age populations. The current analyses have confirmed similarity of C_{max} of teduglutide across age populations including pediatrics subjects 4 month to <1 year of age with SBS, therefore, supporting 0.05 mg/kg daily in this age group patients.

Assessor´s comments

Body weight, age, baseline creatinine clearance (CrCL), injection site, and disease status were identified as significant covariates affecting PK parameters including CL/F, Vc/F, and Ka. Sensitivity analyses did not show any differences in population PK model improvement between with and without including the kidney maturation. Overall, data collected in pediatric subjects 4 months to <1 year did not impact the population PK estimates as compared with the previous population PK for the Japanese submission.

Overall, the MAH considers that pediatric patients 4 months to <18 years are expected to present similar $C_{max,ss}$ values of teduglutide as observed in adults. However, the AUC_{ss} of teduglutide was age-dependent and gradually decreased from adults to pediatric subjects between 4 months and <1 year of age. The Applicant states that C_{max} of teduglutide has been targeted across age populations, and that the current analyses have confirmed similarity of C_{max} of teduglutide across age populations including pediatrics subjects 4 month to <1 year of age with SBS, therefore, supporting 0.05 mg/kg daily in this age group patients.

Pharmacokinetics in Special Subject Populations

Hepatic Impairment

Not applicable.

Renal Impairment

This section presents results from a population PK analysis of teduglutide using data from 18 clinical trials, including data of 101 pediatric subjects 4 months and older collected in Studies TED-C13-003, TED-C14-006, SHP633-302, and SHP633-301. Refer to SHIR-CSC-129_PKglobal.

Descriptive statistics of PK parameters of teduglutide in pediatric subjects with SBS (0.05 mg/kg) with normal renal function and mild renal impairment are presented in the table below.

Table 5 Descriptive Statistics of PK Parameters According to Renal Function in Pediatric Subjects (0.05 mg/kg)

Population	Statistics	Age (years)	Weight (kg)	CL/F (L/h)	Vc/F (L)	CL/F/BW (L/h/kg)	Vc/F/BW (L/kg)	Ka (1/h)	AUC_{ss} (ng•h/mL)	$C_{max,ss}$ (ng/mL)	$t_{1/2}$ (h)
Normal Renal Function (eGFR >90 mL/min/ 1.73 m^2)	n	54	54	54	54	54	54	54	54	54	54
	Mean	5.45	18.7	7.77	11.3	0.456	0.629	0.870	119	33.3	0.980
	SD	3.84	9.65	2.93	6.20	0.138	0.185	0.339	49.0	11.9	0.218
	CV%	70.5	51.8	37.7	55.1	30.2	29.4	38.9	41.1	35.8	22.2
	Median	4.71	16.5	7.13	9.98	0.432	0.624	0.829	112	31.5	0.981
	Min	0.380	5.15	1.69	2.98	0.122	0.235	0.352	58.7	20.7	0.484
	Max	16.0	58.0	18.9	41.1	0.828	1.17	2.04	409	84.9	1.51
Mild	n	2	2	2	2	2	2	2	2	2	2
	Mean	5.95	16.7	5.40	7.50	0.346	0.430	1.40	139	49.7	0.884

Table 5 Descriptive Statistics of PK Parameters According to Renal Function in Pediatric Subjects (0.05 mg/kg)

Population	Statistics	Age (years)	Weight (kg)	CL/F (L/h)	Vc/F (L)	CL/F/BW (L/h/kg)	Vc/F/BW (L/kg)	Ka (1/h)	AUC_{ss} (ng•h/mL)	$C_{max,ss}$ (ng/mL)	$t_{1/2}$ (h)
Renal Impairment (eGFR 60-89 mL/min/ 1.73 m^2)	SD	7.14	12.7	3.33	6.23	0.0626	0.0472	1.07	22.3	18.4	0.254
	CV%	120.0	75.6	61.7	83.1	18.1	11.0	76.6	16.1	36.9	28.8
	Median	5.95	16.7	5.40	7.50	0.346	0.430	1.40	139	49.7	0.884
	Min	0.900	7.79	3.04	3.09	0.302	0.397	0.640	123	36.7	0.704
	Max	11.0	25.7	7.76	11.9	0.390	0.463	2.15	155	62.7	1.06

AUC_{ss}=area under the curve over the dosing interval at steady state; $C_{max,ss}$=maximum concentration at steady state; CL/F=apparent clearance; CL/F/BW=body weight adjusted apparent clearance; CV=coefficient of variability; eGFR=estimated glomerular filtration rate; Ka=rate constant of absorption; Max=maximum; Min=minimum; n=number of subjects; $t_{1/2}$=terminal elimination half-life; Vc/F=apparent central volume of distribution; Vc/F/BW=body weight adjusted apparent central volume of distribution
Source: SHIR-CSC-129_PKglobal, Table 7

As per the population PK model, the CL/F of teduglutide was dependent on CrCL and body weight. The mean body weight adjusted CL/F in pediatric subjects with mild renal impairment was approximately 25% lower than that observed in subjects with normal renal function. The lower body weight adjusted CL/F in pediatric subjects with mild renal impairment resulted in a 17% higher AUC_{ss} relative to those with normal renal function (139 ng•h/mL vs 119 ng•h/mL, respectively).

The mean body weight adjusted Vc/F values in pediatric subjects with mild renal impairment was 32% lower than that observed in subjects with normal renal function. The lower Vc/F in pediatric subjects with mild renal impairment resulted in a 49% higher $C_{max,ss}$ relative to those with normal renal function (49.7 ng/mL vs 33.3 ng/mL, respectively), but the minimum and maximum C_{max} values in pediatric subjects with mild renal impairment were retained within the range of C_{max} values observed in pediatric subjects with normal renal function.

The above increases in AUC_{ss} and $C_{max,ss}$ were not deemed clinically relevant and therefore no dose adjustment is recommended in pediatric subjects with mild renal impairment.

Overall, the above results are consistent with those observed in adult subjects with SBS, whereby slightly lower CL/F and Vc/F in subjects with mild renal impairment did not result in a clinically relevant increase on the AUC_{ss} and $C_{max,ss}$ of teduglutide relative to subjects with normal renal function. Based on a dedicated study (Study CL0600-018) in non-SBS subjects with renal impairment, the mean CL/F values in subjects with moderate, severe renal impairment, and ESRD were approximately 32%, 44%, and 57% lower than those in subjects with normal renal function, respectively. Based on the above results, a 50% dosage reduction is recommended in pediatric patients with moderate to severe renal impairment and ESRD as adult patients with same degrees of renal impairment (refer to SHIR-CSC-129_PKglobal, Appendix 5, Section 15.1 and Section 15.4).

Assessor´s comments

As per the population PK model, the CL/F of teduglutide was dependent on CrCL and body weight. The mean body weight adjusted CL/F in pediatric subjects with mild renal impairment was approximately 25% lower than that observed in subjects with normal renal function. The lower body weight adjusted CL/F in pediatric subjects with mild renal impairment resulted in a 17% higher AUC_{ss} relative to those with normal renal function (139 ng•h/mL vs 119 ng•h/mL, respectively).

The mean body weight adjusted Vc/F values in pediatric subjects with mild renal impairment was 32% lower than that observed in subjects with normal renal function. The lower Vc/F in pediatric subjects with mild renal impairment resulted in a 49% higher $C_{max,ss}$ relative to those with normal renal function

(49.7 ng/mL vs 33.3 ng/mL, respectively), but the minimum and maximum C_{max} values in pediatric subjects with mild renal impairment were retained within the range of C_{max} values observed in pediatric subjects with normal renal function.

The MAH states that the observed increases in AUC_{ss} and $C_{max,ss}$ were not deemed clinically relevant and therefore no dose adjustment is recommended in pediatric subjects with mild renal impairment.

The mean CL/F values in subjects with moderate, severe renal impairment, and ESRD were approximately 32%, 44%, and 57% lower than those in subjects with normal renal function, respectively. Based on the above results, a 50% dosage reduction is recommended in pediatric patients with moderate to severe renal impairment and ESRD as adult patients with same degrees of renal impairment. This is accepted.

Elderly

Not applicable.

Metabolism and Drug-drug Interaction Potential

Not applicable.

Pharmacodynamics

Not applicable.

Immunogenicity Effect

To assess the effect on PK further, anti-drug antibodies (ADA) status was tested in the population PK analyses, as one of covariates, based on data from 3 studies including both adult and pediatric subjects with SBS (according to data availability) (SHIR-CSC-129-Japanese, Population PK Analysis). The results showed that the ADA incidence was small and did not have an impact on PK of teduglutide. Since the updated dataset included only one new concentration in a subject with ADA positive, ADA was not retested in the current analysis.

PK/PD Relationship in PS-dependent Pediatric Subjects with SBS

This section presents results from an exposure-response modelling analyses developed to assess the relationship between

- teduglutide exposure and the change from baseline in PS volume in pediatric subjects (4 months and older) with SBS
- teduglutide exposure and safety endpoints of interest (ie, vomiting; abdominal pain, nausea and diarrhea) in subjects (4 months and older) with SBS.

This exposure-response analysis of teduglutide used data from 10 clinical trials, including data of 101 pediatric subjects 4 months and older collected in Studies TED-C13-003, TED-C14-006, SHP633-302, and SHP633-301. A brief description of each of the 10 clinical studies is provided in SHIR-CSC-129_ERglobal, Appendix 1, Section 11.1 and Section 11.2).

Assessor´s comments

To assess the effect on PK further, anti-drug antibodies (ADA) status was tested in the population PK analyses, as one of covariates, based on data from 3 studies including both adult and pediatric subjects with SBS. The MAH states that the ADA incidence was found small and did not have an impact on PK of teduglutide. Since the updated dataset included only one new concentration in a subject with ADA positive, ADA was not retested in the current analysis. This is accepted.

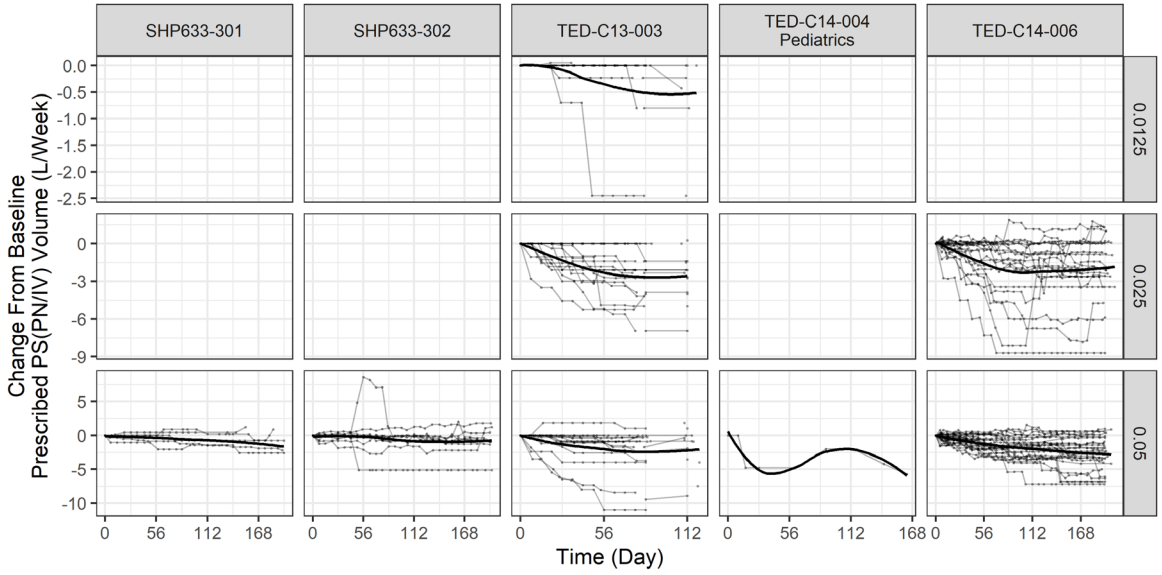
Parenteral Support

The relationship between teduglutide exposure (C_{max} and AUC) and PS volume was evaluated using a time and exposure-response model. Efficacy (PS volume) datasets were from Studies CL0600-004, CL0600-020, CL0600-021, TED-C13-003, TED-C14-004, TED-C14-006, SHP633-301, SHP-633-302, SHP-633-306, and SHP-633-307.

The current analysis therefore included a total of 251 subjects with SBS with both exposure and values of prescribed PS volume at both baseline and the end of each study. The population included a total of 7 pediatric subjects from 4 months to <1 year, 86 pediatric subjects 1 to <12 years, 8 pediatric subjects 12 to <18 years, and 150 adult subjects. The median body weight (range) and age (range) were 48.8 kg (5.26 kg to 87.9 kg) and 35.0 years (0.380 year to 87.9 years), respectively. Descriptive statistics of subjects included in the exposure-response analysis of efficacy is presented in SHIR-CSC-129_ERglobal, Section 8.3.

Individual change from baseline prescribed PS volumes in pediatric subjects as a function of dose are presented. Studies SHP633-301, SHP633-302, TED-C13-003, TED-C14-004, and TED-C14-006 in pediatric subjects were performed up to 112 and 196 days (Week 28) of dosing.

Figure 1 Longitudinal Profiles of Prescribed PS Volume in Pediatric Subjects – Studies SHP633-301, SHP633-302, TED-C13-003, TED-C14-004, and TED-C14-006



PS=parenteral support (same as PN/IV=parenteral nutrition/intravenous)

Note: grey circles and grey lines represent individual subject data; black like represents a smoothing function; Study TED-C14-004 has one 16 years old subject.

Source: SHIR-CSC-129_ERglobal, Figure 9

Various time- and exposure-response models were developed to optimally assess the change from baseline diary PS volume over time. An overview of all models developed for model discrimination is presented in SHIR-CSC-129_ERglobal, Appendix 4, Section 14.5. In a first step, longitudinal data from studies performed over 2 years of more (i.e., CL0600-021 and SHP633-307) were modelled to assess the effect of time.

Based on the above model, the estimated time to 50% of the maximum effect (ET_{50}) was approximately 168 days. The above results suggest that only 50% of the maximum effect is observed at Week 24 (168 days). In a second step, the ET_{50} was fixed to 168 days, and the effect of teduglutide AUC and C_{max} were evaluated. The model with C_{max} (estimated with an exponent in a power model) was associated with a better goodness-of-fit relative to a model with AUC. The time- and exposure-response model based on the C_{max} of teduglutide is described in SHIR-CSC-129_ERglobal, Table 6.

Descriptive statistics of PK and PD parameters (change from baseline prescribed PS volume) in pediatric and adult subjects who received the 0.05 mg/kg teduglutide dosing regimen are presented. The median baseline prescribed PS volume in pediatric and adult subjects were 6.88 L/Week and 10.4 L/Week, respectively.

At Week 24, pediatric and adult subjects presented a median change from baseline of -1.83 L/Week and -2.40 L/Week of prescribed PS volume, respectively. The above changes at Week 24 corresponded to a median percent change from baseline of -27% and -23% in pediatric and adult subjects, respectively.

At steady state, pediatric and adult subjects presented a median maximum change from baseline of -3.67 L/Week and -4.80 L/Week of prescribed PS volume, respectively. The above changes at steady state corresponded to a median percent change from baseline of -53% and -46% in pediatric and adult subjects, respectively.

Table 6 Descriptive Statistics - Change from Baseline Prescribed PS Volume in Pediatric and Adult Subjects with SBS (0.05 mg/kg)

Parameters		Pediatric Subjects (0.05 mg/kg) (N=55)	Adult Subjects (0.05 mg/kg) (N=61)
Baseline	PPSV (L/Week)		
	Mean (CV%)	7.62 (49.6%)	11.3 (52.5%)
	Median [Min, Max]	6.88 [2.43, 21.2]	10.4 [3.50, 35.0]
Week 24	PPSV - Change from Baseline (L/Week)		
	Mean (CV%)	-2.50 (134.0%)	-3.26 (90.4%)
	Median [Min, Max]	-1.83 [-16.3, 2.44]	-2.40 [-12.5, 0.609]
Steady State	PPSV - Maximum Change from Baseline (L/Week)		
	Mean (CV%)	-4.99 (134.0%)	-6.52 (90.4%)
	Median [Min, Max]	-3.67 [-32.6, 4.89]	-4.80 [-24.9, 1.22]
	C_{max} of Teduglutide (ng/mL)		
	Mean (CV%)	33.3 (35.4%)	39.6 (31.4%)
	Median [Min, Max]	32.0 [20.7, 84.9]	39.5 [19.5, 75.3]

C_{max}=maximum concentration; CV=Coefficient of variability; Max=maximum; Min=minimum; N=number of subjects; PPSV=prescribed parenteral support volume

Note: Maximum change from baseline corresponds to the maximum effect derived with the final model. One subject was removed from the descriptive statistics. This subject presented unexpectedly high teduglutide concentrations and no reduction in prescribed PS volume or diary PS volume. Descriptive statistic including this subject is presented in SHIR-CSC-129_ERglobal, Appendix 4 (Section 14.8).

Source: SHIR-CSC-129_ERglobal, Table 7

Descriptive statistics of PK and PD parameters (change from baseline prescribed PS volume) in pediatric subjects (0.05 mg/kg) by age groups are presented. The median baseline PS volume in the 4

months to <1 year, 1 to <6 years, 6 to <12 years, and 12 to 17 years age groups were 3.61 L/Week, 6.68 L/Week, 6.88 L/Week, and 11.7 L/Week, respectively.

At Week 24, the median change from baseline PS volume in the 4 months to <1 year, 1 to <6 years, 6 to <12 years, and 12 to 17 years age groups were -0.620 L/Week, -1.01 L/Week, -2.88 L/Week, and -4.31 L/Week, respectively. These above changes at Week 24 corresponded to median percent change from baseline of -17%, -15%, -42% and -37%, respectively.

At steady state, the median maximum change from baseline PS volume in the 4 months to <1 year, 1 to <6 years, 6 to <12 years, and 12 to 17 years age groups were -1.24 L/Week, -2.02 L/Week, -5.76 L/Week, and -8.63 L/Week, respectively. These above changes at steady state corresponded to a median percent change from baseline of -34%, -30%, -84% and -74%, respectively.

Table 7 Descriptive Statistics - Change from Baseline Prescribed PS Volume in Pediatric Subjects by Age Groups (0.05 mg/kg)

Parameters		4 months to <1 year (N=6)	1 to <6 years (N=28)	6 to <12 years (N=17)	12 to 17 years (N=4)
Baseline	PPSV (L/Week)				
	Mean (CV%)	4.87 (48.6%)	7.16 (39.1%)	8.09 (49.6%)	13.0 (44.8%)
	Median	3.61	6.68	6.88	11.7
	[Min, Max]	[3.06, 8.57]	[2.43, 14.4]	[4.00, 18.7]	[7.48, 21.2]
Week 24	PPSV - Change from Baseline (L/Week)				
	Mean (CV%)	-0.752 (156.6%)	-1.46 (124.1%)	-3.77 (101.6%)	-6.96 (90.4%)
	Median	-0.620	-1.01	-2.88	-4.31
	[Min, Max]	[-2.38, 0.731]	[-5.40, 2.44]	[-14.6, 1.40]	[-16.3, -2.90]
Steady State	PPSV - Maximum Change from Baseline (L/Week)				
	Mean (CV%)	-1.50 (156.6%)	-2.92 (124.1%)	-7.53 (101.6%)	-13.9 (90.4%)
	Median	-1.24	-2.02	-5.76	-8.63
	[Min, Max]	[-4.77, 1.46]	[-10.8, 4.89]	[-29.3, 2.79]	[-32.6, -5.79]
	C_{max} of Teduglutide (ng/mL)				
	Mean (CV%)	28.7 (18.9%)	33.7 (37.8%)	35.5 (35.4%)	28.5 (26.3%)
	Median	27.8	31.5	34.5	26.7
	[Min, Max]	[23.0, 36.4]	[21.8, 84.9]	[20.7, 71.3]	[22.3, 38.0]

C_{max}=maximum Concentration; CV=Coefficient of variability; Max=maximum; Min=minimum; N=number of subjects; PPSV=prescribed parenteral support volume

NA = not applicable. Mean values were only derived for sample size greater than 2.

Note: Maximum change from baseline corresponds to the maximum effect derived with the final model. One subject was removed from the descriptive statistics since this subject presented unexpectedly high teduglutide concentrations and no reduction in prescribed PS volume or diary PS volume. Descriptive statistic including this subject is presented in SHIR-CSC-129_ERglobal, Appendix 4 (Section 14.9).

Source: SHIR-CSC-129_ERglobal, Table 8

Assessor´s comments

The relationship between teduglutide exposure (C_{max} and AUC) and PS volume was evaluated using a time and exposure-response model. Efficacy (PS volume) datasets were from Studies CL0600-004, CL0600-020, CL0600-021, TED-C13-003, TED-C14-004, TED-C14-006, SHP633-301, SHP-633-302, SHP-633-306, and SHP-633-307.

The current analysis therefore included a total of 251 subjects with SBS with both exposure and values of prescribed PS volume at both baseline and the end of each study. The population included a total of 7 pediatric subjects from 4 months to <1 year, 86 pediatric subjects 1 to <12 years, 8 pediatric

subjects 12 to <18 years, and 150 adult subjects. The median body weight (range) and age (range) were 48.8 kg (5.26 kg to 87.9 kg) and 35.0 years (0.380 year to 87.9 years), respectively.

Based on the above model, the estimated time to 50% of the maximum effect (ET_{50}) was approximately Week 24 (168 days). In a second step, the ET_{50} was fixed to 168 days, and the effect of teduglutide AUC and C_{max} were evaluated.

The median baseline PS volume in the 4 months to <1 year, 1 to <6 years, 6 to <12 years, and 12 to 17 years age groups were 3.61 L/Week, 6.68 L/Week, 6.88 L/Week, and 11.7 L/Week, respectively.

At Week 24, the median change from baseline PS volume in the 4 months to <1 year, 1 to <6 years, 6 to <12 years, and 12 to 17 years age groups were -0.620 L/Week, -1.01 L/Week, -2.88 L/Week, and -4.31 L/Week, respectively. These above changes at Week 24 corresponded to median percent change from baseline of -17%, -15%, -42% and -37%, respectively.

At steady state, the median maximum change from baseline PS volume in the 4 months to <1 year, 1 to <6 years, 6 to <12 years, and 12 to 17 years age groups were -1.24 L/Week, -2.02 L/Week, -5.76 L/Week, and -8.63 L/Week, respectively. These above changes at steady state corresponded to a median percent change from baseline of -34%, -30%, -84% and -74%, respectively.

Safety (Vomiting, Diarrhea, Nausea, Abdominal Pain)

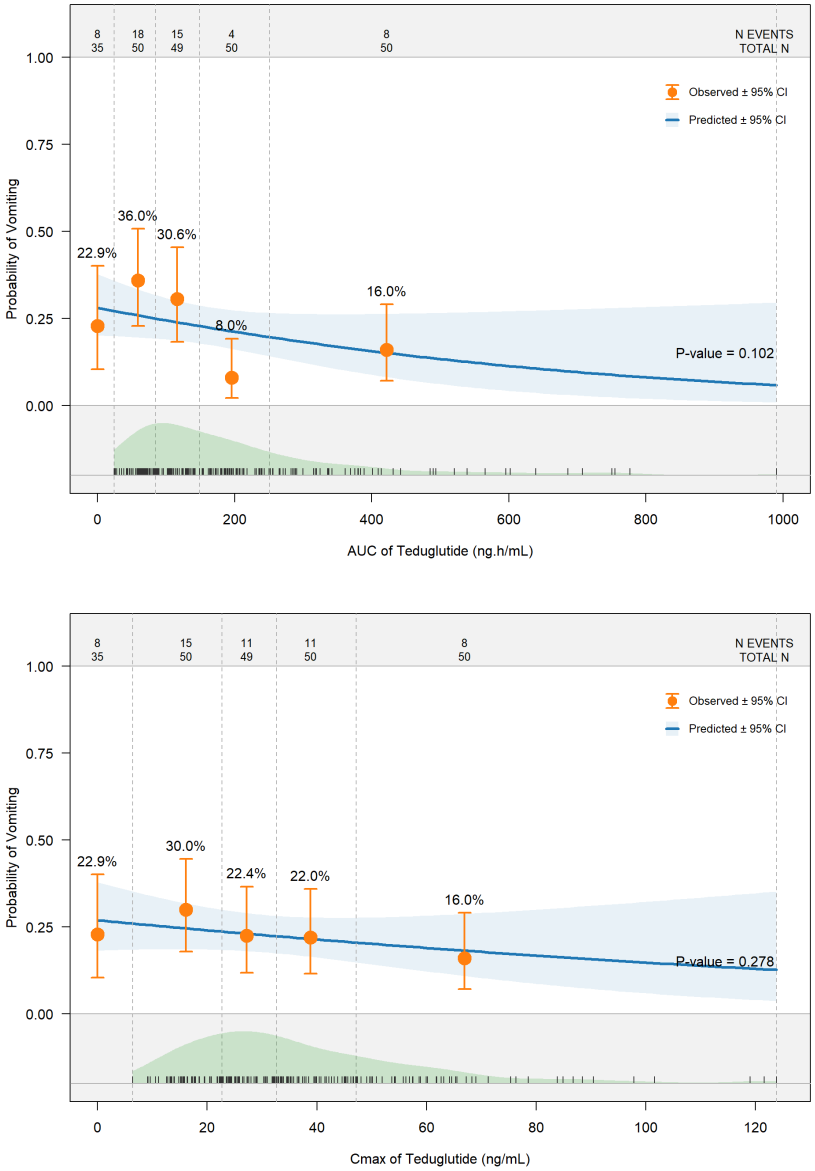
An exposure-response analysis was performed to assess the relationship between teduglutide exposure and the probability of the most frequent treatment emergent adverse events (TEAE) in subjects with SBS. Safety (adverse events) included datasets from Studies CL0600-004, CL0600-020, CL0600-021, TED-C13-003, TED-C14-004, TED-C14-006, SHP633-301, SHP-633-302, SHP-633-306, and SHP-633-307.

A total of 234 subjects with SBS were included in the analysis. Of which 53 (22.6%) presented at least one instance of vomiting, 28 (12.0%) presented at least one instance of diarrhea, 37 (15.8%) presented at least one instance of nausea, and 59 (25.2%) presented at least one instance of abdominal pain. The relationship between teduglutide exposure and the probability of the above TEAE was assessed. Descriptive statistics on the number of subjects by study are presented in SHIR-CSC-129_ERglobal, Section 8.4.

Probability of Vomiting

The probability of vomiting as a function of teduglutide exposure parameters at steady state (C_{max} and AUC) are presented. No exposure-response relationship was observed since the probability of vomiting did not significantly increase with higher C_{max} and AUC values (Wald test p-value >0.05).

Figure 2 Exposure-Response – Impact of C_{max} and AUC on Probability of Vomiting



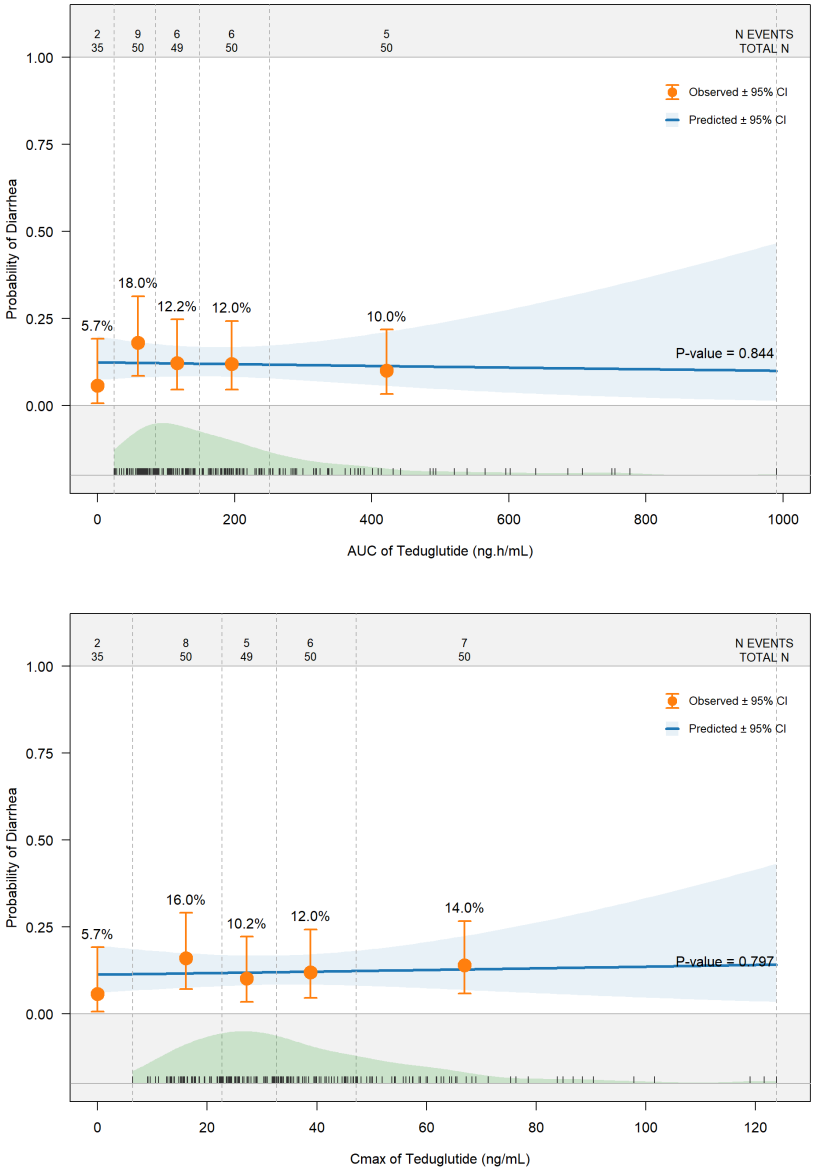
Note: The number of adverse events (N events) and the total numbers of subjects treated with placebo or standard of care (exposure set to zero) and teduglutide exposure values for quartile (C_{max} or AUC values were evenly distributed across 4 groups) are presented in the upper panel. These numbers were used to determine the probability of adverse event for placebo and each quartiles of exposure parameters. The green area represents the distribution of C_{max} or AUC for teduglutide-treated subjects. The black tick marks represent an indicator of individual C_{max} or AUC for teduglutide-treated subjects.

Source: SHIR-CSC-129_ERglobal, Figure 13

Probability of Diarrhea

The probability of diarrhea as a function of teduglutide exposure parameters at steady state (C_{max} and AUC) are presented. No exposure-response relationship was observed since the probability of diarrhea did not significantly increase with higher C_{max} and AUC values (Wald test p-value >0.05).

Figure 3 Exposure-Response – Impact of C_{max} and AUC on Probability of Diarrhea



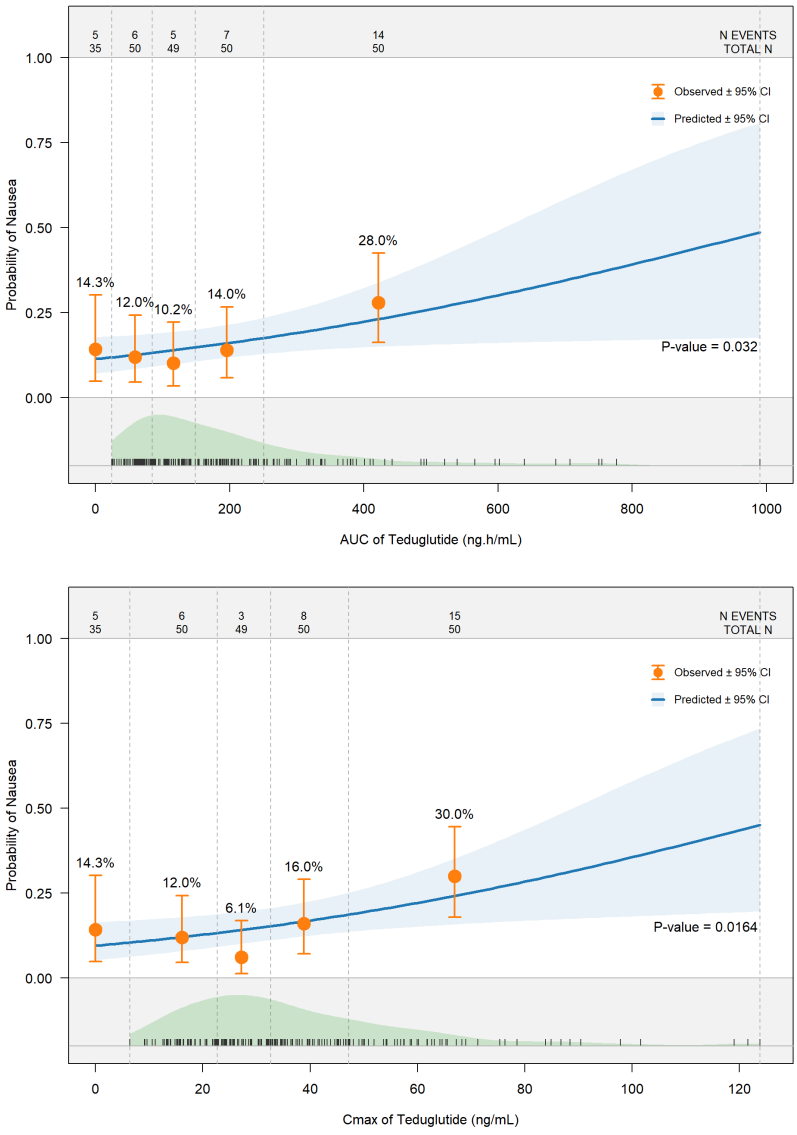
Note: The number of adverse events (N events) and the total numbers of subjects treated with placebo or standard of care (exposure set to zero) and teduglutide exposure values for quartile (C_{max} or AUC values were evenly distributed across 4 groups) are presented in the upper panel. These numbers were used to determine the probability of adverse event for placebo and each quartiles of exposure parameters. The green area represents the distribution of C_{max} or AUC for teduglutide-treated subjects. The black tick marks represent an indicator of individual C_{max} or AUC for teduglutide-treated subjects.

Source: SHIR-CSC-129_ERglobal, Figure 14

Probability of Nausea

The probability of nausea as a function of teduglutide exposure parameters at steady state (C_{max} and AUC) are presented. A statistically significant exposure-response relationship was observed since the probability of nausea increased significantly with higher C_{max} and AUC values (Wald test p-value <0.05). The exposure-response model based on C_{max} was associated with better goodness-of-fit (i.e., lower Akaike Criteria [AIC]) relative to the AUC model (202.7 and 204.0, respectively).

Figure 4 Exposure-Response – Impact of C_{max} and AUC on Probability of Nausea



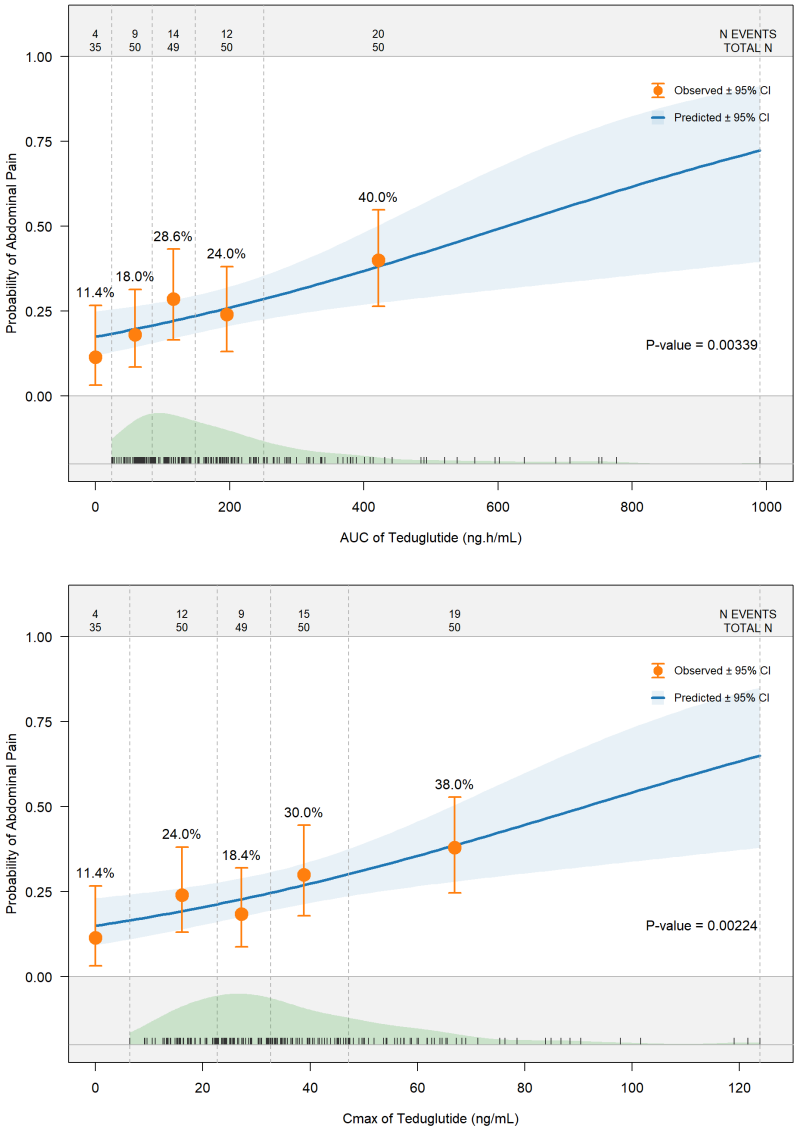
Note: The number of adverse events (N events) and the total numbers of subjects treated with placebo or standard of care (exposure set to zero) and teduglutide exposure values for quartile (C_{max} or AUC values were evenly distributed across 4 groups) are presented in the upper panel. These numbers were used to determine the probability of adverse event for placebo and each quartiles of exposure parameters. The green area represents the distribution of C_{max} or AUC for teduglutide-treated subjects. The black tick marks represent an indicator of individual C_{max} or AUC for teduglutide-treated subjects.

Source: SHIR-CSC-129_ERglobal, Figure 15

Probability of Abdominal Pain

The probability of abdominal pain as a function of teduglutide exposure parameters at steady state (C_{max} and AUC) are presented. A statistically significant exposure-response relationship was observed since the probability of abdominal pain increased significantly with higher C_{max} and AUC values (Wald test p-value <0.01). The exposure-response model based on C_{max} was associated with a lower AIC relative to the AUC model (258.6 and 259.5, respectively).

Figure 5 Exposure-Response – Impact of C_{max} and AUC on Probability of Abdominal Pain



Note: The number of adverse events (N events) and the total numbers of subjects treated with placebo or standard of care (exposure set to zero) and teduglutide exposure values for quartile (C_{max} or AUC values were evenly distributed across 4 groups) are presented in the upper panel. These numbers were used to determine the probability of adverse event for placebo and each quartiles of exposure parameters. The green area represents the distribution of C_{max} or AUC for teduglutide-treated subjects. The black tick marks represent an indicator of individual C_{max} or AUC for teduglutide-treated subjects.

Source: SHIR-CSC-129_ERglobal, Figure 16

Assessor´s comments

An exposure-response analysis was performed to assess the relationship between teduglutide exposure and the probability of the most frequent treatment emergent adverse events (TEAE) in subjects with SBS. Safety (adverse events) included datasets from Studies CL0600-004, CL0600-020, CL0600-021, TED-C13-003, TED-C14-004, TED-C14-006, SHP633-301, SHP-633-302, SHP-633-306, and SHP-633-307.

A total of 234 subjects with SBS were included in the analysis.

A statistically significant exposure-response relationship was observed on the probability of vomiting and abdominal pain since the probability of nausea increased significantly with higher C_{max} and AUC values (Wald test p-value <0.05).

No exposure-response relationship was observed on the probability of vomiting or diarrhea, since the probability did not significantly increase with higher C_{max} and AUC values (Wald test p-value >0.05).

The MAH is asked to discuss the clinical significance of the presented exposure-safety results in regards of nausea and abdominal pain, which should include instructions for prescribing physician e.g. dose adjustments. The MAH should also explain the discrepancy between the results of the probabilities of nausea and vomiting, since these TEAS are normally closely related **(OC)**.

Special Studies

Not applicable.

Discussion

Further population PK and PK/PD modeling and simulation were conducted to support the proposed type II variation in pediatrics 4 months to <1 year A total of 7 pediatrics subjects 4 months to <1 year of age with SBS who are dependent on PS are included.

The PK population included a total of 101 pediatric and 379 adult subjects. The population included a total of 7 pediatric subjects from 4 months to <1 year, 86 pediatric subjects 1 to <12 years, 8 pediatric subjects 12 to <18 years, and 379 adult subjects (≥18 years)

Body weight, age, baseline creatinine clearance (CrCL), injection site, and disease status were identified as significant covariates affecting PK parameters including CL/F, Vc/F, and Ka. Sensitivity analyses did not show any differences in population PK model improvement between with and without including the kidney maturation. Overall, data collected in pediatric subjects 4 months to <1 year did not impact the population PK estimates as compared with the previous population PK for the Japanese submission.

Overall, the MAH considers that pediatric patients 4 months to <18 years are expected to present similar $C_{max,ss}$ values of teduglutide as observed in adults. However, the AUC_{ss} of teduglutide was age-dependent and gradually decreased from adults to pediatric subjects between 4 months and <1 year of age. The Applicant states that C_{max} of teduglutide has been targeted across age populations, and that the current analyses have confirmed similarity of C_{max} of teduglutide across age populations including pediatrics subjects 4 month to <1 year of age with SBS, therefore, supporting 0.05 mg/kg daily in this age group patients.

An exposure-response analysis was performed to assess the relationship between teduglutide exposure and the probability of the most frequent treatment emergent adverse events (TEAE) in subjects with SBS. A total of 234 subjects with SBS were included in the analysis. A statistically significant exposure-response relationship was observed on the probability of vomiting and abdominal pain since the probability of nausea increased significantly with higher C_{max} and AUC values (Wald test p-value <0.05). No exposure-response relationship was observed on the probability of vomiting or diarrhea, since the probability did not significantly increase with higher C_{max} and AUC values (Wald test p-value >0.05).

The MAH is asked to discuss the clinical significance of the presented exposure-safety results in regards of nausea and abdominal pain, which should include instructions for prescribing physician e.g.

dose adjustments. The MAH should also explain the discrepancy between the results of the probabilities of nausea and vomiting, since these TEAS are normally closely related **(OC)**.

7. Clinical Efficacy aspects

7.1. Methods – analysis of data submitted

Study SHP633-301

SHP633-301 was a randomized, open-label study consisting of a 2- to 4-week screening period, a 24 week treatment period, and 4-week follow-up period. All subjects were screened prior to start of treatment to verify the requirements for nutritional support for each subject and to ensure adherence to eligibility parameters. Subjects had to be receiving at least 50% of fluid or calories parenterally and have stable PS requirements for at least 1 month prior to screening and weigh at least 5 kg with a weight for length Z-score greater than -2 at screening and baseline. Subjects were randomized (1:1 ratio) to the teduglutide or standard of care (SOC) treatment arm at the baseline visit (Week 0). Randomization was stratified according to the presence of a small bowel ostomy (e.g., end jejunostomy or ileostomy). During the 24-week treatment period, subjects in the SOC arm received standard medical therapy for SBS while those in the teduglutide arm received 0.05 mg/kg/day subcutaneously in addition to standard medical therapy.

Subjects in both arms followed the same visit schedule and assessments. Subjects were monitored weekly with phone or clinic visits. Clinic visits occurred at Weeks 1, 3, 5, 7, 9, 12, 16, 20, 24, and 28. At all site visits and telephone contacts, safety was monitored and nutritional support was reviewed and adjusted as needed. To maintain consistency across centers, guidance and training were provided to help sites follow the nutritional support adjustment guidelines (developed with SBS expert input and provided in the protocol) related to decisions for PS reduction and advances in enteral feeds based on weight gain, urine and stool output, and clinical stability. Deviations from the guidelines were not considered a protocol deviation.

Blood samples for native GLP-2 measurements were collected at the screening and at end of the treatment (EOT) visits. Native GLP-2 may not have been collected in some subjects if blood volumes were limiting based on subject weight or at the investigator discretion based on weekly/monthly total volume.

Blood samples for PK analysis were collected in the teduglutide treatment arm at baseline (predose, and 1 hour and 4 hours postdose) and at Week 7 (2 hours postdose).

At the end of the treatment period (Week 24), all subjects entered a 4-week follow-up period until the end of study (Week 28/EOS) during which time subjects received standard medical therapy, but no investigational product was administered. At the end of the treatment period, some subjects who completed the study had the opportunity to participate in a long-term extension study, SHP633 304, in which eligible subjects would continue to receive teduglutide. The follow-up period for subjects in the teduglutide treatment arm may have been truncated and the subjects could have proceeded immediately to the EOS visit if at least 1 "escape" criteria was met.

Assessor´s comments

SHP633-301 is described in 6.1. Please refer for Assessors comments.

7.2. Results

Disposition of Subjects

Disposition of subjects is presented in SHP633-301 Clinical Study Report (CSR), Section 10.1.

Eight subjects completed the study. Two subjects discontinued from the study: 1 subject in the teduglutide arm met escape criteria during the follow-up period and 1 subject in the SOC arm discontinued early from the study during the treatment period. In addition, 1 subject interrupted teduglutide treatment following Week 10 visit due to the parents' decision to stop teduglutide administration as they thought several AEs were caused by the study drug; teduglutide treatment never resumed and the subject completed the study.

Demographics and Baseline Characteristics

Demographic and baseline characteristics are presented in SHP633-301 CSR, Section 10.4. The mean corrected gestational age was 8.4±2.71 months. All but 1 subject in the teduglutide arm and 2 subjects in the SOC arm were male. All subjects were white except 1 subject in each treatment arm who were Asian; no subjects were Hispanic or Latino.

The mean baseline weight, length, and weight/length ratio Z-scores for the safety set were at 0.7±1.43, 0.2±1.64, and 0.7±1.12, respectively, and similar between the 2 treatment arms. One subject in the teduglutide arm had baseline weight and weight/length ratio Z-scores of 3.7 and 2.4, respectively, and 1subject in the SOC arm had baseline weight and weight/length ratio Z scores of 2.8 and 2.2, respectively.

Short bowel history is presented in SHP633-301 CSR, Section 10.4.3.1. The main underlying causes of SBS were gastroschisis and necrotizing enterocolitis. One subject in the SOC arm had a colostomy. All subjects had at least some remaining colon and the mean percent of remaining colon was 65.6±23.37 overall; the remnant colon was in continuity in 9 (90.0%) subjects and 1 subject in the teduglutide arm had an ileocecal valve present.

Efficacy Results

Efficacy/PD analyses of PS and enteral nutrition (EN) data were based on weight-normalized PS/EN volume and caloric intake. All efficacy data were presented for the intent-to-treat (ITT) set unless otherwise specified.

Analyses of weekly PS and EN were based on 2 data sources: the subject diary data (also referred to as actual data) and the investigator prescribed data. In previous studies of teduglutide, the subject diary data were considered a more representative measure of efficacy/PD than the investigator prescribed data. However, several subjects in this study had missing or lost diary data at baseline or EOT. Due to limitations in diary data, both data are presented.

Reduction in PS Volume

The reduction in PS volume at EOT and by visit based on subject diary and prescribed data are presented for the ITT set in SHP633-301 CSR, Section 11.1.1.1 and Section 11.1.1.2, respectively.

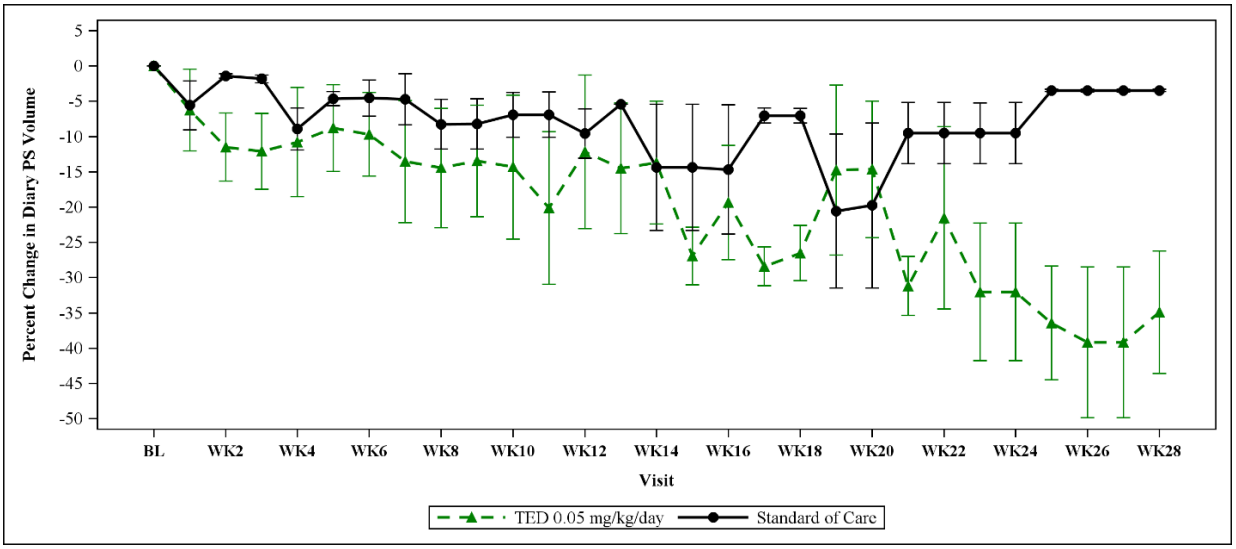
The primary efficacy endpoint is the reduction in weight-normalized PS volume of at least 20% at Week 24/EOT from baseline. Based on subject diary data, 3 (60.0%) subjects enrolled in the teduglutide treatment arm and 1 (20.0%) subject in the SOC arm experienced at least 20% reduction in PS volume at EOT from baseline (2 subjects in the SOC arm had missing data). Based on prescribed data, 3 (60.0%) subjects enrolled in each treatment arm experienced at least 20% reduction in PS volume at EOT from baseline.

Based on subject diary data, the mean (±SD) PS volume at baseline was 95.3±45.93 mL/kg/day for subjects in the teduglutide treatment arm. The mean change in PS volume at EOT from baseline was 21.5±28.91 mL/kg/day, corresponding to a mean percentage change of 24.8±34.72%. The mean PS volume at baseline was 70.9±14.44 mL/kg/day for subjects in the SOC arm. The mean change in PS volume at EOT from baseline was 9.5±7.50 mL/kg/day, corresponding to a mean percentage change of 16.8±16.39%.

Based on prescribed data, the mean (±SD) PS volume at baseline was 94.0±45.03 mL/kg/day for subjects in the teduglutide treatment arm. The mean change in PS volume at EOT from baseline was 22.9±26.94 mL/kg/day, corresponding to a mean percentage change of 27.3±33.52%. The mean PS volume at baseline was 67.7±13.65 mL/kg/day for subjects in the SOC arm. The mean change in PS volume at EOT from baseline was 14.9±12.32 mL/kg/day, corresponding to a mean percentage change of 22.4±17.20%.

The mean ±SE plots of percent change in PS volume by visit based on diary and prescribed data are presented in Figure 1 and Figure 2, respectively.

Figure 6 Mean ±SE Plot of Percent Change in PS Volume by Visit Based on Diary Data (Intent-to-treat Set)



PS=Parenteral Support; SE=Standard Error

Note: Percent change is calculated as (change from baseline at the week / baseline value) * 100, using average daily values normalized by weight at the interval.

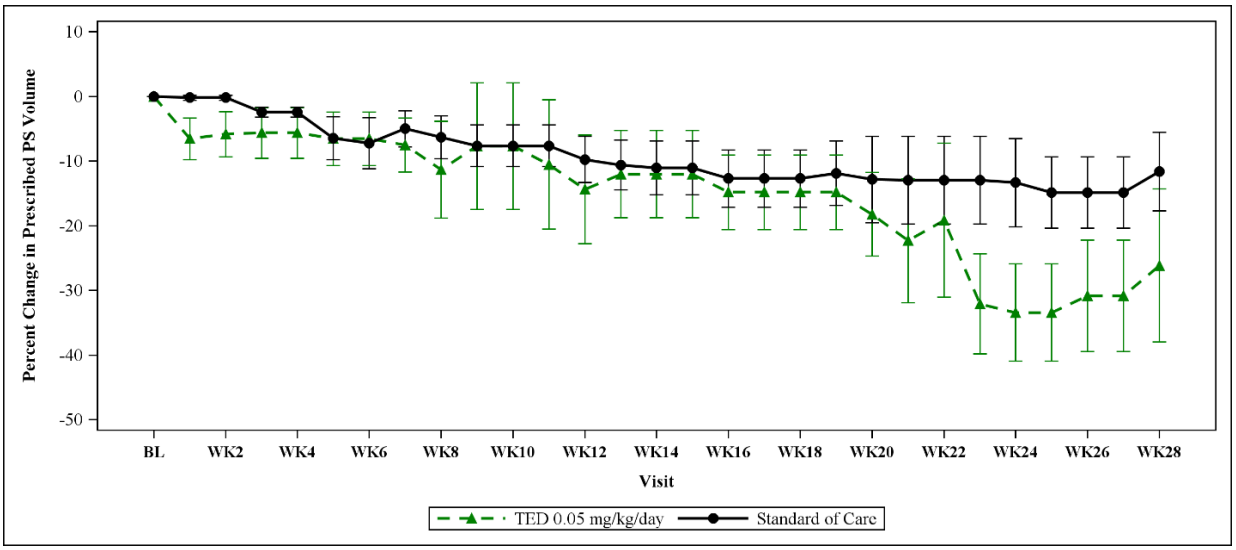
Average daily value is calculated as [(sum of non-missing daily values in the diary / number of days with non-missing values)] / last available body weight prior to the visit.

End of Treatment/Early Termination is defined as the last available visit after the date of first dose (or randomization in standard of care treatment group) during the 24-week treatment period.

For the teduglutide treatment group, baseline is defined as the last available value prior to teduglutide administration. For the standard of care treatment group, baseline is defined as the last available value on or prior to the baseline visit.

Source: SHP633-301 CSR, Figure 14.2.3.4

Figure 7 Mean ±SE Plot of Percent Change in PS Volume by Visit Based on Prescribed Data (Intent-to-treat Set)



PS=Parenteral Support; SE=Standard Error

Note: Percent change is calculated as (change from baseline at the week / baseline value) * 100, using average daily values normalized by weight at the interval.

End of Treatment/Early Termination is defined as the last available visit after the date of first dose (or randomization in standard of care treatment group) during the 24-week treatment period.

For the teduglutide treatment group, baseline is defined as the last available value prior to teduglutide administration. For the standard of care treatment group, baseline is defined as the last available value on or prior to the baseline visit.

Source: SHP633-301 CSR, Figure 14.2.3.5

Assessor´s comments

Demographic and baseline characteristics for study SHP633-301 was described in 6.2, please refer to assessor's comments. The main underlying causes of SBS were gastroschisis and necrotizing enterocolitis. Efficacy/PD analyses of PS and enteral nutrition (EN) data were based on weight-normalized PS/EN volume and caloric intake.

The primary efficacy endpoint is the reduction in weight-normalized PS volume of at least 20% at Week 24/EOT from baseline. Based on subject diary data, 3 (60.0%) subjects enrolled in the teduglutide treatment arm and 1 (20.0%) subject in the SOC arm experienced at least 20% reduction in PS volume at EOT from baseline (2 subjects in the SOC arm had missing data). Based on prescribed data, 3 (60.0%) subjects enrolled in each treatment arm experienced at least 20% reduction in PS volume at EOT from baseline.

Reduction in PS Caloric Intake

The reduction in PS caloric intake at EOT and by visit based on subject diary and prescribed data are presented for the ITT set in SHP633-301 CSR, Section 11.1.1.2.

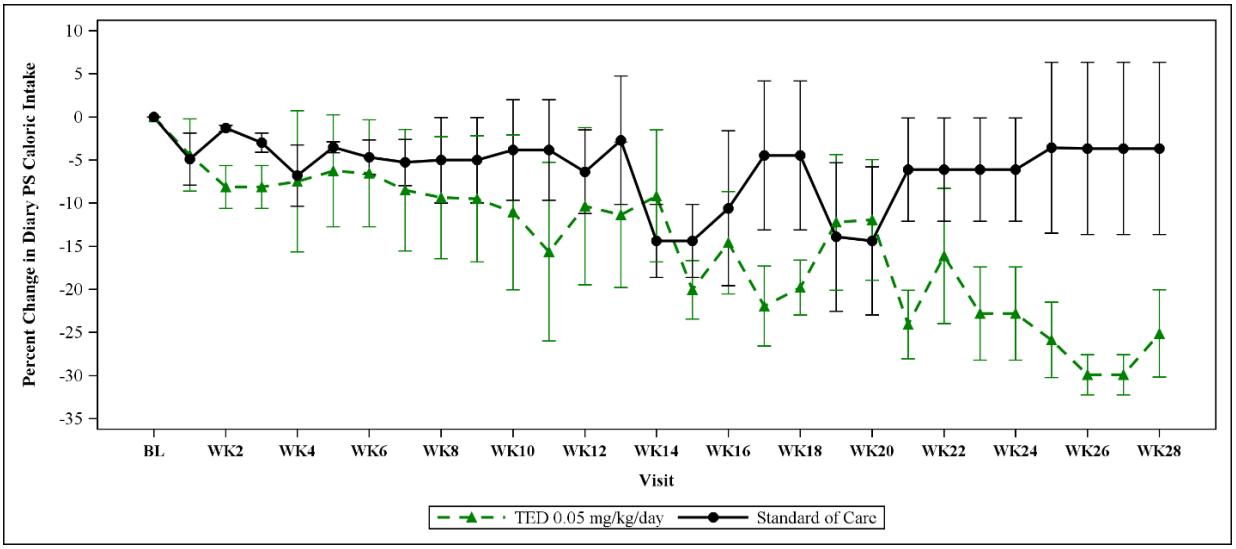
Based on subject diary data, 3 (60.0%) subjects enrolled in the teduglutide treatment arm and 1 (20.0%) subject in the SOC arm experienced at least 20% reduction in PS caloric intake at EOT from baseline (2 subjects in the SOC arm had missing data). Based on prescribed data, 3 (60.0%) subjects enrolled in each treatment arm experienced at least 20% reduction in PS caloric intake at EOT from baseline.

Based on subject diary data, the mean (±SD) PS caloric intake at baseline was 67.3±11.50 kcal/kg/day for subjects in the teduglutide treatment arm. The mean change in PS caloric intake at EOT from baseline was -16.1±17.55 kcal/kg/day, corresponding to a mean percentage change of -27.0±29.47%. The mean PS caloric intake at baseline was 65.1±18.20 kcal/kg/day for subjects in the SOC arm. The mean change in PS caloric intake at EOT from baseline was -6.1±10.39 kcal/kg/day, corresponding to a mean percentage change of -13.7±21.87%.

Based on prescribed data, the mean (±SD) PS caloric intake at baseline was 66.3±14.96 kcal/kg/day for subjects in the teduglutide treatment arm. The mean change in PS caloric intake at EOT from baseline was -15.3±17.84 kcal/kg/day, corresponding to a mean percentage change of -27.8±30.78%. The mean PS caloric intake at baseline was 62.5±18.31 kcal/kg/day for subjects in the SOC arm. The mean change in PS caloric intake at EOT from baseline was -20.4±21.02 kcal/kg/day, corresponding to a mean percentage change of -38.9±39.89%.

The mean ±SE plots of percent change in PS caloric intake by visit based on diary and prescribed data are presented in **Figure 4** and **Figure 5**, respectively.

Figure 8 Mean ±SE Plot of Percent Change in PS Caloric Intake by Visit Based on Diary Data (Intent-to-treat Set)



PS=Parenteral support; SE=Standard error

Note: Percent change is calculated as (change from baseline at the week / baseline value) * 100, using average daily values normalized by weight at the interval.

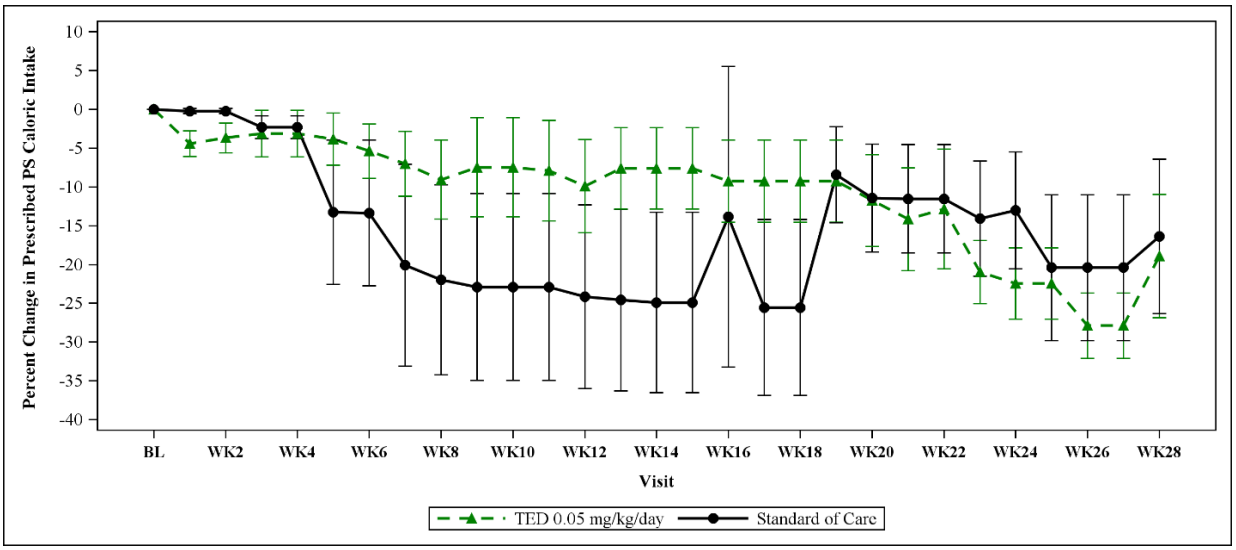
Average daily value is calculated as [(sum of non-missing daily values in the diary / number of days with non-missing values)] / last available body weight prior to the visit.

End of Treatment/Early Termination is defined as the last available visit after the date of first dose (or randomization in standard of care treatment group) during the 24-week treatment period.

For the teduglutide treatment group, baseline is defined as the last available value prior to teduglutide administration. For the standard of care treatment group, baseline is defined as the last available value on or prior to the baseline visit.

Source: SHP633-301 CSR, Figure 14.2.3.6

Figure 9 Mean ±SE Plot of Percent Change in PS Caloric Intake by Visit Based on Prescribed Data (Intent-to-treat Set)



PS=Parenteral support; SE=Standard error

Note: Percent change is calculated as (change from baseline at the week / baseline value) * 100, using average daily values normalized by weight at the interval.

End of Treatment/Early Termination is defined as the last available visit after the date of first dose (or randomization in standard of care treatment group) during the 24-week treatment period.

For the teduglutide treatment group, baseline is defined as the last available value prior to teduglutide administration. For the standard of care treatment group, baseline is defined as the last available value on or prior to the baseline visit.

Source: SHP633-301 CSR, Figure 14.2.3.7

Assessor´s comments

Based on subject diary data, 3 (60.0%) subjects enrolled in the teduglutide treatment arm and 1 (20.0%) subject in the SOC arm experienced at least 20% reduction in PS caloric intake at EOT from baseline (2 subjects in the SOC arm had missing data). Based on prescribed data, 3 (60.0%) subjects enrolled in each treatment arm experienced at least 20% reduction in PS caloric intake at EOT from baseline.

In the TED arm, the mean change in PS caloric intake at EOT from baseline was -16.1±17.55 kcal/kg/day, corresponding to a mean percentage change of -27.0±29.47%. In the SOC arm, the mean change in PS caloric intake at EOT from baseline was -6.1±10.39 kcal/kg/day, corresponding to a mean percentage change of -13.7±21.87%.

The MAH is asked to discuss the clinical relevance of the presented results for "Reduction in PS Caloric Intake" **(OC)**.

Complete Weaning off PS

No subject achieved enteral autonomy (SHP633-301 CSR, Section 11.1.1.2).

Change from Baseline in EN Volume

The change in enteral support volume from baseline is presented in SHP633-301 CSR, Section 11.1.1.2. For this study, EN was defined as specialized formula, and did not include table foods.

Based on subject diary data, 2 (40.0%) subjects enrolled in the teduglutide treatment arm and no subject in the SOC arm experienced at least 20% increase in EN volume at EOT from baseline (3 subjects in each treatment arm had missing data).

Based on subject diary data, the mean (±SD) EN volume at baseline was 9.7±14.71 mL/kg/day for subjects in the teduglutide treatment arm. The mean change in EN volume at EOT from baseline was 16.1±18.68 mL/kg/day, corresponding to a mean percentage change of 273.2±246.78%. The mean EN volume at baseline was 33.6±20.76 mL/kg/day for subjects in the SOC arm. The mean change in EN volume at EOT from baseline was -15.3±31.50 mL/kg/day, corresponding to a mean percentage change of -44.3±78.85%.

Based on prescribed data, no subject enrolled in the teduglutide treatment arm and 2 (40.0%) subjects in the SOC arm experienced at least 20% increase in EN volume at EOT from baseline (4 and 1 subjects had missing data in the teduglutide and SOC arms, respectively).

Based on prescribed data, the mean (±SD) EN volume at baseline was 7.8±15.63 mL/kg/day for subjects in the teduglutide treatment arm. The mean change in EN volume at EOT from baseline was -1.3±2.56 mL/kg/day, corresponding to a mean percentage change of -16.4 (-)%. The mean EN volume at baseline was 31.9±19.89 mL/kg/day for subjects in the SOC arm. The mean change in EN

volume at EOT from baseline was 2.3±22.23 mL/kg/day, corresponding to a mean percentage change of 14.8±69.83%.

Assessor´s comments

No subject achieved enteral autonomy

Based on subject diary data, 2 (40.0%) subjects enrolled in the teduglutide treatment arm and no subject in the SOC arm experienced at least 20% increase in EN volume at EOT from baseline (3 subjects in each treatment arm had missing data).

In the TED arm, the mean change in EN volume at EOT from baseline was 16.1±18.68 mL/kg/day, corresponding to a mean percentage change of 273.2±246.78%. In the SOC arm the mean change in EN volume at EOT from baseline was -15.3±31.50 mL/kg/day, corresponding to a mean percentage change of -44.3±78.85%.

Based on prescribed data, the mean (±SD) EN volume at baseline was 7.8±15.63 mL/kg/day for subjects in the teduglutide treatment arm. The mean change in EN volume at EOT from baseline was -1.3±2.56 mL/kg/day, corresponding to a mean percentage change of -16.4 (-)%. The mean EN volume at baseline was 31.9±19.89 mL/kg/day for subjects in the SOC arm. The mean change in EN volume at EOT from baseline was 2.3±22.23 mL/kg/day, corresponding to a mean percentage change of 14.8±69.83%.

The MAH is asked to discuss the clinical relevance of the presented results for "Reduction in EN volume" **(OC)**.

Change from Baseline in EN Caloric Intake

The change in enteral support calories from baseline is presented in SHP633-301 CSR, Section 11.1.1.2.

Based on subject diary data, 2 (40.0%) subject enrolled in the teduglutide treatment arm and no subject in the SOC arm experienced at least 20% increase in EN caloric intake at EOT from baseline (3 subjects in each treatment arm had missing data).

Based on subject diary data, the mean (±SD) EN caloric intake at baseline was 6.5±9.86 kcal/kg/day for subjects in the teduglutide treatment arm. The mean change in EN caloric intake at EOT from baseline was 9.1±10.66 kcal/kg/day, corresponding to a mean percentage change of 207.1±153.16%. The mean EN caloric intake at baseline was 25.5±18.30 kcal/kg/day for subjects in the SOC arm. The mean change in EN caloric intake at EOT from baseline was -9.4±21.40 kcal/kg/day, corresponding to a mean percentage change of -44.3±78.85%.

Based on prescribed data, no subjects enrolled in the teduglutide treatment arm and 2 (40.0%) subject in the SOC arm experienced at least 20% increase in EN caloric intake at EOT from baseline (4 and 1 subjects had missing data in the teduglutide and SOC arms, respectively).

Based on prescribed data, the mean (±SD) EN caloric intake at baseline was 7.0±14.06 kcal/kg/day for subjects in the teduglutide treatment arm. The mean change in EN caloric intake at EOT from baseline was -1.2±2.31 kcal/kg/day, corresponding to a mean percentage change of -16.4 (-)%. The mean EN caloric intake at baseline was 24.7±19.17 kcal/kg/day for subjects in the SOC arm. The mean change in EN caloric intake at EOT from baseline was 3.1±16.29 kcal/kg/day, corresponding to a mean percentage change of 24.2±78.12%.

Native GLP-2

Of the 4 subjects in the teduglutide arm with native GLP-2 measurements at baseline, 3 subjects who experienced ≥20% reduction in PS volume at EOT had a mean native GLP-2 measurement at baseline of 180.7±38.55 pg/mL and 1 subject who experienced <20% reduction in PS volume at EOT had a native GLP-2 measurement at baseline of 75.0 pg/mL. Among the subjects in the teduglutide arm, the subject with the lowest baseline endogenous GLP-2 levels exhibited a smaller relative reduction in PS volume at EOT.

Change from Baseline in Days per Week and Hours per Day in PS

Based on the subject diary data, the mean (±SD) number of days per week in PS usage at baseline was 6.7±0.45 days/week in the teduglutide treatment arm. The mean change in number of days per week in PS usage at EOT from baseline was -1.9±2.01 days/week, corresponding to a mean percentage change of -28.5±30.05%. The mean number of days per week in PS usage at baseline was 7.0±0.00 days/week in the SOC arm. There was no change in mean daily PS observed at EOT from baseline in the SOC arm.

Based on the subject diary data, the mean (±SD) hours in daily PS usage at baseline was 11.2±0.79 hours in the teduglutide treatment arm. The mean change in daily PS usage at EOT from baseline was -3.1±3.31 hours, corresponding to a mean percentage change of -28.9±30.61%. The mean hours in daily PS usage at baseline was 13.0±1.47 hours in the SOC arm. The mean change in daily PS usage at EOT from baseline was -0.3±0.63 hours, corresponding to a mean percentage change of -1.9±4.59%.

Assessor´s comments

Based on subject diary data, 2 (40.0%) subject enrolled in the teduglutide treatment arm and no subject in the SOC arm experienced at least 20% increase in EN caloric intake at EOT from baseline (3 subjects in each treatment arm had missing data).

Based on subject diary data: in the teduglutide treatment arm. The mean change in EN caloric intake at EOT from baseline was 9.1±10.66 kcal/kg/day, corresponding to a mean percentage change of 207.1±153.16%. In the SOC arm, the mean change in EN caloric intake at EOT from baseline was -9.4±21.40 kcal/kg/day, corresponding to a mean percentage change of -44.3±78.85%.

Based on prescribed data, no subjects enrolled in the teduglutide treatment arm and 2 (40.0%) subject in the SOC arm experienced at least 20% increase in EN caloric intake at EOT from baseline (4 and 1 subjects had missing data in the teduglutide and SOC arms, respectively).

Based on prescribed data: in the teduglutide treatment arm, the mean change in EN caloric intake at EOT from baseline was -1.2±2.31 kcal/kg/day, corresponding to a mean percentage change of -16.4 (-)%. In the SOC arm, the mean change in EN caloric intake at EOT from baseline was 3.1±16.29 kcal/kg/day, corresponding to a mean percentage change of 24.2±78.12%.

In the teduglutide treatment arm, the mean change in number of days per week in PS usage at EOT from baseline was -1.9±2.01 days/week, corresponding to a mean percentage change of -28.5±30.05%. In the SOC arm, there was no change in mean daily PS observed at EOT from baseline in the SOC arm.

Based on the subject diary data, the mean change in daily PS usage at EOT from baseline was -3.1±3.31 hours, corresponding to a mean percentage change of -28.9±30.61% in the TED arm. In the SOC arm, the mean change in daily PS usage at EOT from baseline was -0.3±0.63 hours, corresponding to a mean percentage change of -1.9±4.59%.

The MAH is asked to discuss the clinical relevance of the presented results for change "in daily PS usage" **(OC)**.

7.3. Discussion

SHP633-301 was a randomized, open-label study consisting of a 2- to 4-week screening period, a 24 week treatment period, and 4-week follow-up period.

The main underlying causes of SBS were gastroschisis and necrotizing enterocolitis. Efficacy/PD analyses of PS and enteral nutrition (EN) data were based on weight-normalized PS/EN volume and caloric intake.

The primary efficacy endpoint is the reduction in weight-normalized PS volume of at least 20% at Week 24/EOT from baseline. Based on subject diary data, 3 (60.0%) subjects enrolled in the teduglutide treatment arm and 1 (20.0%) subject in the SOC arm experienced at least 20% reduction in PS volume at EOT from baseline (2 subjects in the SOC arm had missing data). Based on prescribed data, 3 (60.0%) subjects enrolled in each treatment arm experienced at least 20% reduction in PS volume at EOT from baseline.

Based on subject diary data, 3 (60.0%) subjects enrolled in the teduglutide treatment arm and 1 (20.0%) subject in the SOC arm experienced at least 20% reduction in PS caloric intake at EOT from baseline (2 subjects in the SOC arm had missing data). Based on prescribed data, 3 (60.0%) subjects enrolled in each treatment arm experienced at least 20% reduction in PS caloric intake at EOT from baseline.

In the TED arm, the mean change in PS caloric intake at EOT from baseline was -16.1±17.55 kcal/kg/day, corresponding to a mean percentage change of -27.0±29.47%. In the SOC arm, the mean change in PS caloric intake at EOT from baseline was -6.1±10.39 kcal/kg/day, corresponding to a mean percentage change of -13.7±21.87%.

The MAH is asked to discuss the clinical relevance of the presented results for "Reduction in PS Caloric Intake" **(OC)**.

No subject achieved enteral autonomy

Based on subject diary data, 2 (40.0%) subjects enrolled in the teduglutide treatment arm and no subject in the SOC arm experienced at least 20% increase in EN volume at EOT from baseline (3 subjects in each treatment arm had missing data).

In the TED arm, the mean change in EN volume at EOT from baseline was 16.1±18.68 mL/kg/day, corresponding to a mean percentage change of 273.2±246.78%. In the SOC arm the mean change in EN volume at EOT from baseline was -15.3±31.50 mL/kg/day, corresponding to a mean percentage change of -44.3±78.85%.

Based on prescribed data, the mean (±SD) EN volume at baseline was 7.8±15.63 mL/kg/day for subjects in the teduglutide treatment arm. The mean change in EN volume at EOT from baseline was -1.3±2.56 mL/kg/day, corresponding to a mean percentage change of -16.4 (-)%. The mean EN volume at baseline was 31.9±19.89 mL/kg/day for subjects in the SOC arm. The mean change in EN volume at EOT from baseline was 2.3±22.23 mL/kg/day, corresponding to a mean percentage change of 14.8±69.83%.

The MAH is asked to discuss the clinical relevance of the presented results for "Reduction in EN" (**OC**).

Based on subject diary data, 2 (40.0%) subject enrolled in the teduglutide treatment arm and no subject in the SOC arm experienced at least 20% increase in EN caloric intake at EOT from baseline (3 subjects in each treatment arm had missing data).

Based on subject diary data: in the teduglutide treatment arm. The mean change in EN caloric intake at EOT from baseline was 9.1±10.66 kcal/kg/day, corresponding to a mean percentage change of 207.1±153.16%. In the SOC arm, the mean change in EN caloric intake at EOT from baseline was -9.4±21.40 kcal/kg/day, corresponding to a mean percentage change of -44.3±78.85%.

Based on prescribed data, no subjects enrolled in the teduglutide treatment arm and 2 (40.0%) subject in the SOC arm experienced at least 20% increase in EN caloric intake at EOT from baseline (4 and 1 subjects had missing data in the teduglutide and SOC arms, respectively).

Based on prescribed data: in the teduglutide treatment arm, the mean change in EN caloric intake at EOT from baseline was -1.2±2.31 kcal/kg/day, corresponding to a mean percentage change of -16.4 (-)%. In the SOC arm, the mean change in EN caloric intake at EOT from baseline was 3.1±16.29 kcal/kg/day, corresponding to a mean percentage change of 24.2±78.12%.

In the teduglutide treatment arm, the mean change in number of days per week in PS usage at EOT from baseline was -1.9±2.01 days/week, corresponding to a mean percentage change of -28.5±30.05%. In the SOC arm, there was no change in mean daily PS observed at EOT from baseline in the SOC arm.

Based on the subject diary data, the mean change in daily PS usage at EOT from baseline was -3.1±3.31 hours, corresponding to a mean percentage change of -28.9±30.61% in the TED arm. In the SOC arm, the mean change in daily PS usage at EOT from baseline was -0.3±0.63 hours, corresponding to a mean percentage change of -1.9±4.59%.

The MAH is asked to discuss the clinical relevance of the presented results for change "in daily PS usage" **(OC)**.

7.4. Safety

The MAH proposes to update the Summary of Clinical Safety with the results of pediatric investigation plan (PIP) SHP633-301 (PIP Study 8), a study to evaluate the safety, efficacy/PD, and pharmacokinetics (PK) of teduglutide in infants 4 to 12 months of age with SBS who are dependent on parenteral support (PS).

Methods – analysis of data submitted

Description of all Clinical Studies and Narratives of Safety Studies

SHP633-301 was a randomized, multicenter, open-label, consisting of 2- to 4-week screening period, a 24-week treatment period, and a 4-week follow-up period. At the baseline visit (Week 0), subjects were randomized (1:1 ratio) to the teduglutide or standard of care (SOC) treatment arm. Randomization was stratified according to the presence of a small bowel ostomy (eg, end jejunostomy or ileostomy). Subjects had to be receiving at least 50% of fluid or calories parenterally and have stable PS requirements for at least 1 month prior to screening and weigh at least 5 kg with a weight-for-length Z-score greater than -2 at screening and baseline.

During the 24-week treatment period, subjects in the SOC arm received standard medical therapy for SBS; while those in the teduglutide arm received 0.05 mg/kg subcutaneous once daily in addition to

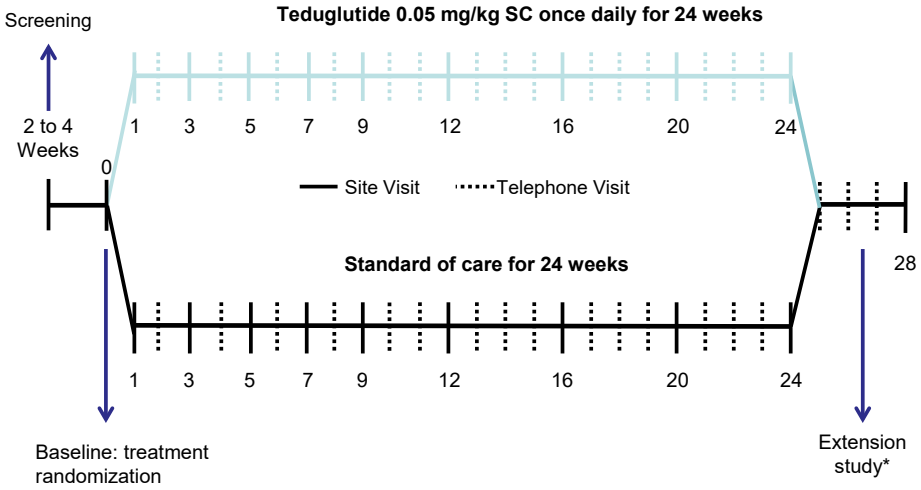
standard medical therapy. Subjects in both arms followed the same visit schedule and assessments. Subjects were monitored weekly with phone or clinic visits. Clinic visits occurred at Weeks 1, 3, 5, 7, 9, 12, 16, 20, 24, and 28. At all site visits and telephone contacts, safety was monitored and nutritional support was reviewed and adjusted as needed.

At the end of the treatment period (Week 24/EOT), all subjects entered a 4-week follow-up period until the end of study (Week 28/EOS) during which time subjects received standard medical therapy, but no investigational product was administered. At EOS, subjects may have enrolled in the SHP633-304 extension study, in which subjects would continue to receive teduglutide. The follow-up period for subjects in the teduglutide treatment arm may have been truncated, and the subjects may have proceeded immediately to the EOS visit if at least 1 of the "escape" criteria was met. Refer to SHP633-301 clinical study report (CSR), Section 9.1 for additional details.

Changes to the study procedures may have been implemented for study participants or study sites that were impacted by the coronavirus disease (COVID-19) pandemic that required physical distancing and may have resulted in subjects missing their visits. Procedural changes implemented in Study SHP633-301 due to the COVID-19 pandemic are presented in SHP633-301 CSR, Section 9.8.1.3. Protocol deviations related to the COVID-19 pandemic impact are provided in SHP633-301 CSR, Section 10.2.2.

A schematic representation of the study design is presented.

Figure 10 SHP633-301 Study Schematic



*At end of study (EOS), all subjects regardless of treatment arm may have enrolled in an extension study if that study was open to enrollment at the time of the SHP633-301 EOS that captured long-term safety data and provided the opportunity for additional teduglutide treatment. The follow-up period for subjects in the teduglutide treatment arm may have been interrupted and the subjects may have proceeded immediately to the EOS if at least 1 "escape" criteria was met.

Source: SHP633-301 CSR, Figure 1

Assessor´s comments

Study SHP633-301was described in 6.1. Please refer to CHMP comments. At the end of the treatment period (Week 24/EOT), all subjects entered a 4-week follow-up period until the end of study (Week 28/EOS) during which time subjects received standard medical therapy, but no investigational product was administered. At EOS, subjects may have enrolled in the SHP633-304 extension study, in which subjects would continue to receive teduglutide. The follow-up period for subjects in the teduglutide treatment arm may have been truncated, and the subjects may have proceeded immediately to the EOS visit if at least 1 of the "escape" criteria was met.

Results

Overall Extent of Exposure

The safety set (SAF) consisted of all subjects who received at least 1 dose of teduglutide and had at least 1 post-baseline safety assessment (teduglutide arm) and of all subjects who had at least 1 post-baseline safety assessment (SOC arm). A total of 10 subjects were randomized in the study, 5 subjects in teduglutide arm and 5 in the SOC arm. The mean duration of exposure to teduglutide in the SAF was 149.4±42.15 days (range 74 days to 169 days). Four subjects had ≥24 weeks (168 days) of treatment and 1 subject had 4 weeks to <12 weeks (28 days to <84 days) of treatment.

Demographic and Other Characteristics of Study Population

Demographic and other characteristics of the study population are presented in SHP633-301 CSR.

All but 1 subject in the teduglutide arm and 2 subjects in the SOC arm were male. All subjects were white except 1 subject in each treatment arm who were Asian; no subjects were Hispanic or Latino. The corrected gestational age of subjects was similar between the 2 treatment arms. Overall, the mean corrected gestational age was 8.4±2.71 months, with the majority (7/10 [70.0%]) of subjects being in the 6 months to 12 months corrected gestational age category. Mean baseline weight, length, and weight/length ratio Z-scores were similar between the 2 treatment arms.

Short bowel history is presented in SHP633-301 CSR. The main underlying causes of SBS were gastroschisis (3 and 2 subjects in the teduglutide and SOC treatment arms, respectively), necrotizing enterocolitis (1 and 2 subjects in the teduglutide and SOC treatment arms, respectively), intestinal atresia (1 subject in the teduglutide treatment arm), and other (1 subject in the SOC arm). One subject in the SOC arm had a stoma. All subjects had some colon remaining, and the mean remaining small intestine was 29.2±25.10 cm overall; the remnant colon was in continuity in 9 (90.0%) subjects, and 1 subject in the teduglutide arm had an ileocecal valve present.

Assessor´s comments

A total of 10 subjects were randomized in the study, 5 subjects in teduglutide arm and 5 in the SOC arm. The mean duration of exposure to teduglutide in the SAF was 149.4±42.15 days (range 74 days to 169 days). Four subjects had ≥24 weeks (168 days) of treatment and 1 subject had 4 weeks to <12 weeks (28 days to <84 days) of treatment.

All but 1 subject in the teduglutide arm and 2 subjects in the SOC arm were male. All subjects were white except 1 subject in each treatment arm who were Asian; no subjects were Hispanic or Latino. The corrected gestational age of subjects was similar between the 2 treatment arms.

The main underlying causes of SBS were gastroschisis and necrotizing enterocolitis.

Adverse Events

Analysis of Adverse Events

Treatment-Emergent Adverse Events

Adverse events are summarized for the SAF set in SHP633-301 CSR, Section 12.2. Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 21.0.

Brief Summary of Adverse Events

Overall, there were a total of 87 treatment-emergent adverse events (TEAEs) reported in 10 (100%) subjects. The TEAEs reported by subjects during the study were mostly mild in severity and deemed not related to study drug by the investigators. There were 9 TEAEs deemed related to study drug by the investigators in 2 (40.0%) subjects in the teduglutide arm. There were 5 treatment-emergent serious adverse events (TESAEs) in 4 (80.0%) subjects in the teduglutide arm and 6 TESAEs in 3 (60.0%) subjects in the SOC arm; no TESAEs were deemed related to study drug by the investigators.

There were 5 TEAEs reported in 1 subject enrolled in the teduglutide arm which led to treatment discontinuation. There were no AESIs and TEAEs leading to death.

Table 8 Overall Summary of Treatment-Emergent Adverse Events (Safety Set)

	Teduglutide (N=5)		Standard of Care (N=5)		Total (N=10)	
Category	n (%)	m	n (%)	m	n (%)	m
Any TEAE	5 (100.0)	58	5 (100.0)	29	10 (100.0)	87
TEAEs Highest Severity[a]						
Mild	2 (40.0)		2 (40.0)		4 (40.0)	
Moderate	2 (40.0)		1 (20.0)		3 (30.0)	
Severe	1 (20.0)		2 (40.0)		3 (30.0)	
TEAE Relationship[b]						
Not Related	3 (60.0)	49	5 (100.0)	29	8 (80.0)	78
Related	2 (40.0)	9	0	0	2 (20.0)	9
Any TESAE	4 (80.0)	5	3 (60.0)	6	7 (70.0)	11
TESAE Relationship[b]						
Not Related	4 (80.0)	5	3 (60.0)	6	7 (70.0)	11
	0	0	0	0	0	0
TEAE Leading to Treatment Discontinuation	1 (20.0)	5	0	0	1 (10.0)	5
TEAE Leading to Death	0	0	0	0	0	0

TEAE=treatment-emergent adverse event; TESAE=treatment-emergent serious adverse event; n=number of subjects experiencing the event; m=number of events

Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.

Percentages are based on the number of subjects in the population in each treatment group.

Subjects were counted by the treatment most recently taken when the event occurred.

Subjects are counted no more than once for incidence, but can be counted multiple times for the number of events.

[a] Subjects are counted once per row, but if there are AEs with more than one degree of severity, they are counted for each row.

[b] Subjects are counted once per row, but if there are AEs with more than one causality, they are counted for each row.0

Source: SHP633-301 CSR, Table 14.3.1.1

Table 9 Summary of Treatment-emergent Adverse Events by System Organ Class and Preferred Term (Safety Set)

	Teduglutide (N=5)		Standard of Care (N=5)		Total (N=10)	
Category	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**
Any TEAE	5 (100.0)	58	5 (100.0)	29	10 (100.0)	87
Blood and lymphatic system disorders	**2 (40.0)**	**2**	**0**	**0**	**2 (20.0)**	**2**
Anaemia	1 (20.0)	1	0	0	1 (10.0)	1
Iron deficiency anaemia	1 (20.0)	1	0	0	1 (10.0)	1
Gastrointestinal disorders	**3 (60.0)**	**24**	**3 (60.0)**	**6**	**6 (60.0)**	**30**
Vomiting	3 (60.0)	8	1 (20.0)	2	4 (40.0)	10
Diarrhoea	2 (40.0)	3	0	0	2 (20.0)	3
Frequent bowel movements	2 (40.0)	2	0	0	2 (20.0)	2
Abdominal discomfort	1 (20.0)	2	0	0	1 (10.0)	2
Abdominal distension	1 (20.0)	3	0	0	1 (10.0)	3
Abnormal faeces	1 (20.0)	1	0	0	1 (10.0)	1
discoloured	1 (20.0)	1	0	0	1 (10.0)	1
Flatulence	1 (20.0)	1	0	0	1 (10.0)	1
Gastrointestinal sounds abnormal	1 (20.0)	1	0	0	1 (10.0)	1
Mucous Stools	1 (20.0)	1	0	0	1 (10.0)	1
Retching	1 (20.0)	1	0	0	1 (10.0)	1
Constipation	0	0	1 (20.0)	1	1 (10.0)	1
Teething	0	0	2 (40.0)	3	2 (20.0)	3
General disorders and administration site conditions	**2 (40.0)**	**4**	**1 (20.0)**	**1**	**3 (30.0)**	**5**
Pyrexia	2 (40.0)	3	1 (20.0)	1	3 (30.0)	4
Secretion discharge	1 (20.0)	1	0	0	1 (10.0)	1
Immune system disorder	**1 (20.0)**	**1**	**0**	**0**	**1 (10.0)**	**1**
Immunization reaction	1 (20.0)	1	0	0	1 (10.0)	1
Infections and infestations	**4 (80.0)**	**8**	**3 (60.0)**	**6**	**7 (70.0)**	**14**
Nasopharyngitis	2 (40.0)	2	0	0	2 (20.0)	2
Gastroenteritis norovirus	1 (20.0)	1	0	0	1 (10.0)	1
Medical device site infection	1 (20.0)	1	0	0	1 (10.0)	1
Respiratory tract infection viral	1 (20.0)	2	0	0	1 (10.0)	2
Upper respiratory tract infection	1 (20.0)	1	2 (40.0)	2	3 (30.0)	3
Viral infection	1 (20.0)	1	1 (20.0)	1	2 (20.0)	2
Device related infection	0	0	2 (40.0)	2	2 (20.0)	2
Hand-foot-and-mouth disease	0	0	1 (20.0)	1	1 (10.0)	1
Injury, poisoning and procedural complications	**1 (20.0)**	**1**	**2 (40.0)**	**2**	**3 (30.0)**	**3**
Lip injury	1 (20.0)	1	0	0	1 (10.0)	1
Contusion	0	0	1 (20.0)	1	1 (10.0)	1
Skin abrasion	0	0	1 (20.0)	1	1 (10.0)	1
Investigations	**2 (40.0)**	**4**	**3 (60.0)**	**5**	**5 (50.0)**	**9**
Alanine aminotransferase increased	1 (20.0)	2	0	0	1 (10.0)	2
Faecal volume increased	1 (20.0)	1	0	0	1 (10.0)	1
Serum ferritin decreased	1 (20.0)	1	0	0	1 (10.0)	1
Blood iron decreased	0	0	1 (20.0)	1	1 (10.0)	1
Respiratory rate increased	0	0	1 (20.0)	1	1 (10.0)	1
Transaminases increased	0	0	1 (20.0)	3	1 (10.0)	3

Table 9 Summary of Treatment-emergent Adverse Events by System Organ Class and Preferred Term (Safety Set)

	Teduglutide (N=5)		Standard of Care (N=5)		Total (N=10)	
Category	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**
Metabolism and nutrition disorders	**2 (40.0)**	**3**	**2 (40.0)**	**2**	**4 (40.0)**	**5**
Decreased appetite	1 (20.0)	2	0	0	1 (10.0)	2
Hypophagia	1 (20.0)	1	0	0	1 (10.0)	1
Hypoglycaemia	0	0	1 (20.0)	1	1 (10.0)	1
Metabolic acidosis	0	0	1 (20.0)	1	1 (10.0)	1
Nervous system disorders	0	0	**1 (20.0)**	1	**1 (10.0)**	**1**
Ataxia	0	0	1 (20.0)	1	1 (10.0)	1
Product issues	**3 (60.0)**	**4**	**2 (40.0)**	**2**	**5 (50.0)**	**6**
Device breakage	2 (40.0)	2	1 (20.0)	1	3 (30.0)	3
Device leakage	1 (20.0)	1	0	0	1 (10.0)	1
Device occlusion	1 (20.0)	1	1 (20.0)	1	2 (20.0)	2
Psychiatric disorders	**2 (40.0)**	**2**	**0**	**0**	**2 (20.0)**	**2**
Irritability	1 (20.0)	1	0	0	1 (10.0)	1
Sleep disorder	1 (20.0)	1	0	0	1 (10.0)	1
Respiratory, thoracic and mediastinal disorders	**2 (40.0)**	**2**	**2 (40.0)**	**2**	**4 (40.0)**	**4**
Cough	1 (20.0)	1	1 (20.0)	1	2 (20.0)	2
Rhinorrhoea	1 (20.0)	1	1 (20.0)	1	2 (20.0)	2
Skin and subcutaneous tissue disorders	**2 (40.0)**	**3**	**1 (20.0)**	**1**	**3 (30.0)**	**4**
Dermatitis diaper	1 (20.0)	2	0	0	1 (10.0)	2
Eczema	1 (20.0)	1	0	0	1 (10.0)	1
Rash papular	0	0	1 (20.0)	1	1 (10.0)	1
Vascular disorder	0	0	**1 (20.0)**	1	**1 (10.0)**	**1**
Hypertension	0	0	1 (20.0)	1	1 (10.0)	1

TEAE=treatment-emergent adverse event; n=number of subjects experiencing the event; m=number of events

Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.

Percentages are based on the number of subjects in the population in each treatment group.

Subjects were counted by the treatment most recently taken when the event occurred.

Subjects are counted no more than once for incidence, but can be counted multiple times for the number of events.

Note: SOCs and PTs were coded using Medical Dictionary for Regulatory Activities (MedDRA) 21.0.

Source: SHP633-301 CSR Table 14.3.1.2

Adverse Events by Relationship

Overall, 9 TEAEs reported in 2 (20.0%) subjects were deemed related to study drug by the investigators; both subjects were enrolled in the teduglutide arm. Details of these TEAEs are provided in SHP633-301 CSR.

One subject experienced 8 of the 9 TEAEs assessed as related to study drug (abdominal distension, gastrointestinal sounds abnormal, vomiting [5 events], and faecal volume increased) as well as multiple non-related TEAEs all linked to the gastrointestinal system. These related TEAEs resolved and were deemed intermittent, mild to moderate in severity by the investigator; the events of vomiting (2 events), gastrointestinal sounds abnormal, and faecal volume increased led the subject's parents decision (it was not the investigator's decision in the interest of safety) to interrupt dosing with study drug which never resumed.

One subject experienced a TEAE of ALT increased (152 U/L; normal range 6-34 U/L) at Week 20 which was deemed related to study drug by the investigator The subject showed elevated AST and ALT values at baseline (224 U/L and 243 U/L, respectively) and intermittently during the study including the last study visit at Week 24 (94 U/L and 88 U/L, respectively). Two events of ALT increased were reported for this subject; only the second event was deemed related to study drug. That TEAE was deemed moderate in severity, resolved at Week 24, and no action with study drug was taken. The subject's bilirubin values remained normal throughout the study (Section 0).

Adverse Events by Severity

Details of TEAEs by severity are provided in SHP633-301 CSR, Section 12.2.3.2.

The majority of TEAEs were mild in severity. There were 3 severe TEAEs were reported during the study, 1 event in a subject in the teduglutide treatment arm (device leakage [related to central venous catheters used to administer PS, not to the teduglutide injection device]) and 1 event in 2 subjects in the SOC arm (device related infection). All severe TEAEs were assessed as serious due to the subjects' hospitalization and not related to study drug by the investigator (Section 0).

Deaths

There were no deaths during the study.

Other Serious Adverse Events

Overall, 11 TESAEs were reported in 7 subjects, 4 (80.0%) subjects in the teduglutide treatment arm and 3 (60.0%) subjects in the SOC arm. All TESAEs were assessed as non-related to teduglutide treatment by the investigators.

For the teduglutide arm, the system organ classes with subjects reporting TESAEs were Product issues (2 [40.0%] subjects), and General disorders and administration site conditions and Immune system disorder (1 [20.0%] subject each. A total of 5 TESAEs were reported in the teduglutide arm: 1 subject experienced 2 events of pyrexia, 1 subject experienced the event of immunisation reaction, 1 subject experienced the event of device breakage and another subject the event of device leakage (both device events related to central venous catheters used to administer PS, not to the teduglutide injection device). The events of pyrexia preceded by non-serious TEAEs of blocked Hickman line, broken Hickman line, and intermittent vomiting, and were reported as serious due to the subject's hospitalization. The event of immunisation reaction was described as fever secondary to immunisations on result of negative blood cultures. The subject presented with pyrexia and vomiting and required hospitalization for sepsis the same day. That same day, the subject was administered intravenous antibacterial treatment, and blood was collected from the central line for blood culture, which showed no growth at 48 hours.

For the SOC arm, the system organ classes with subjects reporting TESAEs were Infections and infestations (2 [40.0%] subjects), and Investigations, Metabolism and nutrition disorders, Nervous system disorders and Product issues (1 [20.0%] subject each). A total of 6 TESAEs were reported in the SOC arm: 2 subjects experienced the events of device related infection, 1 subject experienced the event of transaminases increased, and 1 subject experienced all the events of metabolic acidosis, ataxia, and device occlusion.

All TESAEs were deemed non-related to teduglutide treatment by the investigators, all required hospitalization of the subjects. The TESAEs of device leakage and device related infection were reported as severe.

The mean (±SD) cumulative number of hospitalization days during the treatment period was 4.7±2.89 and 4.0±1.41 in the teduglutide and SOC arms, respectively.

Table 10 Incidence of Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (Safety Set)

	Teduglutide (N=5)		Standard of Care (N=5)		Total (N=10)	
Category	**n (%)**	**m**	**n (%)**	**m**	**n (%)**	**m**
Any TESAE	**4 (80.0)**	**5**	**3 (60.0)**	**6**	**7 (70.0)**	**11**
General disorders and administration site conditions	**1 (20.0)**	**2**	**0**	**0**	**1 (10.0)**	**2**
Pyrexia	1 (20.0)	2	0	0	1 (10.0)	2
Immune system disorder	**1 (20.0)**	**1**	**0**	**0**	**1 (10.0)**	**1**
Immunisation reaction	1 (20.0)	1	0	0	1 (10.0)	1
Infections and infestations	**0**	**0**	**2 (40.0)**	**2**	**2 (20.0)**	**2**
Device related infection	0	0	2 (40.0)	2	2 (20.0)	2
Investigations	**0**	**0**	**1 (20.0)**	**1**	**1 (10.0)**	**1**
Transaminases increased	0	0	1 (20.0)	1	1 (10.0)	1
Metabolism and nutrition disorders	**0**	**0**	**1 (20.0)**	**1**	**1 (10.0)**	**1**
Metabolic acidosis	0	0	1 (20.0)	**1**	1 (10.0)	1
Nervous system disorders	**0**	**0**	**1 (20.0)**	**1**	**1 (10.0)**	**1**
Ataxia	0	0	1 (20.0)	1	1 (10.0)	1
Product issues	**2 (40.0)**	**2**	**1 (20.0)**	**1**	**3 (30.0)**	**3**
Device breakage	1 (20.0)	1	0	0	1 (10.0)	1
Device leakage	1 (20.0)	1	0	0	1 (10.0)	1
Device occlusion	0	0	1 (20.0)	1	1 (10.0)	1

TESAE=treatment-emergent serious adverse event; n=number of subjects experiencing the event; m=number of events

Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm. Adverse events with an unknown date of onset and a stop date after the start of the date of first dose or unknown are included as TEAEs.

Percentages are based on the number of subjects in the population in each treatment group.

Subjects were counted by the treatment most recently taken when the event occurred.

Subjects are counted no more than once for incidence, but can be counted multiple times for the number of events.

Note: SOCs and PTs were coded using MedDRA 21.0.

Source: SHP633-301 CSR Table 14.3.1.4

Other Significant Adverse Events

Discontinuations Resulting from Adverse Events

There were 5 TEAEs reported in 1 subject enrolled in the teduglutide arm that led to study drug discontinuation (vomiting [2 events], gastrointestinal sounds abnormal, irritability, and faecal volume increased). Teduglutide treatment was interrupted at Day 75 (after Week 10 visit) following the parents', not the investigator's, decision to interrupt administration as they thought several AEs were caused by the study drug; it was not the investigator's decision in the interest of safety but he was informed. The TEAEs of vomiting, gastrointestinal sounds abnormal, and faecal volume increased were deemed related to study drug and mild in severity by the investigator (except for 1 event of vomiting deemed moderate in severity). The event of irritability was deemed non-related to study drug and mild

in severity by the investigator. All events recovered and resolved. Teduglutide treatment was never resumed. SHP633-301 CSR, Section provides a complete narrative for this subject.

Adverse Events of Special Interest

There were no AESIs (events of polyps of the colon, benign neoplasia of the gastrointestinal tract, or tumor-promoting ability) reported during the study.

Analysis of Adverse Events by Organ System or Syndrome

Teduglutide was generally well tolerated in infants aged 4 months to 12 months corrected gestational age with SBS, and no new safety issues were identified. The safety profile was favorable and consistent with the safety profile seen in other pediatric studies, the underlying disease, and previous experience with teduglutide in adult subjects with SBS. The benefit-risk profile for teduglutide remains favorable and unchanged.

Narratives

Narratives for subjects who experienced an SAE during the study are provided in SHP633-301 CSR, Section.

Clinical Laboratory Evaluations

Laboratory Values Over Time

Overall, no clinically meaningful mean changes in hematology values or urinalysis values were observed during the study. There were no clinically meaningful changes in serum chemistry values during the study other than increased ALT (1 subject in the teduglutide treatment arm) and both increased ALT and increased transaminases (each in 1 subject in the SOC arm). Liver enzyme parameters (alkaline phosphatase, ALT, AST, direct bilirubin, bilirubin, and GGT) over time are presented graphically by visit in the SHP633-301 CSR.

Individual Clinically Significant Abnormalities in Laboratory Values

No clinically significant abnormal values for hematology were reported during the study (SHP633-301 CSR. For individually clinically significant chemistry laboratory abnormalities, a markedly increased ALT value >8 x ULN was noted in 1 subject in the SOC arm. The subject had several elevated (higher than the normal range [6-34 U/L]) ALT values, with a markedly increased ALT value (101 U/L, >8 x upper limit of normal) at Week 16. The subject also had elevated AST (normal range 10-56 U/L) and GGT (normal range 0-24 U/L) values at both Week 12 and Week 16. The subject's bilirubin values remained mostly low or normal throughout the study; C-reactive protein values were elevated on 2 unscheduled visits at Week 12 and Week 21). No adverse events were reported for any of these elevated laboratory values.

A markedly high international normalized ratio (INR) >1.5 value was noted in 1 subject in each treatment arm. The subject in the teduglutide arm had a markedly high INR value (2.4) at the baseline visit; the INR decreased to 1.1 at EOS (Week 28); this subject had ongoing prophylactic heparin treatment when receiving intravenous nutrition. The subject in the SOC arm, who presented a stable INR between 1.0 and 1.2 during the study, experienced a single elevated INR at 2.0 at the Week 16 visit, which was accompanied by an elevated prothrombin time (20.5 seconds [normal range of 9.7-12.3 seconds]). No adverse events were reported for these elevated values.

Vital Signs, Physical Findings, and Other Observations Related to Safety

Vital Signs

Overall, no clinically meaningful changes were observed in vital signs (pulse rate, systolic blood pressure, diastolic blood pressure, or temperature other than increased ALT and increased transaminases values each in 1 subject in the SOC arm and increased ALT in 1 subject in the teduglutide treatment arm.

Body Weight, Length, Weight/Length Ratio, and Head Circumference Z-score

Changes in body weight, length, and weight/length ratio Z-scores were within the expected range for the subjects' age group and comparable between the teduglutide treatment arm and the SOC arm. Head circumference Z-scores observed in the SOC arm seemed to drop further over time compared with the teduglutide treatment arm.

Fecal and Urine Outputs

No clinically meaningful changes in mean urine output or stool output were observed in either the teduglutide or SOC arm. In the teduglutide arm, the mean average number of stools per day at Week 24 was 2.3±1.44 stools/day from a baseline of 5.2±2.23 stools/day, corresponding to a change of -3.3±3.55 stools/day. In the SOC arm, the mean average number of stools per day at Week 24 was 5.2±1.04 stools/day from a baseline of 2.5±1.66 stools/day, corresponding to a change of 1.7±1.76 stools/day.

Antibodies to Teduglutide

None of the 3 subjects in the teduglutide arm who were tested at the Week 12 and Week 28 (EOS) visits had antibodies to teduglutide detected (SHP633-301 CSR, Section 12.5.3.4).

Assessor´s comments

Overall, there were a total of 87 treatment-emergent adverse events (TEAEs) reported in 10 (100%) subjects. The TEAEs reported by subjects during the study were mostly mild in severity and deemed not related to study drug by the investigators. There were 9 TEAEs deemed related to study drug by the investigators in 2 (40.0%) subjects in the teduglutide arm. There were 5 treatment-emergent serious adverse events (TESAEs) in 4 (80.0%) subjects in the teduglutide arm and 6 TESAEs in 3 (60.0%) subjects in the SOC arm; no TESAEs were deemed related to study drug by the investigators.

There were 5 TEAEs reported in 1 subject enrolled in the teduglutide arm which led to treatment discontinuation. There were no AESIs and TEAEs leading to death.

Overall, 9 TEAEs reported in 2 (20.0%) subjects were deemed related to study drug by the investigators; both subjects were enrolled in the teduglutide arm. Details of these TEAEs are provided in SHP633-301 CSR.

One subject experienced 8 of the 9 TEAEs assessed as related to study drug (abdominal distension, gastrointestinal sounds abnormal, vomiting [5 events], and faecal volume increased) as well as

multiple non-related TEAEs all linked to the gastrointestinal system. These related TEAEs resolved and were deemed intermittent, mild to moderate in severity by the investigator; the events led the subject's parents decision to interrupt dosing with study drug which never resumed.

One subject experienced a TEAE of ALT increased (152 U/L; normal range 6-34 U/L) at Week 20 which was deemed related to study drug by the investigator. The subject showed elevated AST and ALT values at baseline (224 U/L and 243 U/L, respectively) and intermittently during the study including the last study visit at Week 24 (94 U/L and 88 U/L, respectively). Two events of ALT increased were reported for this subject; only the second event was deemed related to study drug. That TEAE was deemed moderate in severity, resolved at Week 24, and no action with study drug was taken. The subject's bilirubin values remained normal throughout the study.

The majority of TEAEs were mild in severity. There were 3 severe TEAEs were reported during the study, 1 event in a subject in the teduglutide treatment arm (device leakage [related to central venous catheters used to administer PS, not to the teduglutide injection device]) and 1 event in 2 subjects in the SOC arm (device related infection).

Overall, 11 TESAEs were reported in 7 subjects, 4 (80.0%) subjects in the teduglutide treatment arm and 3 (60.0%) subjects in the SOC arm. All TESAEs were assessed as non-related to teduglutide treatment by the investigators.

There were no AESIs (events of polyps of the colon, benign neoplasia of the gastrointestinal tract, or tumor-promoting ability) reported during the study.

Changes in body weight, length, and weight/length ratio Z-scores were within the expected range for the subjects' age group and comparable between the teduglutide treatment arm and the SOC arm. Head circumference Z-scores observed in the SOC arm seemed to drop further over time compared with the teduglutide treatment arm. The MAH should discuss the drop in head circumference Z-scores observed in the SOC arm as compared to the TED arm **(OC)**.

Safety in Special Groups and Situations

Not applicable.

Post-marketing Data

Not applicable.

Discussion

At the end of the treatment period (Study SHP633-301, week 24/EOT), all subjects entered a 4-week follow-up period until the end of study (Week 28/EOS) during which time subjects received standard medical therapy, but no investigational product was administered. At EOS, subjects may have enrolled in the SHP633-304 extension study, in which subjects would continue to receive teduglutide. The follow-up period for subjects in the teduglutide treatment arm may have been truncated, and the subjects may have proceeded immediately to the EOS visit if at least 1 of the "escape" criteria was met.

A total of 10 subjects were randomized in the study, 5 subjects in teduglutide arm and 5 in the SOC arm. The mean duration of exposure to teduglutide in the SAF was 149.4±42.15 days (range 74 days to 169 days). Four subjects had ≥24 weeks (168 days) of treatment and 1 subject had 4 weeks to <12 weeks (28 days to <84 days) of treatment.

All but 1 subject in the teduglutide arm and 2 subjects in the SOC arm were male. All subjects were white except 1 subject in each treatment arm who were Asian; no subjects were Hispanic or Latino. The corrected gestational age of subjects was similar between the 2 treatment arms.

The main underlying causes of SBS were gastroschisis and necrotizing enterocolitis.

Overall, there were a total of 87 treatment-emergent adverse events (TEAEs) reported in 10 (100%) subjects. The TEAEs reported by subjects during the study were mostly mild in severity and deemed not related to study drug by the investigators. There were 9 TEAEs deemed related to study drug by the investigators in 2 (40.0%) subjects in the teduglutide arm. There were 5 treatment-emergent serious adverse events (TESAEs) in 4 (80.0%) subjects in the teduglutide arm and 6 TESAEs in 3 (60.0%) subjects in the SOC arm; no TESAEs were deemed related to study drug by the investigators.

There were 5 TEAEs reported in 1 subject enrolled in the teduglutide arm which led to treatment discontinuation. There were no AESIs and TEAEs leading to death.

Overall, 9 TEAEs reported in 2 (20.0%) subjects were deemed related to study drug by the investigators; both subjects were enrolled in the teduglutide arm. Details of these TEAEs are provided in SHP633-301 CSR.

One subject experienced 8 of the 9 TEAEs assessed as related to study drug (abdominal distension, gastrointestinal sounds abnormal, vomiting [5 events], and faecal volume increased) as well as multiple non-related TEAEs all linked to the gastrointestinal system. These related TEAEs resolved and were deemed intermittent, mild to moderate in severity by the investigator; the events led the subject’s parents decision to interrupt dosing with study drug which never resumed.

One subject experienced a TEAE of ALT increased (152 U/L; normal range 6-34 U/L) at Week 20 which was deemed related to study drug by the investigator. The subject showed elevated AST and ALT values at baseline (224 U/L and 243 U/L, respectively) and intermittently during the study including the last study visit at Week 24 (94 U/L and 88 U/L, respectively). Two events of ALT increased were reported for this subject; only the second event was deemed related to study drug. That TEAE was deemed moderate in severity, resolved at Week 24, and no action with study drug was taken. The subject's bilirubin values remained normal throughout the study.

The majority of TEAEs were mild in severity. There were 3 severe TEAEs were reported during the study, 1 event in a subject in the teduglutide treatment arm (device leakage [related to central venous catheters used to administer PS, not to the teduglutide injection device]) and 1 event in 2 subjects in the SOC arm (device related infection).

Overall, 11 TESAEs were reported in 7 subjects, 4 (80.0%) subjects in the teduglutide treatment arm and 3 (60.0%) subjects in the SOC arm. All TESAEs were assessed as non-related to teduglutide treatment by the investigators.

There were no AESIs (events of polyps of the colon, benign neoplasia of the gastrointestinal tract, or tumor-promoting ability) reported during the study.

Changes in body weight, length, and weight/length ratio Z-scores were within the expected range for the subjects' age group and comparable between the teduglutide treatment arm and the SOC arm. Head circumference Z-scores observed in the SOC arm seemed to drop further over time compared with the teduglutide treatment arm. The MAH should discuss the drop in head circumference Z-scores observed in the SOC arm as compared to the TED arm **(OC)**.

8. Changes to the Product Information

As a result of this variation, sections 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC are being updated. The Package Leaflet (PL) is updated accordingly.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

9. Request for supplementary information

9.1. Major objections

Clinical aspects

No major objections were raised.

9.2. Other concerns

Clinical aspects

1. The MAH is asked to present the number of plasma samples collected and used for analysis in study SHP633-301
2. The MAH is asked to discuss the clinical significance of the presented exposure-safety results in regards of nausea and abdominal pain, which should include instructions for prescribing physician e.g. dose adjustments. The MAH should also explain the discrepancy between the results of the probabilities of nausea and vomiting, since these TEAS are normally closely related
3. The MAH is asked to discuss the clinical relevance of the presented results for reduction or change in:
    a) PS Caloric Intake
    b) EN volume
    c) daily PS usage
4. Head circumference Z-scores observed in the SOC arm seemed to drop further over time compared with the teduglutide treatment arm. The MAH should discuss the drop in head circumference Z-scores observed in the SOC arm as compared to the TED arm.

10. Assessment of the responses to the request for supplementary information

10.1. Major objections

None

10.2. Other concerns

Clinical aspects

Question 1

The MAH is asked to present the number of plasma samples collected and used for analysis in study SHP633-301

MAH's response

Per protocol of study SHP633-301, subjects had blood samples taken for teduglutide PK analysis at predose, 1 hour ±10 minutes, and 4 hours ±10 minutes postdose at baseline (Visit 0, baseline visit). The predose sample was not collected from subjects who weighed less than 7 kg. Some subjects also had blood samples taken for teduglutide PK analysis at 2 hours ±10 minutes postdose at Week 7 (Visit 7) of the treatment period. By definition, the PK set consisted of all subjects who received at least 1 dose of teduglutide and had at least 1 evaluable and interpretable postdose PK concentration value. Therefore, the PK set consisted of 5 subjects with a total of 19 PK samples collected via a sparse sample collection approach.

Table 1 presents the PK sample concentration results from 5 subjects receiving teduglutide treatment. Since time-independent PK properties of teduglutide were confirmed during drug development, sparse PK sample collections are considered adequate for evaluation of PK in infant subjects. All of the aforementioned PK concentrations were presented in the CSR for Study SHP633-301, Table 19 for PK evaluation. The sparse samples were also included in the population PK analysis to characterize PK properties in pediatric subjects less than 1 year of age, confirming the Cmax similarity across age groups, and thereby supporting 0.05 mg daily dosing in pediatric subjects who are 4 months to less than 1 year of age (refer to Table 12.1, SHIR-CSC-129_PKglobal).

Table 11 PK Samples Collected in Study SHP633-301

Subject Number	PK Sample Concentration (ng/mL)	Study Visit	Nominal Sampling Time
PPD	BLQ (<1.00)	BASELINE DOSING WEEK 0	0-HOUR (PREDOSE)
	25.7	BASELINE DOSING WEEK 0	1-HOUR POSTDOSE
	3.86	BASELINE DOSING WEEK 0	4-HOUR POSTDOSE
	2.21	DOSING WEEK 12	2-HOUR POSTDOSE
	6.07	BASELINE DOSING WEEK 0	4-HOUR POSTDOSE
	BLQ (<1.00)	BASELINE DOSING WEEK 0	0-HOUR (PREDOSE)
	7.25	BASELINE DOSING WEEK 0	1-HOUR POSTDOSE
	22.5	BASELINE DOSING WEEK 0	4-HOUR POSTDOSE
	29	DOSING WEEK 12	2-HOUR POSTDOSE
	BLQ (<1.00)	BASELINE DOSING WEEK 0	0-HOUR (PREDOSE)
	BLQ (<1.00)	BASELINE DOSING WEEK 0	1-HOUR POSTDOSE
	BLQ (<1.00)	BASELINE DOSING WEEK 0	4-HOUR POSTDOSE
	19.1	DOSING WEEK 7	2-HOUR POSTDOSE
	26.8	DOSING WEEK 12	2-HOUR POSTDOSE
	BLQ (<1.00)	BASELINE DOSING WEEK 0	0-HOUR (PREDOSE)
	16.3	BASELINE DOSING WEEK 0	1-HOUR POSTDOSE
	10.7	BASELINE DOSING WEEK 0	4-HOUR POSTDOSE
	14.8	DOSING WEEK 7	2-HOUR POSTDOSE
	24.5	DOSING WEEK 12	2-HOUR POSTDOSE

Source Data: CSR for Study SHP633-301, Appendix 16.2.5, Listing 16.2.5.4.

Assessment of the MAH's response

The MAH has presented the number of plasma samples collected and used for analysis in study SHP633-301 as requested. The MAH states that the PK set consisted of 5 subjects with a total of 19 PK samples collected via a sparse sample collection approach. The sparse samples were included in the population PK analysis to characterize PK properties in pediatric subjects less than 1 year of age. The MAH states that C_{max} similarity was observed across age groups supporting 0.05 mg daily dosing in pediatric subjects who are 4 months to less than 1 year of age.

In the SmPC section 5.2 the MAH is asked to delete "which drives the efficacy" to keep data factual for the prescriber:

"Paediatric population

Following subcutaneous administration, similar C_{max} of teduglutide across age groups (4 months to 17 years) was demonstrated by population pharmacokinetics modelling. ~~which drives the efficacy responses.~~ However, lower exposure (AUC) and shorter halflife were seen in paediatric patients 4 months to 17 years of age, as compared with adults. The pharmacokinetic profile of Revestive in this paediatric population, as evaluated by clearance and volume of distribution, was different from that observed in adults after correcting for body weights. Specifically, clearance decreases with increasing age from 4 months to adults. No data are available for paediatric patients with moderate to severe renal impairment and endstage renal disease (ESRD)."

Please also refer to SmPC section 5.2.

Conclusion

Issue solved with SmPC update.

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐No need to update overall conclusion and impact on benefit-risk balance

Question 2

The MAH is asked to discuss the clinical significance of the presented exposure-safety results in regards of nausea and abdominal pain, which should include instructions for prescribing physician e.g. dose adjustments. The MAH should also explain the discrepancy between the results of the probabilities of nausea and vomiting, since these TEAS are normally closely related

MAH's response

Clinical Significance for Nausea and Abdominal Pain

The exposure-safety analysis results showed a statistically significant relationship between steady state teduglutide exposure C_{max} or AUC versus nausea or abdominal pain (refer to SHIR-CSC-129_ERglobal). The results suggested that increased teduglutide exposure was associated with an increased probability of nausea or abdominal pain. In the analyses (using C_{max} as an example), 234 subjects who received either placebo, 0.0125, 0.025, 0.05 or 0.1 mg/kg daily doses were included in the datasets, which were split into placebo and 4 quartiles, based on exposure, with N of 35, 50, 49, 50, and 50, respectively.

The distributions of C_{max} across quartiles are presented in Table 2, which shows that approximately 83% of C_{max} values in Q4 quartiles were observed for the 0.10 mg/kg dose regimen. Conversely,

approximately 70% of the C_{max} values in the 2nd or 3rd quartiles were observed for the 0.05 mg/kg dose regimen. Figure 15 (C_{max} versus nausea) and Figure 16 (C_{max} versus abdominal pain) of SHIR-CSC-129_ERglobal show that a total of 15 and 19 respective subjects had exposures that were within the exposure distribution range of Q4 quartiles, respectively. The majority of these subjects received 0.1 mg/kg daily treatment with teduglutide. Overall, the above results suggest that C_{max} values in the Q4 quartiles, which were mainly observed for the 0.10 mg/kg regimen, were associated with a higher probability of nausea or abdominal pain. Since a 0.05 mg/kg daily dose only provides a small percentage of subjects with potential exposure in the Q4 quartiles, no dose adjustment is recommended based on these evaluations. Nausea and abdominal pain are both listed in the Summary of Product Characteristics (SmPC), Section 4.8 as very common adverse reactions of teduglutide and the SmPC, Section 4.2 instructs prescribers that efficacy and safety in all patients should be closely monitored on an ongoing basis according to clinical treatment guidelines. The MAH therefore concludes that no further update to the SmPC is currently warranted.

Table 2 Distribution of Teduglutide C_{max} Across Quartiles and Doses

C_{max}_ng/mL [min, max]	Control	0.0125 mg/kg (N=8)	0.025 mg/kg (N=37)	0.05 mg/kg (N=124)	0.1 mg/kg (N=30)
Control	35 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Q1 [6.39, 22.7]	0 (0%)	8 (100%)	31 (83.3%)	11 (8.9%)	0 (0%)
Q2 [22.7, 32.7]	0 (0%)	0 (0%)	6 (16.2%)	**43 (34.7%)**	1 (3.3%)
Q3 [32.7, 47.2]	0 (0%)	0 (0%)	0 (0%)	**45 (36.3%)**	4 (13.3%)
Q4 [47.2, 124]	0 (0%)	0 (0%)	0 (0%)	25 (20.2%)	25 (83.3%)

Source Data: CSR for Study SHIR-CSC-129 ERglobal, Table 12.

Datasets for Nausea and Vomiting

The exposure-safety results showed a statistically significant relationship between steady state teduglutide exposure C_{max} or AUC versus nausea, but not versus vomiting (refer to SHIR-CSC-129_ERglobal). The MAH agrees that the TEAEs of nausea and vomiting are usually closely related. However, a review of the SBS datasets reveals the following:

- Among 50 subjects of the Q4 quartiles, 8 subjects had vomiting (SHIR-CSC-129_ERglobal, Figure 5) and 15 subjects had nausea (SHIR-CSC-129_ERglobal, Figure 16).
- Among the 8 subjects with vomiting, 1 subject had vomiting only, and 7 subjects had both nausea and vomiting.
- Among the 15 subjects with nausea, 8 subjects had nausea only and 7 subjects had both nausea and vomiting.

Based on the findings above, the majority of vomiting subjects did have nausea concurrently, suggesting the subjects having both vomiting and nausea were part of the nausea group and had more severe symptoms. The majority of nausea subjects did not have vomiting, suggesting the two datasets are not greatly overlapping. The 15/50 nausea subjects in the Q4 quartile roughly doubles the number of vomiting subjects (8/50), which makes the exposure-safety curve for nausea go up significantly (p-value = 0.0164) and drives the difference in the exposure-safety relationships between exposure-nausea and exposure-vomiting. These evaluations are expected to represent the true exposure-safety relationships, given the significant size of the datasets obtained in the SBS populations.

Assessment of the MAH's response

The MAH agrees that the TEAEs of nausea and vomiting are closely related as the majority of vomiting subjects did have nausea concurrently. Furthermore, the MAH clarifies that 15/50 nausea subjects in the Q4 quartile roughly doubles the number of vomiting subjects (8/50), which makes the exposure-safety curve for nausea go up significantly (p-value = 0.0164) and drives the difference in the exposure-safety relationships between exposure-nausea and exposure-vomiting. In addition, the SmPC, Section 4.2 instructs prescribers that efficacy and safety in all patients should be closely monitored on an ongoing basis according to clinical treatment guidelines. The MAH therefore concludes that no further update to the SmPC is currently warranted. This is accepted. But the MAH is asked to move the sentence in section 4.8 to section 5.1 and a minor modification is requested. Please also refer to SmPC.

Conclusion

Issue solved with SmPC update.

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐No need to update overall conclusion and impact on benefit-risk balance

Question 3

The MAH is asked to discuss the clinical relevance of the presented results for reduction or change in:

a) PS Caloric Intake

b) EN volume

c) daily PS usage

MAH's response

Parenteral support (PS)–dependent children with short bowel syndrome–associated intestinal failure (SBS-IF) have a high disease burden. Long-term administration of parenteral support (PS = parenteral nutrition and/or intravenous fluids) is life-saving but is often associated with potentially life-threatening complications, including IF associated liver disease, central line-associated blood stream infections, and central venous thrombosis. Therefore, accelerating the adaptive process and achieving enteral autonomy is a clinically relevant and urgent goal for all patients with SBS who are dependent on PS (Khan et al., 2015; Squires et al., 2012). Clinical parameters that would usually change in association with weaning-off of parenteral support include decreased PS caloric intake, increased EN volume/EN caloric intake, and a decrease in hours/day of PS.

a) PS Caloric Intake

In Study SHP633-301, the observed changes in PS caloric intake are always reflective of the observed changes in PS volume given the stable concentration of PS. Further, the subject diary data for PS volume are generally considered a more representative measure of efficacy/PD than the investigator prescribed data, since those data reflect the actual volume of PS taken by the subject. Therefore, the diary data results are discussed below (prescribed data are located in the CSR for Study SHP633-301, Section 11.1.1.2).

A clinically meaningful reduction in weight-normalized PS caloric intake is a reduction of at least 20% at Week 24/EOT. Three (60.0%) subjects enrolled in the teduglutide treatment arm and 1 (20.0%)

subject in the SOC arm experienced at least 20% reduction in PS caloric intake at EOT from baseline (2 subjects in the SOC arm had missing diary data at baseline).

This translates to an average difference of -16.1 kcal/kg/day (-27.0%) caloric intake per day at EOT from a baseline mean caloric intake of 67.3 kcal/kg/day for the teduglutide treatment arm, versus an average difference of -6.1 kcal/g/day (-13.7%) at EOT from a baseline mean caloric intake of 65.1 kcal/kg/day for the SOC arm.

Overall, the results from the subject diary data showed a relatively higher number of subjects achieving clinically meaningful reductions in PS calories and a higher percentage of the average reductions in PS calories within the teduglutide arm than the SOC arm (CSR for Study SHP633-301, Section 11.1.1.2).

b) Change From Baseline in EN Volume

The effect of PS volume reduction can also be seen in an increase in enteral feeds. Consistent with the earlier 24-week Phase 3 study in 50 pediatric subjects with SBS (TED-C14-006 study results) and the 12-week open label study in 46 pediatric subjects (TED-C13-003), Study SHP633-301 has shown that teduglutide treatment resulted in increases in EN volume and EN caloric intake. A clinically meaningful increase in EN volume and EN caloric intake is an increase of at least 20% from baseline. EN volume changes do not necessarily correspond to proportionate PS volume changes because other factors (ie, nutritional deficiencies, fluid or electrolyte disequilibrium, etc) would also affect enteral feeding (Vanderhoof and Matya, 1999).

The subject diary data showed that 2 subjects (40%) in the teduglutide arm had a 20% increase from baseline in EN volume and EN caloric intake at EOT versus no subjects in the SOC arm.

c) Daily PS Usage

Nutrition plays an important role in the management of short bowel syndrome. The institution of early and aggressive enteral therapy is the most important stimulus for intestinal adaptation and the eventual discontinuation of parenteral therapy. A decrease in daily PS usage indicates less dependence on parenteral therapy.

In the teduglutide arm, the mean reduction of time required for daily PS was -3.1 hours (-28.9%) at EOT from a baseline of 11.2 hours. In the SOC arm, the mean change was -0.3 hours (-1.9%) from a baseline of 13.0 hours.

Enhancing intestinal adaptation minimizes dependence on PS, thereby reducing the risk of complications and potentially improving quality of life. Beyond potentially decreasing the occurrence of PS comorbidities, more time off PS may lead to more opportunities to normalize daily function for both subjects and their parents, thereby offering further opportunities to continue working on oral rehabilitation during off PN/IV hours (Blüthner et al., 2020; Chen et al., 2020).

Consistent with prior studies, long term administration of teduglutide was temporally associated with significant reductions in PS volumes while the SBS subjects continued to maintain their nutritional status. These reductions in PS volume, PS calories and daily PS usage were also associated with substantial increases in EN volume and calories. Although enteral autonomy was not achieved in both treatment arms of the study, these parameters, collectively, indicate progress towards weaning off from parenteral support with long term teduglutide use in these subjects.

Assessment of the MAH's response

The MAH has discussed the clinical relevance of the presented results as requested:

a) PS Caloric Intake

A clinically meaningful reduction in weight-normalized PS caloric intake is a reduction of at least 20% at Week 24/EOT. Three (60.0%) subjects enrolled in the teduglutide treatment arm and 1 (20.0%) subject in the SOC arm experienced at least 20% reduction in PS caloric intake at EOT from baseline (2 subjects in the SOC arm had missing diary data at baseline). This translates to an average difference of -16.1 kcal/kg/day (-27.0%) caloric intake per day at EOT from a baseline mean caloric intake of 67.3 kcal/kg/day for the teduglutide treatment arm, versus an average difference of -6.1 kcal/g/day (-13.7%) at EOT from a baseline mean caloric intake of 65.1 kcal/kg/day for the SOC arm.

b) Change From Baseline in EN Volume

A clinically meaningful increase in EN volume and EN caloric intake is an increase of at least 20% from baseline. EN volume changes do not necessarily correspond to proportionate PS volume changes because other factors (i.e., nutritional deficiencies, fluid or electrolyte disequilibrium, etc). The subject diary data showed that 2 subjects (40%) in the teduglutide arm had a 20% increase from baseline in EN volume and EN caloric intake at EOT versus no subjects in the SOC arm.

c) Daily PS Usage

A decrease in daily PS usage indicates less dependence on parenteral therapy. In the teduglutide arm, the mean reduction of time required for daily PS was -3.1 hours (-28.9%) at EOT from a baseline of 11.2 hours. In the SOC arm, the mean change was -0.3 hours (-1.9%) from a baseline of 13.0 hours.

Conclusion

Issue solved.

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐No need to update overall conclusion and impact on benefit-risk balance

Question 4

Head circumference Z-scores observed in the SOC arm seemed to drop further over time compared with the teduglutide treatment arm. The MAH should discuss the drop in head circumference Z-scores observed in the SOC arm as compared to the TED arm.

MAH's response

The head circumference z-score is a standardized measure with the adjustment for the median values among the normal population at the same age, according to the World Health Organization z-score calculation charts. A drop in the head circumference z-scores over time may be interpreted to mean that subjects in the SOC arm are delayed in their head circumference development when compared to the median growth reference standards per the WHO definition.

Additionally, Table 3 shows that while one subject had a slight increase in head circumference over time, subject's head circumference z-scores decreased concurrently, which drove the mean values by visit in the SOC arm to the lower end. Further, this subject was the only subject with recorded head circumference z-scores, -2.44 and -2.44 for the Week 24 and EOT/ET study visits, respectively.

Table 3 Head Circumference Z-Scores By Study Visit – Study SHP633-301; SOC Treatment Arm

	Subject Number Head Circumference Z-Score (measured value in cm)					
	PPD					
Baseline	-0.30 (44.00)	-1.70 (42.40)	-0.75 (41.00)		-0.36 (45.20)	2.76 (48.70)
Week 1						
Week 3						
Week 5	0.03 (45.00)	-2.02 (42.50)	-0.37 (42.20)		-0.42 (45.50)	
Week 7						
Week 9						
Week 12					0.19 (46.70)	
Week 16		-2.54 (42.70)	0.03 (44.00)		0.17 (46.90)	
Week 20		-2.81 (42.60)	-0.23 (44.00)		0.10 (47.00)	
Week 24		-2.36 (43.40)			-0.04 (47.00)	
EOT/ET	-0.85 (44.00)	-2.36 (43.40)			-0.04 (47.00)	
Week 28		-2.44 (43.50)				
End of Study		-2.44 (43.50)				

Source Data: CSR for Study SHP633-301, Listing 16.2.8.7.

Assessment of the MAH's response

The MAH states that drop in the head circumference z-scores over time may be interpreted to mean that subjects in the SOC arm are delayed in their head circumference development when compared to the median growth reference standards per the WHO definition. The MAH has presented data illustrating that one subject had a slight increase in head circumference over time, his head circumference z-scores decreased concurrently, which drove the mean values by visit in the SOC arm to the lower end. Further, this subject was the only subject with recorded head circumference z-scores, -2.44 and -2.44 for the Week 24 and EOT/ET study visits, respectively.

This is accepted.

Conclusion

Issue solved.

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐No need to update overall conclusion and impact on benefit-risk balance

11. Request for 2. supplementary information

The MAH is asked to update the SmPC in line with the comments made in the appended PI.

12. Assessment of the responses to the request for supplementary information

Question

The MAH is asked to update the SmPC in line with the comments made in the appended PI.

MAH's response

The MAH took into consideration the latest comments for the PI, shared along with the Updated CHMP Rapporteur Assessment Report, dated 12 Oct 2021 and would like to propose one related change.

- Section 4.8 of the SmPC

The MAH agrees with the minor modification to remove the statement *"Teduglutide was well tolerated in these infant subjects.".* However, the MAH would respectfully ask if it would be possible to keep the proposed statement in 4.8, as initially submitted, instead of moving it to section 5.1 of the SmPC.

We are of the opinion that this statement would be more suitable in the section 4.8, rather than section 5.1, as it refers to the reported adverse events: *"Adverse events reported in the study were consistent with the safety profile seen in the previous paediatric studies and no new safety issues were identified.".*

Also, we would like to note that section 5.1 of the SmPC has already been updated with the relevant information related to this study: *"A 24¬-week, randomized, open-label, multicentre study was conducted in 10 infant patients 4 to 12 months of age with SBS dependent on parenteral support. The objective was to evaluate safety, efficacy/pharmacodynamics and pharmacokinetics of teduglutide. Subjects were randomized into 2 groups, standard of care (SOC) arm (n=5) and teduglutide 0.05 mg/kg/day treatment (TED) arm (n=5).".* The MAH considers that, by moving the statement proposed in section 4.8 to the section 5.1, this would result in having some of the information duplicated.

Based on the above, we would kindly request to reevaluate the proposal to move the statement from

section 4.8 to section 5.1 of the SmPC.

- Section 5.2 of the SmPC

The MAH agrees with the changes suggested for the section 5.2

An updated PI is included as part of this submission, in line with the MAH`s comments.

Assessment of the MAH's response

The MAH has agreed to remove the sentence *"Teduglutide was well tolerated in these infant subjects."* from section 4.8 in the SmPC but argues to keep the statement in section 4.8. The MAH is of the opinion that the statement would be more suitable in section 4.8 and also highlights that section 5.1 already has been updated with the relevant information regarding this study.

The assessor accepts the MAH's explanation and agrees with the proposed wording in section 4.8:

"In a completed clinical trial in paediatric subjects (aged 4 to 12 months corrected gestational age), a total of 10 subjects were randomized, 5 in the teduglutide arm and 5 in the Standard of Care arm, of which eight subjects completed the study. Adverse events reported in the study were consistent with the safety profile seen in the previous paediatric studies and no new safety issues were identified."

Regarding section 5.2 the MAH has amended the section as requested and deleted the sentence *"Which drives the efficacy responses"*.

Conclusion

Issue solved.

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐No need to update overall conclusion and impact on benefit-risk balance