26 April 2023
EMA/281521/2023
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Revestive

International non-proprietary name: teduglutide

Procedure No. EMEA/H/C/002345/II/0054/G

## Note

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

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# List of abbreviations

| | |
|---|---|
| ADA | anti-drug antibodies |
| ANY TED | subjects who received teduglutide treatment in their core and/or extension study |
| $AUC_{ss}$ | area under the concentration-time curve under steady state |
| CL/F | apparent clearance |
| $C_{max}$ | maximum concentration |
| $C_{max,ss}$ | maximum concentration under steady state |
| CrCL | creatinine clearance |
| CSR | clinical study report |
| EC | European Commission |
| EOT | end of treatment |
| EU | European Union |
| FDA | Food and Drug Administration |
| GLP-2 | glucagon-like peptide-2 |
| Ka | rate constant of absorption |
| NTT | no teduglutide treatment |
| NTT/NTT | subjects who received no teduglutide treatment in their core study and extension study |
| NTT/TED | subjects who received standard of care only in their core study and subsequently received teduglutide treatment in their extension study |
| PD | pharmacodynamic(s) |
| PK | pharmacokinetic(s) |
| PN | parenteral nutrition, synonymous with parenteral support |
| PS | parenteral support |
| SBS | short bowel syndrome |
| SC | subcutaneous(ly) |
| $t_{1/2}$ | elimination half-life |
| TEAE | treatment-emergent adverse event |
| TED | teduglutide |
| TED/NTT | subjects who received teduglutide treatment in their core study and standard of care only in their extension study |
| TED/TED | subjects who received teduglutide treatment in both their core and extension study |
| TESAE | treatment-emergent serious adverse event |
| US | United States |

| | |
|---|---|
| Vc/F | apparent volume of distribution |

# 1. Background information on the procedure

## *1.1. Type II group of variations*

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Takeda Pharmaceuticals International AG Ireland Branch submitted to the European Medicines Agency on 27 July 2021 an application for a group of variations.

The following variations were requested in the group:

| **Variations requested** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.11.z | C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation | Type IB | I, II and IIIB |
| C.I.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | Type II | I, II and IIIB |

Extension of indication to include patients from 4 months corrected gestational aged 1 year and above for the treatment of Short Bowel Syndrome. Consequently sections 4.1, 4.2, 4.8, 5.1 and 5.2 are updated. The Package leaflet is updated accordingly. Version 9.2 of the RMP has also been submitted.

Update of annex II to amend the date of completion of the post authorisation study to Q2 2032.
The MAH took the opportunity to also amend local representatives.

## *Information relating to orphan designation*

Revestive was designated as an orphan medicinal product EU/3/01/077 on 11 December 2001.
Revestive was designated as an orphan medicinal product in the following indication: Treatment of short-bowel syndrome.

## *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.

## *Information relating to orphan market exclusivity*

## Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

### *Protocol assistance*

The MAH did not seek Protocol Assistance at the CHMP.

## *1.2. Steps taken for the assessment of the product*

| Timetable | Actual dates |
|---|---|
| Submission date | 27 July 2021 |
| Start of procedure: | 14 August 2021 |
| CHMP Rapporteur Assessment Report | 15 October 2021 |
| PRAC Rapporteur Assessment Report | 15 October 2021 |
| PRAC Outcome | 28 October 2021 |
| CHMP members comments | 29 October 2021 |
| Updated CHMP Rapporteur(s) (Joint) Assessment Report | 6 November 2021 |
| Request for supplementary information (RSI) | 11 November 2021 |
| CHMP Rapporteur Assessment Report | 25 March 2022 |
| PRAC Rapporteur Assessment Report | 25 March 2022 |
| PRAC members comments | 30 March 2022 |
| Updated PRAC Rapporteur Assessment Report | 1 April 2022 |
| PRAC Outcome | 7 April 2022 |
| CHMP members comments | 11 April 2022 |
| Updated CHMP Rapporteur Assessment Report | 13 April 2022 |
| 2nd Request for supplementary information (RSI) | 22 April 2022 |
| CHMP Rapporteur Assessment Report | 16 August 2022 |
| PRAC Rapporteur Assessment Report | 16 August 2022 |
| PRAC members comments | 24 August 2022 |
| PRAC Outcome | 1 September 2022 |
| CHMP members comments | 5 September 2022 |
| Updated CHMP Rapporteur Assessment Report | 9 September 2022 |
| 3rd Request for supplementary information (RSI) | 15 September 2022 |
| CHMP Rapporteur Assessment Report | 28 March 2023 |
| PRAC Rapporteur Assessment Report | 28 March 2023 |
| PRAC Outcome | 14 April 2023 |
| CHMP members comments | 17 April 2023 |
| Updated CHMP Rapporteur Assessment Report | 20 April 2023 |
| Opinion | 26 April 2023 |

# 2. Scientific discussion

## *2.1. Introduction*

### 2.1.1. Problem statement

At present, Revestive is indicated for the treatment of patients aged 1 year and above with Short Bowel Syndrome (SBS). With this variation, the applicant is intending to extend the indication to include the age group of patients from 4 months corrected gestational age to 1 year of age with short bowel syndrome (SBS).

### *Disease or condition*

Short bowel syndrome (SBS) is a serious, disabling, socially incapacitating and potentially life-threatening condition. SBS results from surgical resection, congenital defect, or disease-associated loss of absorption and is characterised by the inability to maintain protein-energy, fluid, electrolyte, or micronutrient balances when on a conventionally accepted, normal diet.

Short bowel syndrome (SBS) is a rare disorder. Estimates of the incidence and prevalence of SBS in children and adults are difficult to make. Most estimates are based on data describing patients requiring long-term home parenteral nutrition (HPN) for SBS. Home parenteral nutrition may be used as a surrogate marker for severe intestinal failure. Surveys on HPN in Europe indicated an incidence of 2 to 3 patients per million and the prevalence was reported to be about 4 per million with a broad range.

The clinical characteristics of SBS in children are similar to those in adult, defined as a disease where there is diminished absorptive capacity for fluids and/or nutrients, sometimes requiring a dependence on parenteral nutrition and intravenous fluids (PN/IV) support to maintain energy and clinical status. There is heterogeneity within SBS. Where some patients with intestinal insufficiency are able to adapt metabolically and compensate for their malabsorption of fluids, electrolytes, trace elements, vitamins or nutrients by increasing oral/enteral intake, other patients with intestinal failure depend on PN/IV for nutritional support. Although PN/IV can provide nutritional support for patients with compromised fluid and nutritional status, it is also associated with serious complications, such as infections and liver damage. The risk for these effects increases over time with longer duration of PN/IV support. In severe cases of SBS, intestinal transplantation may be undertaken, which presents additional comorbidities, especially in infants. Intestinal transplantation in infants is more challenging than other organ transplants, as the incidence of acute rejection after intestinal transplantation is approximately 85%, and there may also be an increased incidence of sepsis as a result of bacterial translocation.

### *State the claimed the therapeutic indication*

Revestive is indicated for the treatment of patients 4 months corrected gestational age and above with Short Bowel Syndrome (SBS). Patients should be stable following a period of intestinal adaptation after surgery.

### 2.1.2. About the product

Teduglutide, [gly2]-hGLP-2, is a recombinant analogue of the human glucagon-like peptide-2 (GLP-2) a peptide that is secreted primarily from the lower gastrointestinal tract. Teduglutide is a 33 amino acid peptide that differs from GLP-2 in the substitution of glycine for alanine at the second position at the N-terminus. The single amino acid substitution relative to naturally occurring GLP-2 results in resistance to in vivo degradation by the enzyme dipeptidyl peptidase-IV (DPP-IV).

The product had first been licensed for the indication "Short Bowel Syndrome in adults" in the year 2012.

### 2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The applicant did not seek Protocol Assistance at the CHMP.

### 2.1.4. General comments on compliance with GCP

According to the MAH, all studies were conducted in accordance with the principles of the following: International Conference on Harmonisation (ICH) Good Clinical Practices, the Declaration of Helsinki, the US Code of Federal Regulations (CFR), and the EU Clinical Trials Directive, as well as Japanese regulations and other applicable local/regional regulations and guidelines regarding the conduct of clinical studies. No studies were prematurely terminated. The Japanese clinical study plans were developed in consultation with Pharmaceuticals and Medical Devices Agency (PMDA) prior to study start and recommendations were incorporated into the clinical development plans, including aspects related to study designs, dose selection, and analyses.

## *2.2. Non-clinical aspects*

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

### 2.2.1. Ecotoxicity/environmental risk assessment

A claim for not submitting environmental risk assessment studies is made according to Section 2 of the 2006 CHMP Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (ERA Guideline corr 2) because teduglutide is a peptide that differs from hGLP-2 in the substitution of glycine for alanine at the second position at the N-terminus. Per the ERA Guideline, vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids are exempt from ERA study requirements because by their nature they are unlikely to result in significant risk to the environment.

### 2.2.2. Conclusion on the non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

The extended indication does not lead to a significant increase in environmental exposure further to the use of teduglutide.

## *2.3. Clinical aspects*

### 2.3.1. Introduction

### GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Four clinical studies with teduglutide enrolled infants aged 4 months to <1 year corrected gestational age (a premature baby's chronological age minus the number of weeks or months he/she was born early): 2 completed core studies, 1 completed long-term extension study, and 1 ongoing long-term extension study with an expected completion dated of 31 Dec 2021 (**Table 1**).

**Table 1. Phase 3 Clinical Studies with Infant Subjects with Short Bowel Syndrome**

| Study Number | Study Description |
|---|---|
| SHP633-301 | A Randomized, Open-label, 24-Week Safety, Efficacy, and Pharmacokinetic Study of Teduglutide in Infants 4 to 12 Months of Age with Short Bowel Syndrome who are Dependent on Parenteral Support |
| SHP633-302 | A 24-Week Safety, Efficacy, Pharmacodynamic, and Pharmacokinetic Study of Teduglutide in Japanese Pediatric Subjects, Aged 4 Months through 15 Years, with Short Bowel Syndrome who are Dependent on Parenteral Support |
| SHP633-304 | A Prospective, Open-Label, Long-Term Safety and Efficacy Study of Teduglutide in Pediatric Patients with Short Bowel Syndrome who Completed TED-C14-006 or SHP633-301 |
| SHP633-305 | A Prospective, Open-Label, Long-Term Safety and Efficacy Study of Teduglutide in Japanese Pediatric Patients with Short Bowel Syndrome who Completed SHP633-302 |

**Characteristics of Clinical Studies with Enrolled Infants**

Selected characteristics Selected characteristics of the teduglutide studies that enrolled infants are provided in **Table 2**, below. The 4 studies are open-label studies.

**Table 2. Clinical Studies of Teduglutide with Enrolled Infants**

| Type of Study | Study ID | Country | Status | Objectives of the Study | Study Design | Subjects In Treatment Group(s) (Safety Population) | Healthy subjects or Diagnosis of patients | Treatment Duration | CSR Location |
|---|---|---|---|---|---|---|---|---|---|
| **Pediatric Phase 3 Studies** | | | | | | | | | |
| Safety, efficacy, PK | SHP633-301 | Finland, France, UK | Complete | Safety, efficacy, and PK in infants with SBS | A Randomized, Open-label, 24-Week Safety, Efficacy, and Pharmacokinetic Study of Teduglutide in Infants 4 to 12 Months of Age with Short Bowel Syndrome Who are Dependent on Parenteral Support | 5 teduglutide 0.05 mg/kg/day SC[a] 5 standard of care<br><br>Infants, n=10 | Infant patients with SBS | 24 weeks | Module 5.3.5.2 |
| Safety, efficacy, and PK | SHP633-302 | Japan | Complete | Safety, efficacy/PD, and PK in pediatric patients with SBS | A 24-week Safety, Efficacy, Pharmacodynamic, and Pharmacokinetic Study of Teduglutide in Japanese Pediatric Subjects, Aged 4 Months through 15 Years, with Short Bowel Syndrome who are Dependent on Parenteral Support | 10 teduglutide 0.05 mg/kg/day SC<br><br>Children, n=8, Infants, n=2 | Pediatric patients with SBS | 24 weeks | Module 5.3.5.2 |
| Uncontrolled Clinical Study | SHP633-304 | Belgium, Canada, Finland, Italy, UK, US | Complete | Long-term safety and efficacy in pediatric patients with SBS | A Prospective, Open-label, Long-term Safety and Efficacy Study of Teduglutide in Pediatric Patients with Short Bowel Syndrome Who Completed TED-C14-006 or SHP633-301 | 61 total 54 teduglutide 0.05 mg/kg/day SC; 7 no teduglutide<br><br>Infants, n=6 NTT/NTT=1 NTT/TED = 1 TED/TED = 4 | Pediatric patients with SBS | Long-term extension[b] | Module 5.3.5.2 |

**Table 2. Clinical Studies of Teduglutide with Enrolled Infants**

| Type of Study | Study ID | Country | Status | Objectives of the Study | Study Design | Subjects In Treatment Group(s) (Safety Population) | Healthy subjects or Diagnosis of patients | Treatment Duration | CSR Location |
|---|---|---|---|---|---|---|---|---|---|
| **Pediatric Phase 3 Studies** | | | | | | | | | |
| Uncontrolled Clinical Study | SHP633-305 | Japan | Ongoing[c] | Long-term safety and efficacy in pediatric patients with SBS | A Prospective, Open-label, Long-term Safety and Efficacy Study of Teduglutide in Japanese Pediatric Subjects with Short Bowel Syndrome Who Completed SHP633-302 | Ongoing[c] 9 teduglutide 0.05 mg/kg/day SC<br><br>Children, n=7, Infants, n=2 | Pediatric patients with SBS | Long-term extension[b] | Module 5.3.5.2 |

CSR=clinical study report; NTT=no-teduglutide treatment; PD=pharmacodynamic; PK=pharmacokinetic; PS=parenteral support; QD=once daily; SBS=short bowel syndrome; SC=subcutaneous; TED=teduglutide; UK=United Kingdom; US=United States

[a] In Study SHP633-301, subjects were randomly assigned to teduglutide 0.05 mg/kg/day also received standard of care.

[b] Extension studies SHP633-304 and SHP633-305 include multiple treatment cycles of 24 weeks each.

[c] For ongoing Study SHP633-305, the data cutoff date was 14 Jul 2020 for infants. The data presented in this document and Study SHP633-305 Interim CSR include at least 6 months of data for the 2 subjects in the infant cohort.

## Plasma Concentrations of Teduglutide in Infants

Measured plasma concentrations of teduglutide in Study SHP633-301 and Study SHP633-302 in plasma samples collected via a sparse sample collection scheme are presented in SHP633-301 clinical study report (CSR), Section 11.2.10 and SHP633-302 CSR, Section 11.2.10, respectively, see **Tables 3** and **4** below.

**Table 3. Teduglutide Concentrations Safety Set SHP633-301 CSR**

Treatment: 0.05 mg/kg/day Teduglutide

| Subject | Visit | Time Point | Date/Time of Assessment | Actual Time Relative to Dose (HH:MM) | Deviation from Scheduled Time (minutes) | Teduglutide Concentration (ng/mL) [a] | Not Done: Reason |
|---|---|---|---|---|---|---|---|
| | Baseline | 0-HOUR (PREDOSE) | 2018-09-25T14:25 | -0:52 | -52 | BLQ | |
| | | 1-HOUR POSTDOSE | 2018-09-25T16:15 | 0:58 | -2 | 25.7 | |
| | | 4-HOUR POSTDOSE | 2018-09-25T19:35 | 4:18 | 18 | 3.86 | |
| | Week 7 | | | | | | NOT DONE: Unable to gain samples |
| | Week 12 | 2-HOUR POSTDOSE | 2018-12-19T13:35 | 5:35 | 215 | 2.21 | |
| | Baseline | 0-HOUR (PREDOSE) | 2020-03-02T14:17 | -1:17 | -77 | | |
| | | 1-HOUR POSTDOSE | 2020-03-02T16:43 | 1:09 | 9 | | |
| | | 4-HOUR POSTDOSE | 2020-03-02T19:32 | 3:58 | -2 | 6.07 | |
| | Week 7 | | | | | | NOT DONE: Subject did not attend site due to COVID 19 Pandemic |
| | Week 12 | | | | | | NOT DONE: Subject did not attend site due to COVID 19 guidance |
| | Baseline | 0-HOUR (PREDOSE) | 2018-11-21T10:40 | -1:25 | -85 | BLQ | |
| | | 1-HOUR POSTDOSE | 2018-11-21T13:15 | 1:10 | 10 | 7.25 | |
| | | 4-HOUR POSTDOSE | 2018-11-21T16:30 | 4:25 | 25 | 22.5 | |
| | Week 7 | | | | | | NOT DONE: will be done wk 12 |
| | Week 12 | 2-HOUR POSTDOSE | 2019-02-11T13:45 | 2:05 | 5 | 29.0 | |

| Subject | Visit | Time Point | Date/Time of Assessment | Actual Time Relative to Dose (HH:MM) | Deviation from Scheduled Time (minutes) | Teduglutide Concentration (ng/mL) [a] | Not Done: Reason |
|---|---|---|---|---|---|---|---|
| | Baseline | 0-HOUR (PREDOSE) | 2019-07-23T13:59 | -0:39 | -39 | BLQ | |
| | | 1-HOUR POSTDOSE | 2019-07-23T15:47 | 1:09 | 9 | BLQ | |
| | | 4-HOUR POSTDOSE | 2019-07-23T18:39 | 4:01 | 1 | BLQ | |
| | Week 7 | 2-HOUR POSTDOSE | 2019-09-10T14:25 | 2:03 | 3 | 19.1 | |

| Subject | Visit | Time Point | Date/Time of Assessment | Actual Time Relative to Dose (HH:MM) | Deviation from Scheduled Time (minutes) | Teduglutide Concentration (ng/mL) [a] | Not Done: Reason |
|---|---|---|---|---|---|---|---|
| | Week 12 | 2-HOUR POSTDOSE | 2019-10-15T14:57 | 2:07 | 7 | 26.8 | |
| | Baseline | 0-HOUR (PREDOSE) | 2019-12-20T08:35 | -0:17 | -17 | BLQ | |
| | | 1-HOUR POSTDOSE | 2019-12-20T09:50 | 0:58 | -2 | 16.3 | |
| | | 4-HOUR POSTDOSE | 2019-12-20T12:44 | 3:52 | -8 | 10.7 | |
| | Week 7 | 2-HOUR POSTDOSE | 2020-02-05T12:40 | 2:05 | 5 | 14.8 | |
| | Week 12 | 2-HOUR POSTDOSE | 2020-03-10T12:33 | 2:05 | 5 | 24.5 | |

**Table 4. Pharmacokinetic Concentrations and Population SHP633-302 CSR**

| Cohort | Subject | Visit | Date/Time of Study Drug Administration (Study Day) | Study Drug Injection Volume (mL) | Scheduled Sample Timepoint | Date/Time of Sample Timepoint | Location of Injection | Study Drug Injection Performed by | Concentration (ug/L) | Not Done: Reason Not Done |
|---|---|---|---|---|---|---|---|---|---|---|
| Infant | | Baseline | 27FEB2019 (11:53) (1) | 0.15 | 0-hour (pre-dose) | 27FEB2019 (10:18) (1) | ABDOMEN | PI | BLQ<(1.00) | |
| | | Baseline | 27FEB2019 (11:53) (1) | 0.15 | 1-hour postdose | 27FEB2019 (12:53) (1) | ABDOMEN | PI | 88.5 | |
| | | Baseline | 27FEB2019 (11:53) (1) | 0.15 | 6-hour postdose | 27FEB2019 (17:32) (1) | ABDOMEN | PI | 3.55 | |
| | | Week 4 | 27MAR2019 (11:00) (29) | 0.15 | 0-hour (pre-dose) | 27MAR2019 (09:48) (29) | THIGH | SUBJCT | BLQ<(1.00) | |
| | | Week 4 | 27MAR2019 (11:00) (29) | 0.15 | 2-hour postdose | 27MAR2019 (13:05) (29) | THIGH | SUBJCT | 42.6 | |
| | | Week 4 | 27MAR2019 (11:00) (29) | 0.15 | 4-hour postdose | 27MAR2019 (15:10) (29) | THIGH | SUBJCT | 13.1 | |
| Infant | | Baseline | 09JUL2019 (10:07) (1) | 0.1 | 0-hour (pre-dose) | 09JUL2019 (09:00) (1) | ARM | PI | BLQ<(1.00) | |
| | | Baseline | 09JUL2019 (10:07) (1) | 0.1 | 1-hour postdose | 09JUL2019 (11:13) (1) | ARM | PI | 38.9 | |
| | | Baseline | 09JUL2019 (10:07) (1) | 0.1 | 6-hour postdose | 09JUL2019(1) | ARM | PI | | NOT DONE: For infant subject. |
| | | Week 4 | 06AUG2019 (09:20) (29) | 0.1 | 0-hour (pre-dose) | 06AUG2019(29) | ARM | SUBJCT | | NOT DONE: The subject is an infant. |
| | | Week 4 | 06AUG2019 (09:20) (29) | 0.1 | 2-hour postdose | 06AUG2019 (11:20) (29) | ARM | SUBJCT | 19.7 | |

BLQ=below the lower limit of quantification, PI=principal investigator.

Note: Infants are of 4 - <12 months corrected gestational age.

Note: Children who began treatment before protocol amendment 3 are marked with an asterisk.

Note: Study Day is calculated relative to the date of first study drug administration.

A total of 7 paediatric subjects 4 months to <1 year of age with PK information were available from Study SHP633-301 (5 subjects) and from Study SHP633-302 (2 subjects).

The PK set contains all subjects who received at least 1 dose of teduglutide and had at least 1 evaluable and interpretable post-dose PK concentration value. All 5 subjects randomized in the teduglutide arm are included in the PK set; 1 subject missed the Week 7 post-dose sample collection due to the COVID-19 pandemic.

## 2.3.2. Pharmacokinetics

### *Absorption*

**Study SHP633-301**

The summary of mean, median, minimum, and maximum teduglutide plasma concentrations by timepoint is presented in **Table 5**. The median post-dose 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 post-dose teduglutide plasma concentrations were 2.21 ng/mL and 29.00 ng/mL over the sample collection time during the treatment, respectively.

**Table 5. Summary of Mean Teduglutide Plasma Concentrations by Subject and Timepoint**

| | | 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 | | 3.86/22.5 |
| 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

**SHP633-302**

The population estimate of **rate of absorption** of teduglutide following SC dosing was 0.330 h-1. The **absorption lag time** was 0.299 h, corresponding to 17.9 minutes.

### *Distribution*

The PK of teduglutide was described using a one-compartmental model with linear elimination. An allometric component accounting for the effect of body weight on first-order rate constant of absorption (Ka), apparent clearance (CL/F), and apparent volume of distribution (Vc/F) was included in the base PK model. The population estimate of **Vc/F** of teduglutide was 33.9 L.

**Key covariate effects on CL/F of teduglutide**:

- The CL/F of teduglutide was dependent on body weight. The exponent for the effect of weight CL/F was 0.493 [(Body Weight/70)0.493], suggesting lower CL/F values in lighter subjects.
- Teduglutide mainly undergoes renal excretion. The CL/F of teduglutide was dependent on baseline creatinine clearance (CrCL). The exponent for the effect of CrCL on CL/F was 0.341 [(CrCL/99.35)0.341], suggesting lower CL/F values in subjects with lower CrCL.

**Key covariate effects on Vc/F of teduglutide:**

- The Vc/F of teduglutide was highly dependent on body weight. The exponent for the effect of weight Vc/F was 1.36 [(Body Weight/70)1.36], suggesting lower Vc/F values in lighter subjects.
- The Vc/F of teduglutide was dependent on age. The exponent for the effect of age on Vc/F was -0.316 [(Age/34)-0.316], suggesting higher Vc/F values in younger subjects.

**Covariate effects on Ka, lag time, and relative bioavailability of teduglutide**

- The Ka of teduglutide was dependent on body weight. The exponent for the effect of body weight on Ka was -0.790 [(Body Weight/70)-0.790], suggesting higher Ka values in subjects with lower body weight.
- The typical Ka in subjects receiving SC dosing in the arm or thigh were 23% lower relative to those who received SC dosing in the abdomen.
- The lag time of absorption following administration in the thigh and arm were 1.46 times longer than that observed for the abdomen, corresponding to 26.1 min. The lag time of absorption following administration of formulation strength >10 mg/vial was 52% shorter than that observed for formulation strength ≤10 mg/vial. The lag time of absorption following administration of a supra-therapeutic dose (ie, 80 mg) was 78% longer than that observed for a therapeutic dose (≤20 mg). The above effects on lag time do not have an impact on the maximum concentration under steady state ($C_{max,ss}$) and area under the concentration-time curve under steady state ($AUC_{ss}$) of teduglutide.
- The relative bioavailability of teduglutide following SC administration in the thigh and arm was 6.5% lower than that observed following SC administration in the abdomen.
- Descriptive statistics of PK parameters of teduglutide were derived in paediatric subjects with SBS (4 months to <18 years) and adult subjects with SBS treated with the 0.05 mg/kg dose.
- The mean CL/F of teduglutide in paediatric subjects (4 months to <18 years) was approximately 45% lower than that observed in adult subjects. The above change in CL/F was associated with a 45% reduction in $AUC_{ss}$ in paediatric subjects relative to adult subjects with SBS.
- The mean Vc/F of teduglutide in paediatric subjects (4 months to <18 years) was approximately 55% lower than that observed in adult subjects. Conversely, the mean Ka of teduglutide in paediatric subjects was approximately 2-fold higher than that observed in adult subjects. As a result, the mean $C_{max,ss}$ of teduglutide in paediatric and adult subjects with SBS were similar (33.9 ng/mL and 39.6 ng/mL, respectively).
- The mean elimination half-life (t1/2) in paediatric (4 months to <18 years) and adult subjects with SBS were 0.977 h and 1.22 h, respectively. Overall, the mean $C_{max,ss}$ and t1/2 of teduglutide in paediatric subjects were within 20% of those observed in adult subjects, respectively.

The relative bioavailability of teduglutide following SC administration in the thigh and arm was 6.5% lower than that observed following SC administration in the abdomen. The difference in bioavailability can be explained by differences in local absorption. The Applicant proposes a method of administration in infants that is consistent with the adult and pediatric administration, which is to administer teduglutide through subcutaneous injection alternating between 1 of the 4 quadrants of the abdomen with a shift to a thigh site in cases where injection into the abdomen is hampered by pain, scarring or hardening of the tissue. Due to the chronic dosing requirement, alternating sites of injection are expected and unavoidable. However, these variations are not expected to yield a difference in the PS volume reduction, due to chronic daily administration and alteration of injection sites over the course of treatment.

**Additional comparisons within each age group**

- Mean $C_{max,ss}$ values of teduglutide in paediatric subjects with SBS across age groups (mean range: 28.5 ng/mL to 43.0 ng/mL) were consistent with that observed in adult subjects with SBS (mean: 39.6 ng/mL). Moreover, the range of individual $C_{max,ss}$ values of teduglutide in paediatric subjects with SBS across age groups (20.7 ng/mL 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 t1/2 values of teduglutide in paediatric 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 $AUC_{ss}$ 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 paediatric subjects between 4 months and <1 year.

Upon CHMP's request, updated popPK models were submitted. None of the new models improved the description of data from infants and young children compared to the original popPK model. Recognising that the original model could not be optimised based on the sparse data, the CHMP requested additional boxplots with observed concentrations at steady state by age group, following 0.05 mg/kg dosing: one with observed concentrations around Cmax (pooling all PK data collected ⩽3 hours after dose), and one with observed concentrations in the elimination phase (pooling all PK data collected >3 hours after dose; mainly observations 4 and 6 hours after dose).

It was requested to present observed PK concentrations in pediatric patients including infants. A total of 57 pediatric patients from Studies SHP633-301, SHP633-302; TED-C13-003, TED-C14-004, and TED-C14-006 had 183 measurable plasma teduglutide concentrations following a daily dose of 0.05 mg/kg (**Table 6**). These samples were taken at scheduled times defined by individual study protocol during the treatment. Teduglutide concentrations by age groups and sampling time windows (≤3 after dose or >3 h after dose) along with the number of samples are presented in **Table 6**, which suggests that a reasonable number of PK samples were collected in this infant population.

**Table 6. Teduglutide Concentrations in Pediatric Patients by Age and Time Windows of PK Sampling – 0.05 mg/kg**

| Statistics | Observed Teduglutide Concentration (ng/mL) Post Dose | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | <1 year | | ≥1 to <6 years | | ≥6 to <12 years | | ≥12 to <17 years | |
| | ≤3 h (N=13) | >3 h (N=7) | ≤3 h (N=53) | >3 h (N=39) | ≤3 h (N=32) | >3 h (N=20) | ≤3 h (N=11) | >3 h (N=8) |
| Mean (CV%) | 27.3 (78.8%) | 8.73 (84.3%) | 27.7 (57.3%) | 14.1 (127.0%) | 31.0 (54.7%) | 17.3 (65.6%) | 19.9 (54.5%) | 16.5 (56.1%) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Median [Min, Max] | 24.5 [2.21, 88.5] | 6.07 [1.32, 22.5] | 24.0 [11.5, 91.8] | 12.1 [1.03, 114] | 27.5 [5.05, 86.5] | 17.8 [1.88, 39.0] | 17.5 [4.42, 36.6] | 15.7 [2.64, 31.7] |
| Number of BLQs excluded* | 0 | 0 | 1 | 9 | 0 | 6 | 0 | 2 |

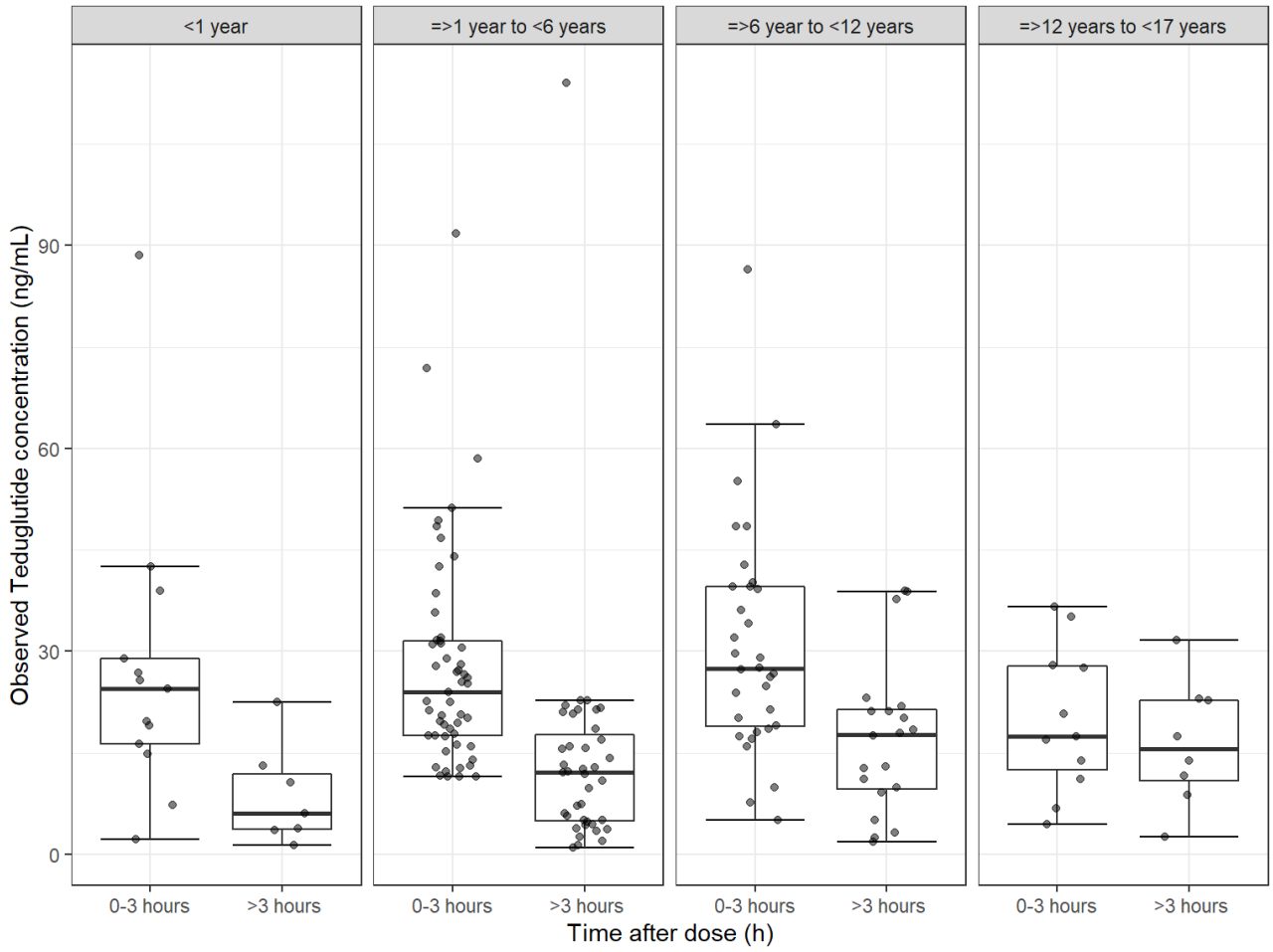
CV=coefficient of variation; Min=minimum; Max=maximum; PK=pharmacokinetic

Note: N is the number of PK samples post dose.

*Number of BLQs excluded from this table summary, which were not included in the table summary using 183 measurable post-dose samples; subjects could have more than one sample within each time window.

The requested boxplots are presented in **Figure 1**. The figure has 2 boxplots within each of 4 age categories; the first boxplot (left side within each age category) presents observed concentrations around $C_{max}$ (pooling all PK data collected ≤3 hours after dose), the other (right side within each age category) presents observed concentrations in the elimination phase (pooling all PK data collected >3 hours after dose; mainly observations at 4 and 6 hours after dose).

**Figure 1. Observed Teduglutide Concentrations in Pediatric Patients – 0.05 mg/kg**




The figure shows that teduglutide concentrations over the ≤3 h after dose PK sampling window were consistent across age groups, with mean values in subjects <1, ≥1 to <6, ≥6 to <12, and ≥12 to <17 years of 27.3, 27.7, 31.0, and 19.9 ng/mL, respectively. The mean observed concentrations over the ≤3 h PK sampling window are consistent with the Cmax predicted by the population PK Model 009. It is of note that the high variability for the mean values was due to concentrations being collected within a time window, rather than at a particular timepoint (such as $T_{max}$).

Teduglutide concentrations for the >3 h PK sampling window were variable across age groups with mean values in subjects <1, ≥1 to <6, ≥6 to <12, and ≥12 to <17 years of 8.73, 14.1, 17.3, and 16.5 ng/mL, respectively. This variable exposure is possibly due to the samples being collected in the wider time window over the elimination phase of teduglutide.

The left-hand plots for the ≤3 h window around Cmax show large overlap of observed concentrations across the age-groups, in particular across the age-groups <1 year and =>1 year to <6 years. This is reassuring because the number of observations is relatively high in the age-group =>1 year to <6 years indicating the box plot estimates in this group are reliable for comparisons. For the age-groups =>6 years to <12 years and =>12 years to <17 years, the overlap of the box plots with the younger age-groups is also large.

For the right-hand plots of the >3 h window (corresponding to the elimination phase) the overlap of concentrations across the age-group is also large.

## *Elimination*

Population estimate of **CL/F** was 16.0 L/h and the typical **half-life** of teduglutide was 1.47 h.

## *Dose proportionality and time dependencies*

### Study SHP633-302

The individual plasma concentration-time profiles of teduglutide following a single SC administration at the dose of 0.05 mg/kg are presented in **Figure 2** (Day 1) and **Figure 3** (Week 4).

**Figure 2. Plasma Teduglutide Concentrations-Time Profiles After SC Single Administration of Teduglutide 0.5 mg/kg (Spaghetti Plots All Subjects) – Day 1**

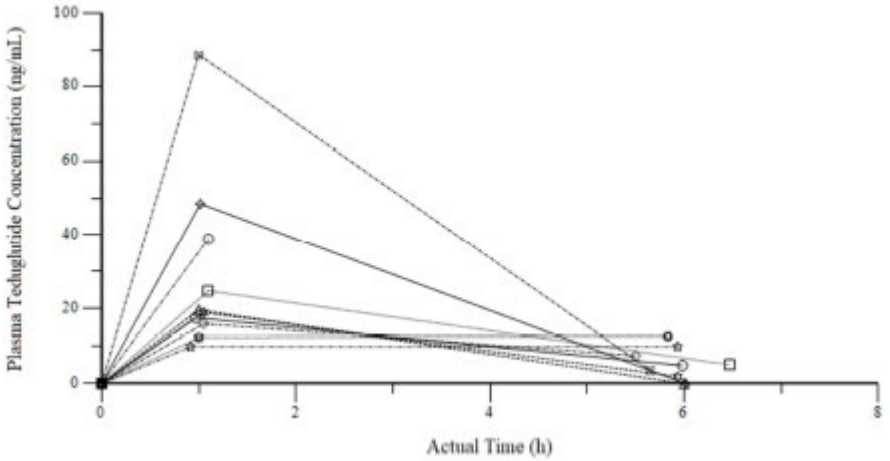
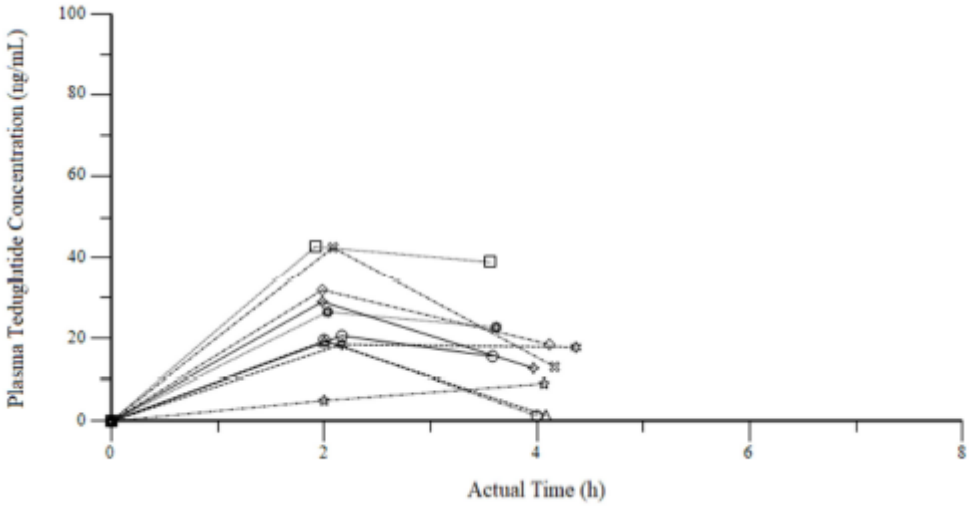



**Figure 3. Plasma Teduglutide Concentrations-Time Profiles After SC Single Administration of Teduglutide 0.5 mg/kg (Spaghetti Plots All Subjects) – Visit 6 (Week 4)**

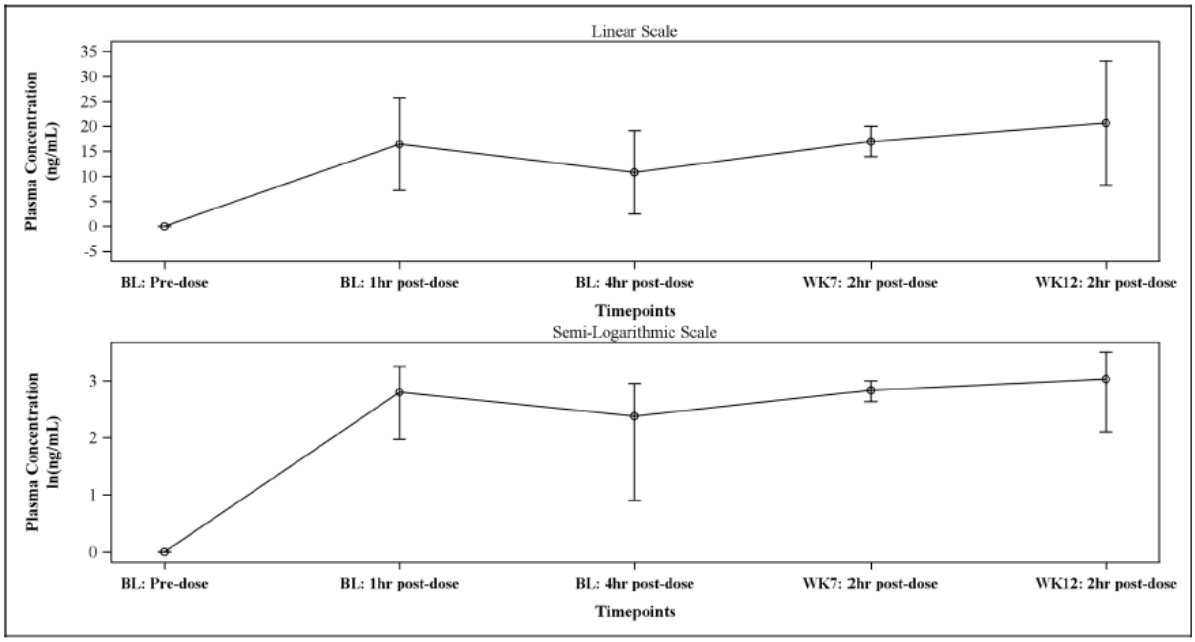


Systemic exposure to teduglutide was demonstrated over the time of the treatment. Mean plasma teduglutide concentration at 1 hour after single dose was 23.7±12.82 ng/mL in the children enrolled after protocol amendment 3 and 63.7±35.07 ng/mL in infants. Plasma concentrations 6 hours after single dose were 6.1±4.57 ng/mL in the children and 3.6 ng/mL in infants (n=1).

Plasma concentrations in total children were also similar to those in the children enrolled after protocol amendment 3 both after the single and multiple dosing. Plasma concentrations in the 2 children enrolled before amendment 3 were also detected in all sampling points.

The mean ±SD teduglutide plasma concentrations over time are presented in **Figure 4**, below, in both linear and semi-log scales.

**Figure 4. Mean ±SD Teduglutide Plasma Concentrations over Time**




Cross-reference: Table 14.2.2.15
Missing value presented as 0.
Program: s:\sgattex\shp633-301\2020-csr\report\figures\f-mean-plas.sas Output: f-mean-plas.rtf 15DEC2020 10:10

## *Special populations*

As part of a previous population PK analysis, no statistically significant effects were observed for race, and markers of liver function (ie, aspartate transaminase, alanine transaminase, total bilirubin). As part of the current population PK analysis, no residual effects for the above covariates were identified confirming that none of these covariates affected the PK of teduglutide.

## *Pharmacokinetic interaction studies*

No PK interaction studies have been presented.

PK and pharmacodynamics related drug-drug interactions (if there are any) in infants are expected to be the same as that indicated in the SmPC for adult and paediatric (>1 year) subjects with SBS, and caution should be used in infants when used concurrently with drugs that are also cleared through the kidneys.

## 2.3.3. Pharmacodynamics

### *Mechanism of action*

The naturally occurring human glucagon-like peptide-2 (GLP-2) is a peptide secreted by L cells of the intestine which is known to increase intestinal and portal blood flow, inhibit gastric acid secretion, and decrease intestinal motility. Teduglutide is an analogue of GLP-2. In several nonclinical studies, teduglutide has been shown to preserve mucosal integrity by promoting repair and normal growth of the intestine through an increase of villus height and crypt depth.

### *Primary and secondary pharmacology*

**PK/PD Relationship in Parenteral Support-dependent Pediatric Subjects with SBS**

This exposure-response analysis of teduglutide used data from 10 clinical trials, including data of 101 paediatric subjects 4 months and older collected in Studies TED-C13-003, TED-C14-006, SHP633-302, and SHP633-301).

Longitudinal profiles of PS volume were assessed in paediatric and adult subjects with SBS. Change from baseline values of prescribed PS volume were used for the primary analysis. A time- and exposure-response model was associated with an adequate goodness-of-fit. Briefly, the model included a saturable time effect estimated with a time to 50% of the maximum effect and a drug effect based on the maximum concentration ($C_{max}$) of teduglutide.

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.

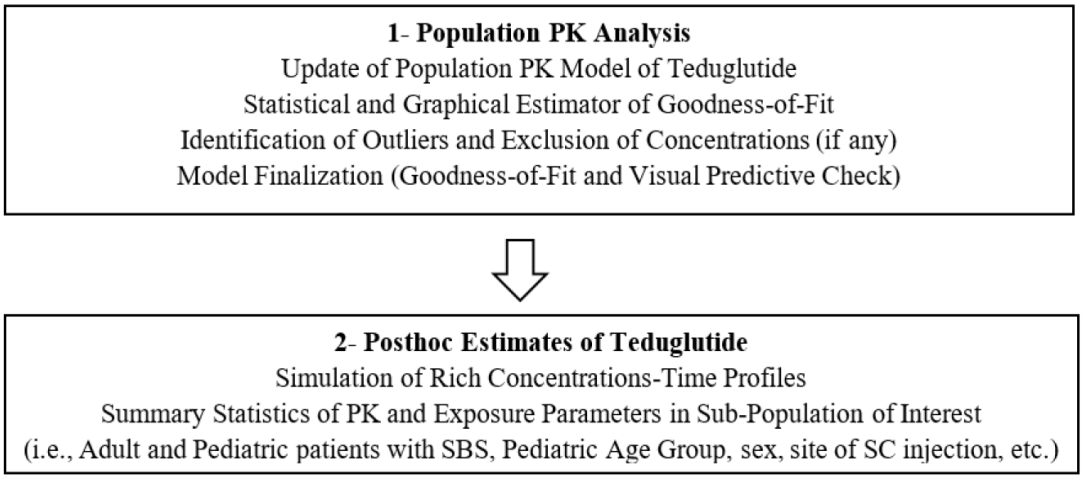
At Week 24, the median change from baseline PS volume in the 4 months to <1 year, 1 to <6 years, 6 to <12 years, and 12 to 17 years age groups were -0.620 L/Week, -1.01 L/Week, -2.88 L/Week, and -4.31 L/Week, respectively. These above changes at Week 24 corresponded to median percentage change from baseline 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 percentage change from baseline of -34%, -30%, -84% and -74%, respectively.

## 2.3.4. PK/PD modelling

**Teduglutide (SHP633)**

An overview of the population PK modelling steps is presented in **Figure 5**.

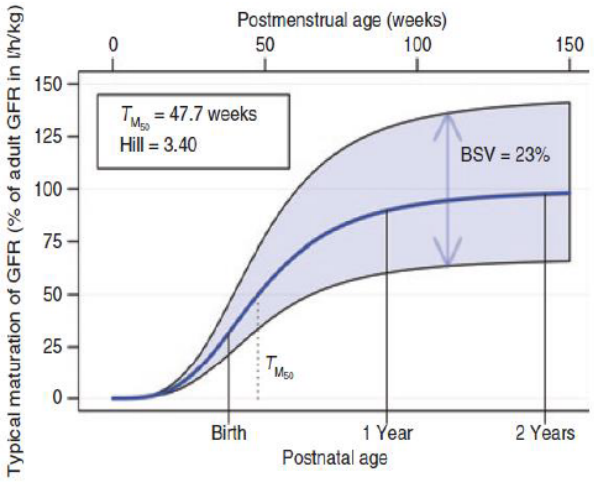
**Figure 5. Overview of Modeling Steps (Model Decision Tree): Population PK Modeling of Teduglutide**




***Effect of Kidney Maturation***

Teduglutide mainly undergoes urinary excretion. Age-related changes in organ maturation are well described in the literature. The maturation of kidney function in pediatric patients was described as presented in **Figure 6**.

**Figure 6. Typical Maturation of Renal Function in Paediatric Patients**




BSV = between-subjects variability; PMA = postmenstrual age; $T_{M50}$ = time associated with 50% maturation; Hill = coefficient for the slope of maturation function; MF = maturation function. Note: the shaded lines represented the variability around the point estimate (slide blue line)

**Dosing Information and Baseline Characteristics**

Two additional paediatric patients (4 to < 1 year) enrolled in study SHP633-301 were included as part of the current analysis. Both were treated with SC dosing of teduglutide 0.05 mg/kg in the thigh. A total of 5 paediatric patients (4 months to < 1 year) with PK information were 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 paediatric and 379 adult subjects.

Descriptive statistics of categorical baseline characteristics in the PK population are presented in **Table 7**.

**Table 7. Descriptive Statistics of Baseline Characteristics in non-SBS Subjects and Patients with SBS – Categorical Variables**

| Characteristics | | Non-SBS Subjects (N=259) | Patients with SBS (N=221) | Overall (N=480) |
|---|---|---|---|---|
| Sex | Male | 177 (68.3%) | 127 (57.5%) | 304 (63.3%) |
| | Female | 82 (31.7%) | 94 (42.5%) | 176 (36.7%) |
| Race | White | 224 (86.5%) | 167 (75.6%) | 391 (81.5%) |
| | Black | 26 (10.0%) | 17 (7.7%) | 43 (9.0%) |
| | Japanese | 0 (0%) | 25 (11.3%) | 25 (5.2%) |
| | Other | 7 (2.7%) | 7 (3.2%) | 14 (2.9%) |
| | Asian | 2 (0.8%) | 5 (2.3%) | 7 (1.5%) |
| Age Groups | Adult: ≥18 years | 259 (100.0%) | 120 (54.3%) | 379 (79.0%) |
| | Pediatric: 12 to <18 years | 0 (0%) | 8 (3.6%) | 8 (1.7%) |
| | Pediatric: 8 to < 12 years | 0 (0%) | 21 (9.5%) | 21 (4.4%) |
| | Pediatric: 6 to < 8 years | 0 (0%) | 12 (5.4%) | 12 (2.5%) |
| | Pediatric: 4 to < 6 years | 0 (0%) | 23 (10.4%) | 23 (4.8%) |
| | Pediatric: 2 to < 4 years | 0 (0%) | 26 (11.8%) | 26 (5.4%) |
| | Pediatric: 1 to < 2 years | 0 (0%) | 4 (1.8%) | 4 (0.8%) |
| | Pediatric: 4 months to <1 year | 0 (0%) | 7 (3.2%) | 7 (1.5%) |
| Renal Impairment Categories[a] | Normal Renal Function | 222 (85.7%) | 127 (57.5%) | 349 (72.7%) |
| | Mild Renal Impairment | 19 (7.3%) | 59 (26.7%) | 78 (16.2%) |
| | Moderate Renal Impairment | 6 (2.3%) | 34 (15.4%) | 40 (8.3%) |
| | Severe Renal Impairment | 6 (2.3%) | 1 (0.5%) | 7 (1.5%) |
| | ESRD | 6 (2.3%) | 0 (0%) | 6 (1.2%) |
| Hepatic Impairment | Normal Hepatic Function | 253 (97.7%) | 221 (100%) | 474 (98.8%) |
| | Moderate Hepatic Impairment | 6 (2.3%) | 0 (0%) | 6 (1.2%) |

CrCL = creatinine clearance (mL/min); eGFR = estimated glomerular filtration rate (mL/min/1.73m$^2$); ESRD = end-stage renal disease; n = number of subjects; SBS = short bowel syndrome.
[a] renal impairment categories are based on CrCL levels (mL/min) for subjects ≥12 years and on eGFR (mL/min/1.73m$^2$) for subjects <12 years. CrCL was imputed for one subject in study CL0600-004 (ID CL0600-004-0133-0003) for the covariate analysis.

Descriptive statistics of continuous baseline characteristics in the PK population are presented in **Table 8** below.

**Table 8. Descriptive Statistics of Baseline Characteristics in non-SBS Subjects and Patients with SBS – Continuous Variables**

| Characteristics | Mean (CV%) Median [Min, Max] | | |
|---|---|---|---|
| | Non-SBS Subjects (N=259) | Patients with SBS (N=221) | Overall (N=480) |
| Age (years) | 37.6 (36.7%)<br>36.0 [18.0, 74.0] | 28.9 (81.3%)<br>27.0 [0.380, 80.0] | 33.6 (57.7%)<br>34.0 [0.380, 80.0] |
| Body Weight (kg) | 78.0 (17.5%)<br>78.4 [50.3 ,127] | 41.0 (53.8%)<br>45.0 [5.15, 87.9] | 61.0 (42.83%)<br>65.3 [5.15, 127] |
| Height (cm) | 173 (5.4%)<br>174 [116,194] | 139 (24.5%)<br>158 [62.0,190] | 158 (18.7%)<br>168 [62.0,194] |
| ALT (U/L) | 24.7 (120.4%)<br>20.0 [3.00, 412] | 50.3 (80.1%)<br>36.0 [6.00, 243] | 36.5 (102.0%)<br>25.0 [3.00, 412] |
| AST (U/L) | 24.0 (92.6%)<br>21.0 [10.0,297] | 41.2 (60.8%)<br>35.0 [11.0,244] | 31.9 (78.5%)<br>24.0 [10.0,297] |
| Bilirubin (mg/dL) | 0.504 (48.3%)<br>0.486 [0.100 ,1.80] | 0.509 (127.5%)0.398<br>[0.0500,7.80] | 0.506 (93.8%)0.400<br>[0.0500,7.80] |
| Serum Creatinine (mg/dL) | 1.09 (97.7%)<br>0.900 [0.430,9.89] | 0.703 (56.8%)<br>0.701 [0.100,2.00] | 0.914 (93.2%)<br>0.803 [0.100,9.89] |
| Creatinine Clearance (mL/min) | 116 (31.1%)<br>116 [11.4, 236] | 80.0 (41.1%)<br>74.6 [26.0, 251] | 99.6 (39.2%)<br>99.4 [11.4, 251] |

ALT = alanine aminotransferase at baseline; AST = aspartate aminotransferase at baseline; CV = coefficient of variation; Max = maximum; Min = minimum; n = number of subjects.

A summary of dosing information (dose, site of SC injection, formulation strength) in the PK population are presented in **Table 9**.

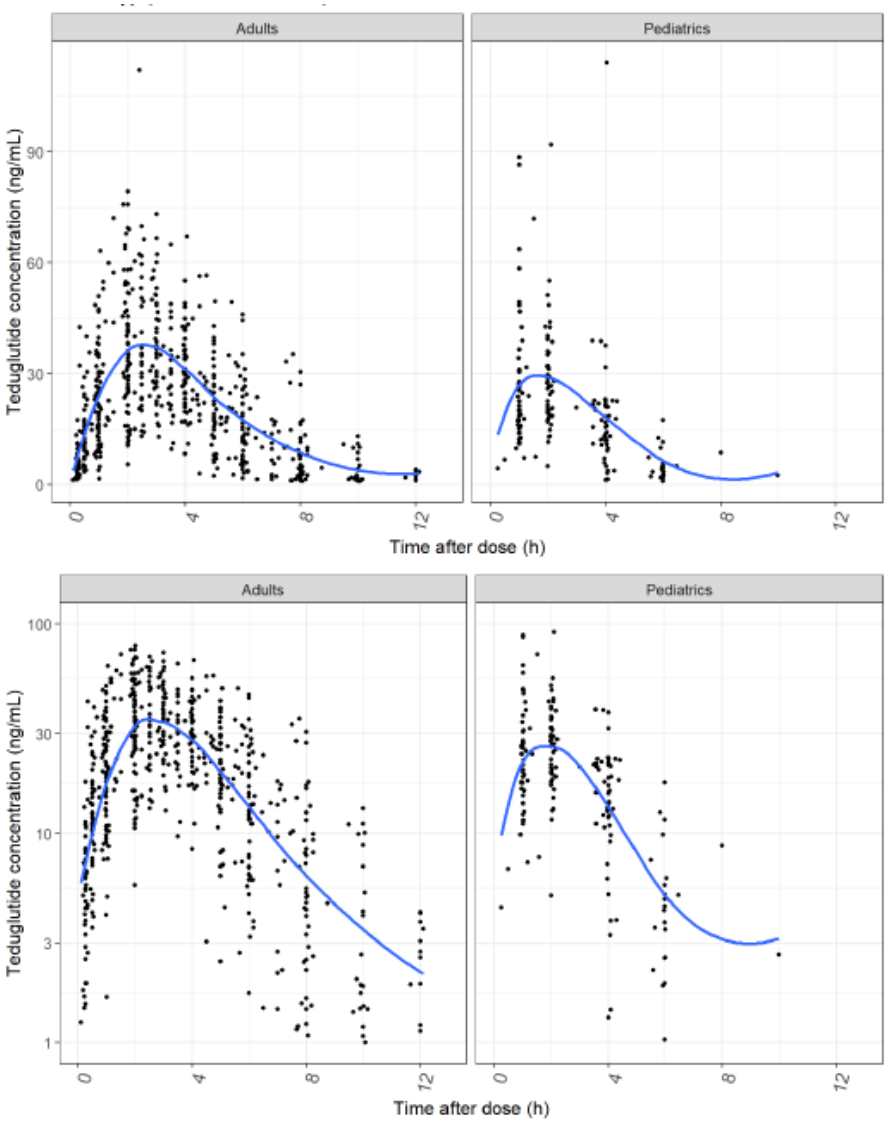
**Table 9. Dosing information (Dose, Site of Injection and Formulation Strength).**

| Characteristics | | Non-SBS Subjects (N=259) | Patients with SBS (N=221) | Overall (N=480) |
|---|---|---|---|---|
| Planned Study First Dose | 0.0125 mg/kg | 0 (0%) | 8 (3.6%) | 8 (1.7%) |
| | 0.025 mg/kg | 0 (0%) | 37 (16.7%) | 37 (7.7%) |
| | 0.03 mg/kg | 0 (0%) | 3 (1.4%) | 3 (0.6%) |
| | 0.05 mg/kg | 0 (0%) | 124 (56.1%) | 124 (25.8%) |
| | 0.1 mg/kg | 0 (0%) | 43 (19.5%) | 43 (9.0%) |
| | 0.12 mg/kg | 14 (5.4%) | 0 (0%) | 14 (2.9%) |
| | 0.15 mg/kg | 0 (0%) | 6 (2.7%) | 6 (1.2%) |
| | 2.5 mg | 6 (2.3%) | 0 (0%) | 6 (1.2%) |
| | 5 mg | 42 (16.2%) | 0 (0%) | 42 (8.8%) |
| | 7 mg | 6 (2.3%) | 0 (0%) | 6 (1.2%) |
| | 10 mg | 69 (26.6%) | 0 (0%) | 69 (14.4%) |
| | 15 mg | 9 (3.5%) | 0 (0%) | 9 (1.9%) |
| | 20 mg | 78 (30.1%) | 0 (0%) | 78 (16.2%) |
| | 25 mg | 9 (3.5%) | 0 (0%) | 9 (1.9%) |
| | 30 mg | 9 (3.5%) | 0 (0%) | 9 (1.9%) |
| | 50 mg | 9 (3.5%) | 0 (0%) | 9 (1.9%) |
| | 80 mg | 8 (3.1%) | 0 (0%) | 8 (1.7%) |
| Dose Levels | Therapeutic < 20 mg (actual dose) | 146 (56.4%) | 221 (100%) | 367 (76.5%) |
| | Supra-therapeutic ≥ 20 mg (actual dose)* | 113 (43.6%) | 0 (0%) | 113 (23.5%) |
| Site of Injection[a] | Abdomen | 247 (95.4%) | 122 (55.2%) | 369 (76.9%) |
| | Arm | 6 (2.3%) | 27 (12.2%) | 33 (6.9%) |
| | Thigh | 6 (2.3%) | 48 (21.7%) | 54 (11.2%) |
| | Missing | 0 (0%) | 24 (10.9%) | 24 (5.0%) |
| Formulation Strength | 1.25 mg/vial | 0 (0%) | 17 (7.7%) | 17 (3.5%) |
| | 2.5 mg/vial | 0 (0%) | 62 (28.1%) | 62 (12.9%) |
| | 5 mg/vial | 108 (41.7%) | 90 (40.7%) | 198 (41.2%) |
| | 10 mg/vial | 38 (14.7%) | 52 (23.5%) | 90 (18.8%) |
| | 20 mg/vial | 87 (33.6%) | 0 (0%) | 87 (18.1%) |
| | 65 mg/vial | 26 (10.0%) | 0 (0%) | 26 (5.4%) |

N/n = number of subjects; SBS = short bowel syndrome.
[a] Site of the first injection (note: subjects may have received the injection in more than one sites of injection)
* In study C09-001, a supra-therapeutic dose of 20 mg was used to assess the effect of teduglutide on cardiac repolarization and conduction. All doses ≥20 mg were considered as supra-therapeutic

Individual concentration-time profiles of teduglutide in adult and pediatric patients with SBS are presented in **Figure 7**.

**Figure 7. Concentration-Time Profile of Teduglutide Following SC Administration of 0.05 mg/kg in Adult and Paediatric Patients with SBS on Linear (Top Panel) and Semi-log (Bottom Panel) Scale.**




Teduglutide was rapidly absorbed following SC dosing and concentrations declined rapidly over time in pediatric and adult patients with SBS treated with the 0.05 mg/kg dose. The dataset included 6781 (89.8%) measurable teduglutide concentrations and 768 (10.2%) BLQ concentrations.

Population PK parameters of teduglutide derived with the final model are presented in **Table 10**.

**Table 10. Population PK Analysis of Teduglutide: Final Parameter Estimates**

| PK Parameters | Typical Values | RSE (%) | BSV (%) | Shrinkage (%) |
|---|---|---|---|---|
| **CL/F (L/h)** | 16.0<br>× (Body Weight/70)$^{0.493}$<br>× (CRCLT/99.35)$^{0.341}$<br>× 0.667 if non-SBS patients<br>× 0.933 if Female | 11.4 | 22.3 | 16.2 |
| **Vc/F (L)** | 33.9<br>× (Body Weight/70)$^{1.36}$<br>× (Age/34.0)$^{-0.316}$ | 6.2 | 31.1 | 9.9 |
| **Ka ($h^{-1}$)** | 0.330<br>× (Body Weight/70)$^{-0.790}$<br>× 0.767 for SC administration other than abdomen | 5.6 | 23.2 | 13.2 |
| **ALAG (h)** | 0.299<br>× 1.457 for SC administration other than abdomen<br>× 0.476 for Formulation strength ≥10 mg/vial<br>× 1.784 for Supra-therapeutic dose level | 34.9 | NA | NA |
| **F1** | 1, Fixed<br>× 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 |

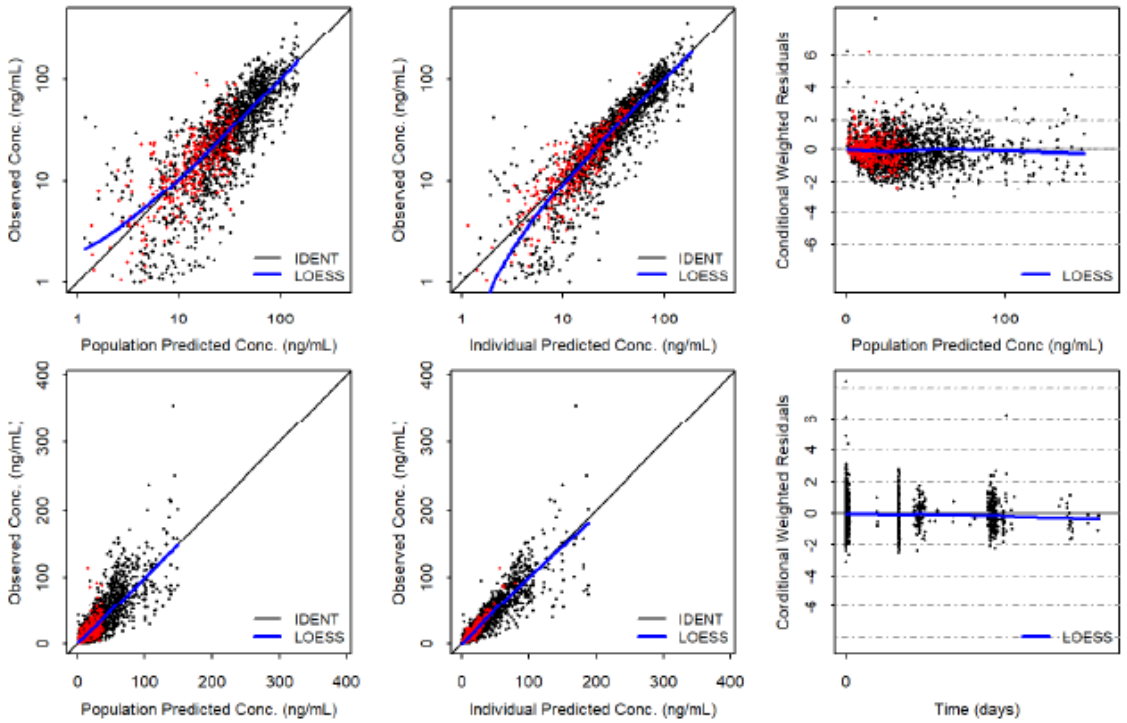
ALAG = Lag time; BSV = between-subjects variability; CL/F = apparent clearance; CRCLT = baseline creatinine clearance capped to 150 mL/min; F1 = relative bioavailability; Ka = first-order rate constant of absorption; PK= Pharmacokinetic; RSE = relative standard error; Vc/F = apparent central volume of distribution; NA= Not applicable.
Note: the reference subject is a 34 year, 70-kg male patient 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 Appendix 2, Section 12.2.

Overall, data collected in the 2 additional pediatric patients 4 months to < 1 year after the completion of study SHP633-301 did not impact the population estimates.

Since ADA was not measure in healthy subjects, this represents only 20/480 = 4.2% of the PK population. The impact of ADA as a time-varying covariate on CL/F was formally tested in the previous covariate analysis and not found significant. Since the updated dataset included only one new concentration in a patient with ADA positive, ADA was not re-tested in the current analysis.

The goodness-of-fit derived with the final population PK model in pediatric and adult patients with SBS are presented in **Figure 8**.

**Figure 8. Population PK Analysis of Teduglutide: Goodness-For-Fit in Adult and Paediatric Patients with SBS**



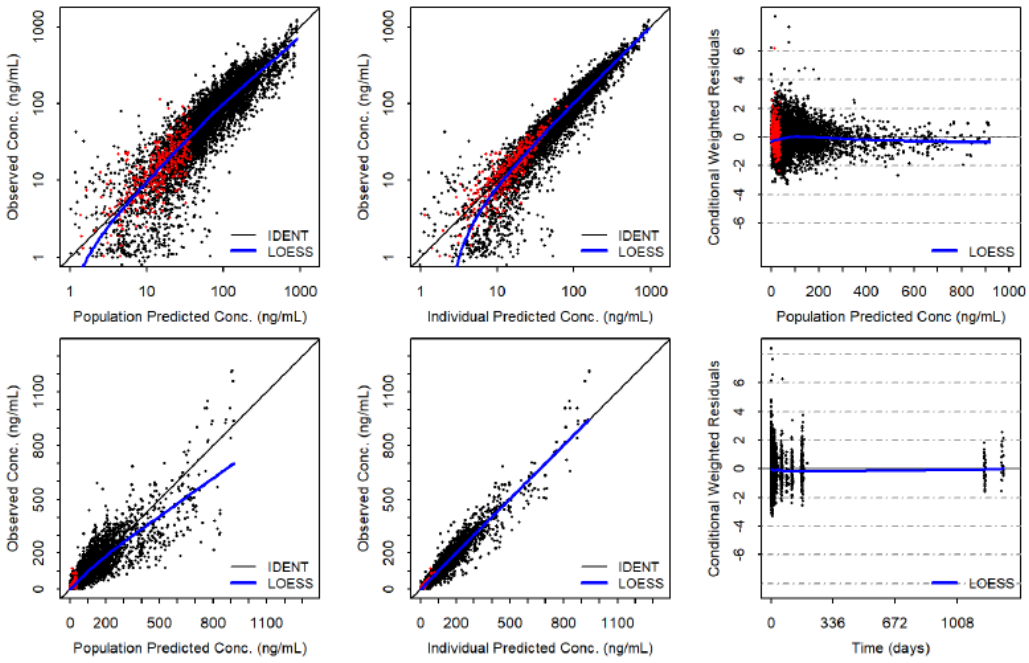

Red circles: pediatric patients with SBS; Black circles: adult patients with SBS
Line of identity, LOESS: Locally weighted smoothing scatterplot function; IDENT= Line of identity.
Conc = Concentration; PK= Pharmacokinetic. Note: only values above the LOQ are presented in the above figure. For better visualization, time > 100 days was not shown in the CWRES vs Time figure.

The LOESS regression of observed concentrations of teduglutide versus both individual and population predicted values fell along the line of identity. The CWRES were homogeneously distributed according to population prediction, and as a function time. Overall, the final population PK model was deemed to be appropriately specified, with population typical values and covariate effects, precisely estimated.

The goodness-of-fit derived with the final population PK model (run009) in all subjects (adult and pediatric patients with SBS, healthy volunteers and special populations) are presented in **Figures 9** and **10**. The model resulted in adequate goodness of fit, but a bias was observed for the prediction of concentrations associated with supra-therapeutic concentrations of teduglutide (20 mg) in healthy subjects.

The observed slightly higher LOESS regression relative to the line of identity for very low concentrations on the log-log scale on the top panel in the response does not affect the goodness-of-fit. This is because a truncated likelihood method that takes into account the censoring (M3 method) of samples with concentrations below the limit of quantitation was implemented in the population PK model.

**Figure 9. Final Population PK Model for Teduglutide – Goodness-For-Fit (1/2) All Subjects**




Red circles: Adult subjects (patients with SBS, healthy volunteers, and special population); Black circles: Pediatric patients
Conc = Concentration; IDENT= Line of identity; LOESS = Locally weighted scatter plot smoothing; PK= Pharmacokinetic.
Note: only values above the LOQ are presented in the above figure

**Figure 10. Final Population PK Model for Teduglutide – Goodness-For-Fit (2/2) All Subjects**

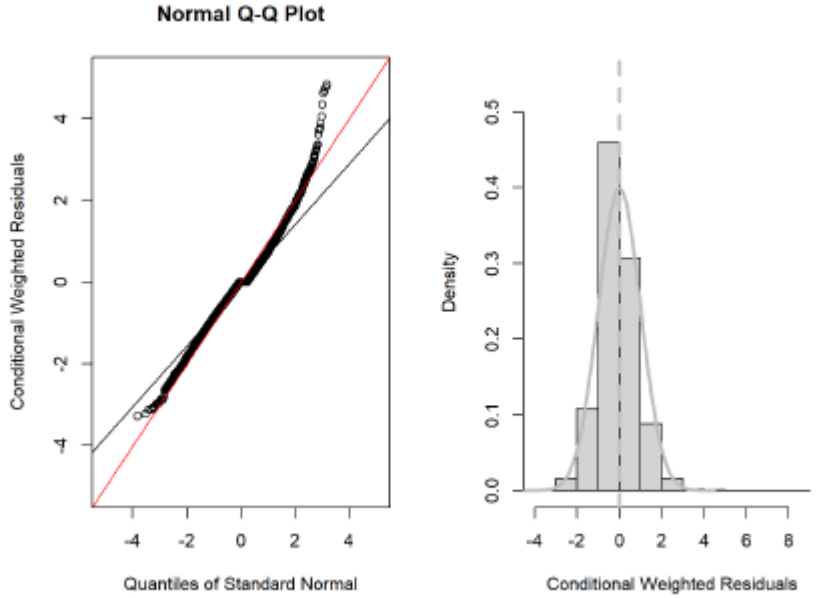
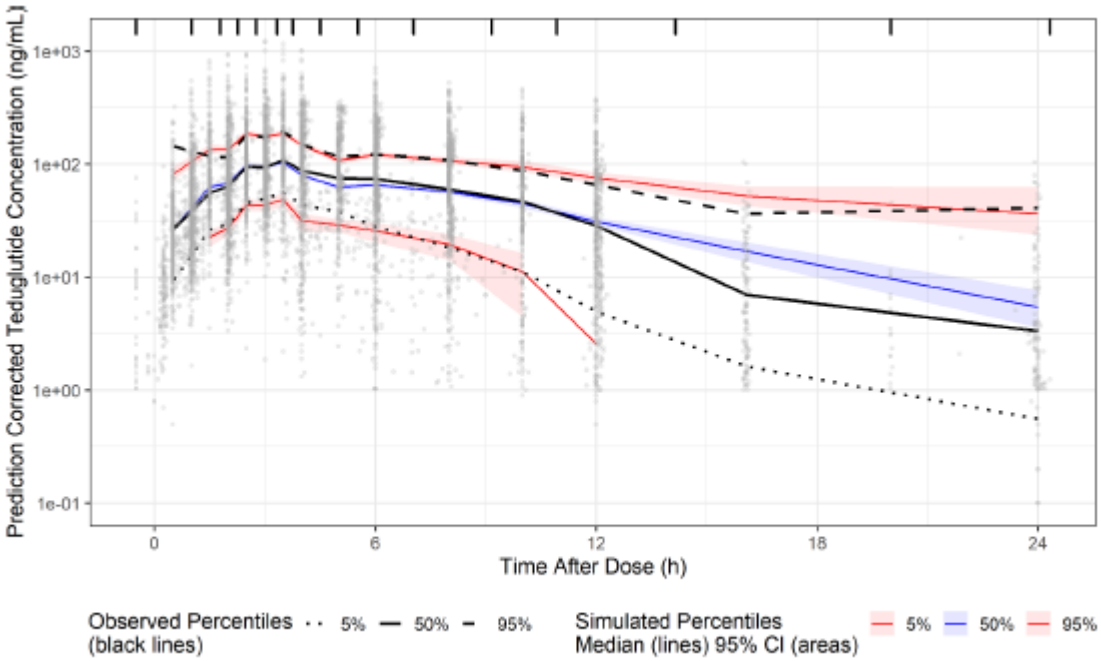
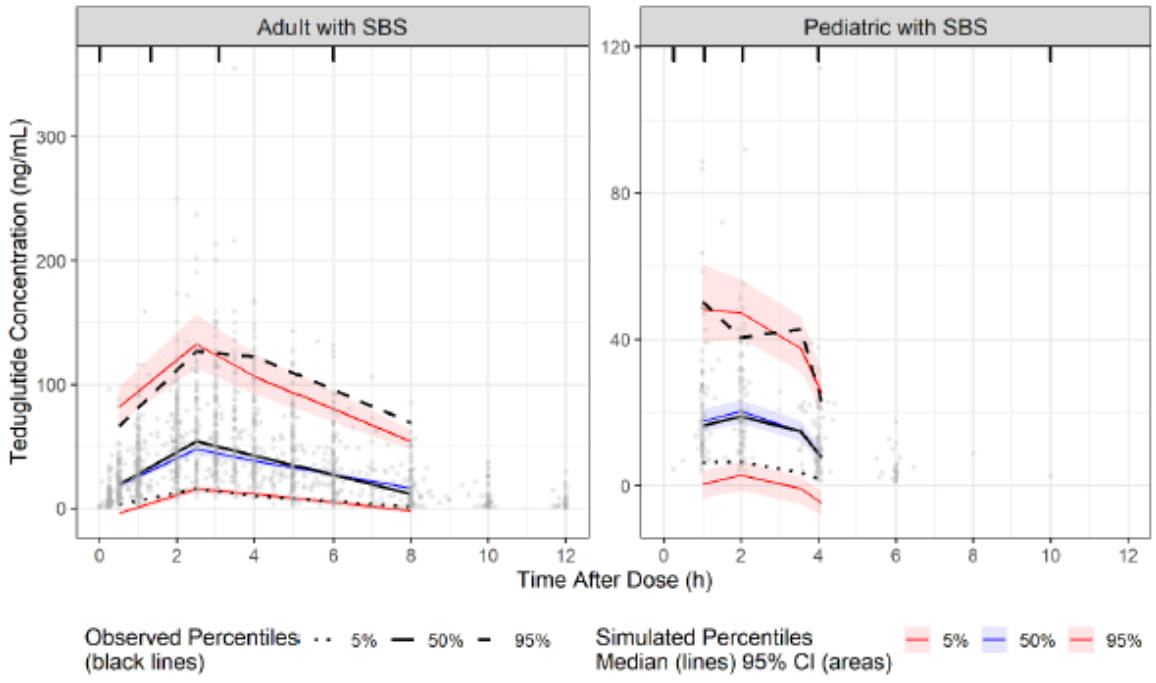


**Figure 11. Final Population PK Model of Teduglutide – Prediction-Corrected Visual Predictive Check All Subjects**




VPC were performed to qualify the model, whereby 1000 replicates of the observed subjects were simulated (**Figure 11**). The VPC for concentrations of teduglutide in adult and pediatric patients with SBS are presented in **Figure 12**.

**Figure 12. Visual Predictive Check of Teduglutide Concentrations in Adults and Paediatric Patients with SBS.**



Observed median, 5th and 95th percentiles of teduglutide concentrations were contained within the model-predicted ranges (shaded areas) in adult and pediatric patients with SBS.

**Descriptive Statistics of PK Parameters in Pediatric and Adult Patients**

Pediatric Patients with SBS (4 months to < 18 years) vs. Adult Patients with SBS. Descriptive statistics of PK parameters in pediatric patients with SBS (4 months to < 18 years) and adult patients (≥18 years) with SBS are presented in **Table 11**.

**Table 11. Descriptive Statistics of PK and Exposure Parameters of Teduglutide in Paediatric (4 months to <18 years) and Adult Patients with SBS (0.05 mg/kg)**

| Descriptive Statistics | Pediatric Patients with SBS (0.05 mg/kg) | | | | | | Adult Patients with SBS (0.05 mg/kg) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | CL/F (L/h) | Vc/F (L) | Ka (1/h) | $AUC_{ss}$ (ng.h/mL) | $C_{max,ss}$ (ng/mL) | $t_{1/2}$ (h) | CL/F (L/h) | Vc/F (L) | Ka (1/h) | $AUC_{ss}$ (ng.h/mL) | $C_{max,ss}$ (ng/mL) | $t_{1/2}$ (h) |
| n | 56 | 56 | 56 | 56 | 56 | 56 | 68 | 68 | 68 | 68 | 68 | 68 |
| Mean | 7.69 | 11.1 | 0.889 | 120 | 33.9 | 0.977 | 13.8 | 24.2 | 0.411 | 223 | 39.6 | 1.22 |
| SD | 2.94 | 6.19 | 0.376 | 48.4 | 12.3 | 0.217 | 3.58 | 8.68 | 0.113 | 58.3 | 12.4 | 0.298 |
| CV% | 38.3 | 55.6 | 42.2 | 40.3 | 36.4 | 22.2 | 25.9 | 35.8 | 27.5 | 26.1 | 31.2 | 24.4 |
| Median | 7.13 | 9.98 | 0.829 | 115 | 32.0 | 0.981 | 13.7 | 23.6 | 0.395 | 209 | 38.6 | 1.25 |
| Min | 1.69 | 2.98 | 0.352 | 58.7 | 20.7 | 0.484 | 7.36 | 11.5 | 0.225 | 119 | 19.5 | 0.691 |
| Max | 18.9 | 41.1 | 2.15 | 409 | 84.9 | 1.51 | 23.2 | 49.9 | 0.657 | 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; 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.

The mean CL/F of teduglutide in pediatric patients was approximately 45% lower than that observed in adult patients. The above change in CL/F was associated with a 45% reduction in $AUC_{ss}$ in pediatric patients relative to adult patients with SBS. For example, a typical 70-kg adult patient treated with a 0.05 mg/kg dose (3.5 mg) and a CL/F of 13.8 L/h is expected to have an $AUC_{ss}$ of 253 ng.h/mL (3,500,000 ng / 13,800 mL/h). Conversely, a typical 20-kg pediatric patient treated with a 0.05 mg/kg dose (1 mg) and a CL/F of 7.69 L/h is expected to have an $AUC_{ss}$ of 130 ng.h/mL (1,000,000 ng / 7,690 mL/h).

The mean Vc/F of teduglutide in pediatric patients was approximately 55% lower than that observed in adult patients. Conversely, the mean Ka of teduglutide in pediatric patients was approximately 2-fold higher than that observed in adult patients, respectively. As a result, the mean $C_{max,ss}$ of teduglutide in pediatric and adult patients with SBS were similar (33.9 and 39.6 ng/mL, respectively). The mean $t_{1/2}$ in pediatric and adult patients with SBS were 0.977 and 1.22 h, respectively. Overall, the mean $C_{max,ss}$ and $t_{1/2}$ of teduglutide in pediatric patients were within 20% of those observed in adult patients, respectively.

Descriptive statistics of PK parameters by age groups in pediatric and adult patients with SBS (0.05 mg/kg) are presented in **Table 12**.

**Table 12. Descriptive Statistics of PK and Exposure Parameters of Teduglutide in Paediatric Patients 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 | 0.380 | 5.15 | 3.04 | 2.98 | 58.7 | 23.0 | 0.484 |
| | Max | 0.971 | 10.3 | 5.76 | 9.40 | 123 | 62.7 | 1.13 |
| ≥1 to < 2 years | n | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| | Mean | 1.67 | 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 | 1.67 | 10.5 | 4.92 | 6.95 | 102 | 33.0 | 0.979 |
| | Min | 1.67 | 10.5 | 4.92 | 6.95 | 102 | 33.0 | 0.979 |
| | Max | 1.67 | 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 |
| | Min | 6.00 | 16.4 | 6.37 | 5.98 | 86.5 | 25.6 | 0.538 |
| | Max | 7.00 | 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 | 14.1 | 38.0 | 11.4 | 16.1 | 135 | 22.3 | 0.979 |
| | Max | 16.0 | 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; $C_{max,ss}$ = 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

Mean $C_{max,ss}$ values of teduglutide in pediatric patients with SBS across age groups (mean range: 28.5 to 43.0 ng/mL) were consistent with that observed in adult patients with SBS (mean: 39.6 ng/mL). Moreover, the range of individual $C_{max,ss}$ values of teduglutide in pediatric patients with SBS across age groups (20.7 to 84.9 ng/mL) was similar to that observed in adult patients with SBS (19.5 to 75.3 ng/mL). In addition, mean t1/2 values of teduglutide in pediatric patients with SBS across age groups (mean range: 0.813 to 1.17 h) were consistent with that observed in adult patients with SBS (mean: 1.22 h).

Mean $AUC_{ss}$ 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 patients 4 months to < 1 year. 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 patients between 4 months and <1 year of age. Clinical 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.

Therefore, the safety profile of the 0.05 mg/kg dose, which was well tolerated and effective across age groups, was selected as the safe and effective dose in pediatric patients with SBS from 4 months and older.

**Descriptive Statistics of PK Parameters in Pediatric Patients According to Renal Function**

Descriptive statistics of PK parameters of teduglutide in pediatric patients with SBS (0.05 mg/kg) with normal renal function and mild renal impairment are presented in **Table 13**.

**Table 13. Descriptive Statistics of PK Parameters According to Renal Function in Paediatric Patients (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 Renal Impairment (eGFR 60-89 mL/min/1.73 $m^2$) | 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 |
| | 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 |

CL/F = apparent clearance; CL/F/BW = body weight adjusted apparent clearance; CV = coefficient of variability; eGFR = estimated glomerular filtration rate; n = number of subjects; Vc/F = apparent central volume of distribution; Vc/F/BW = body weight adjusted apparent central volume of distribution; Ka = rate constant of absorption.

As per the population PK model, the CL/F of teduglutide was mainly dependent on creatinine clearance (CrCL) and body weight. The mean body weight adjusted CL/F in pediatric patients with mild renal impairment was approximately 25% lower than that observed in patients with normal renal function. The lower body weight adjusted CL/F in pediatric patients with mild renal impairment resulted in a 17% higher $AUC_{ss}$ relative to those with normal renal function (139 vs. 119 ng.h/mL, respectively). The mean body weight adjusted Vc/F values in pediatric patients with mild renal impairment was 32% lower than that observed in patients with normal renal function. The lower Vc/F in pediatric patients with mild renal impairment resulted in a 49% higher $C_{max,ss}$ relative to those with normal renal function (49.7 vs. 33.3 ng/mL respectively), but the minimum and maximum $C_{max}$ values in pediatric patients with mild renal impairment were contained within the range of $C_{max}$ values observed in pediatric patients with normal renal function.

The above increase in $AUC_{ss}$ and $C_{max,ss}$ were not deemed clinically relevant and therefore no dose adjustment is recommended in pediatric patients with mild renal impairment. Overall, the above results are consistent with those observed in adult patients with SBS, whereby slightly lower CL/F and

Vc/F in patients with mild renal impairment did not result in a clinically relevant increase on the $AUC_{ss}$ and $C_{max,ss}$ of teduglutide relative to patients with normal renal function. Based on a dedicated study 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 patients with moderate to severe renal impairment and ESRD.

Upon CHMP's request, descriptive statistics of baseline characteristics in patients <1 year and ≥1 year are presented in the **Table 14** below.

**Table 14. Baseline Characteristics in Patients with SBS <1 Year and ≥1 Year**

| Characteristics | <1 year (N=7) | ≥1 year (N=214) |
|---|---|---|
| **Age (years)** | | |
| Mean (CV%) | 0.741 (30.0%) | 29.8 (78.2%) |
| Median [Min,Max] | 0.807 [0.380,0.971] | 31.0 [1.00,80.0] |
| **Body Weight (kg)** | | |
| Mean (CV%) | 7.51 (21.4%) | 42.1 (51.2%) |
| Median [Min,Max] | 7.51 [5.15,10.3] | 46.4 [10.1,87.9] |
| **Creatinine Clearance (mL/min)** | | |
| Mean (CV%) | 101 (17.9%) | 79.7 (41.4%) |
| Median [Min,Max] | 103 [75.0,130] | 74.4 [26.0,251] |
| **Sex** | | |
| Male | 5 (71.4%) | 122 (57.0%) |
| Female | 2 (28.6%) | 92 (43.0%) |
| **Race** | | |
| White | 4 (57.1%) | 163 (76.2%) |
| Black | 0 (0%) | 17 (7.9%) |
| Asian | 1 (14.3%) | 4 (1.9%) |
| Other | 0 (0%) | 7 (3.3%) |
| Japanese | 2 (28.6%) | 23 (10.7%) |
| **Renal Impairment Categories** | | |
| Normal Renal Function | 5 (71.4%) | 61 (28.5%) |
| Mild Renal Impairment | 2 (28.6%) | 93 (43.5%) |
| Moderate Renal Impairment | 0 (0%) | 59 (27.6%) |
| Severe Renal Impairment | 0 (0%) | 1 (0.5%) |
| ESRD | 0 (0%) | 0 (0%) |
| Missing | 0 (0%) | 0 (0%) |

CrCL = creatinine clearance (mL/min); ESRD = end-stage renal disease; n = number of subjects; SBS = short bowel syndrome.
Normal renal function (CrCL ≥ 90 mL/min); mild renal impairment (CrCL = 60 to 89 mL/min); moderate renal impairment (CrCL = 30 to 59 mL/min); severe renal impairment, not on dialysis (CrCL = 15 to 29 mL/min); end-stage renal disease (ESRD) (CrCL< 15 mL/min or requiring dialysis).

As shown in **Table 14**, The mean CrCL in infants <1 year was higher than that observed in patients ≥1 year (101 vs. 79.7 mL/min vs. respectively). This is due to the fact that patients ≥1 year had a greater proportion of patients with renal impairments including mild, moderate and severe, thereby reducing the mean value of CrCL in patients ≥1 year.

Descriptive statistics of baseline characteristics in subjects <1 year and ≥1 year with normal renal function and mild renal impairment are presented in **Table 15**. The mean CrCL in infants <1 year was approximately 10% higher than that observed in subjects ≥1 year (101 vs. 92.0 mL/min vs. respectively). This is due to the fact that patients ≥1 year had a greater proportion of subjects with mild renal impairment, thereby reducing the mean CrCL in patients ≥1 year.

**Table 15. Baseline Characteristics in Patients with SBS <1 Year and ≥1 Year – Patients with Normal Renal Function and Mild Renal Impairment**

| Characteristics | <1 year (N=7) | ≥1 year (N=154) |
|---|---|---|
| **Age (years)** | | |
| Mean (CV%) | 0.741 (30.0%) | 28.1 (75.4%) |
| Median [Min, Max] | 0.807 [0.380,0.971] | 25.0 [2.00,67.0] |
| **Body Weight (kg)** | | |
| Mean (CV%) | 7.51 (21.4%) | 43.9 (49.0%) |
| Median [Min, Max] | 7.51 [5.15,10.3] | 47.7 [10.4,87.9] |
| **Creatinine Clearance (mL/min)** | | |
| Mean (CV%) | 101 (17.9%) | 92.0 (33.2%) |
| Median [Min, Max] | 103 [75.0,130] | 83.3 [60.0,251] |
| **Sex** | | |
| Male | 5 (71.4%) | 92 (59.7%) |
| Female | 2 (28.6%) | 62 (40.3%) |
| **Race** | | |
| White | 4 (57.1%) | 117 (76.0%) |
| Black | 0 (0%) | 8 (5.2%) |
| Asian | 1 (14.3%) | 2 (1.3%) |
| Other | 0 (0%) | 6 (3.9%) |
| Japanese | 2 (28.6%) | 21 (13.6%) |
| **Renal Impairment Categories** | | |
| Normal Renal Function | 5 (71.4%) | 61 (39.6%) |
| Mild Renal Impairment | 2 (28.6%) | 93 (60.4%) |

CrCL: creatinine clearance (mL/min); ESRD: end-stage renal disease; n: number of subjects; SBS: short bowel syndrome. Normal renal function (CrCL ≥ 90 mL/min); mild renal impairment (CrCL = 60 to 89 mL/min); moderate renal impairment (CrCL = 30 to 59 mL/min); severe renal impairment, not on dialysis (CrCL = 15 to 29 mL/min); end-stage renal disease (ESRD) (CrCL < 15 mL/min or requiring dialysis)

Descriptive statistics of baseline characteristics in subjects <1 year and ≥1 year with normal renal function only is presented in **Table 16.** The mean CrCL in infants <1 year with normal renal function was approximately 10% lower than that observed in patients ≥1 year (109 vs. 119 mL/min vs. respectively).

**Table 16. Baseline Characteristics in Patients with SBS <1 Year and ≥1 Year –Normal Renal Function Only**

**Renal Function Only**

| Characteristics | <1 year (N=5) | ≥1 year (N=61) |
|---|---|---|
| **Age (years)** | | |
| Mean (CV%) | 0.781 (23.4%) | 22.6 (77.8%) |
| Median [Min, Max] | 0.807 [0.488,0.971] | 15.0 [2.00,62.0] |
| **Body Weight (kg)** | | |
| Mean (CV%) | 7.54 (25.8%) | 45.1 (48.4%) |
| Median [Min, Max] | 7.51 [5.15,10.3] | 47.0 [10.6,87.9] |
| **Creatinine Clearance (mL/min)** | | |
| Mean (CV%) | 109 (12.8%) | 119 (26.6%) |
| Median [Min, Max] | 110 [91.9,130] | 107 [90.0,251] |
| **Sex** | | |
| Male | 4 (80.0%) | 44 (72.1%) |
| Female | 1 (20.0%) | 17 (27.9%) |
| **Race** | | |
| White | 3 (60.0%) | 43 (70.5%) |
| Black | 0 (0%) | 6 (9.8%) |
| Asian | 1 (20.0%) | 0 (0%) |
| Other | 0 (0%) | 1 (1.6%) |
| Japanese | 1 (20.0%) | 11 (18.0%) |
| **Renal Impairment Categories** | | |
| Normal Renal Function | 5 (100%) | 61 (100%) |

CrCL = creatinine clearance (mL/min); ESRD = end-stage renal disease; n = number of subjects; SBS = short bowel syndrome.
Normal renal function (CrCL ≥ 90 mL/min); mild renal impairment (CrCL = 60 to 89 mL/min); moderate renal impairment (CrCL = 30 to 59 mL/min); severe renal impairment, not on dialysis (CrCL = 15 to 29 mL/min); end-stage renal disease (ESRD) (CrCL<15 mL/min or requiring dialysis).

As shown in **Table 14**: "Baseline characteristics in patients with SBS <1 year and ≥1 year" and **Table 15**: "Baseline characteristics in patients with SBS <1 year and ≥1 year – patients with normal renal function and mild renal impairment", the population level median renal function (CrCl) depends on the proportion of patients with mild, moderate and severe renal impairments.

The data presented in **Table 16**: "Baseline characteristics in patients with SBS <1 year and ≥1 year – normal renal function only" shows that the normal renal function (CrCl) in the age-group <1 year was approximately 10% lower than that observed in patients ⩾1 year (109 vs. 119 mL/min vs. respectively).

A further age break-down within the <1-year group showed that CrCL in infants 4 to <6 months was approximately 15% lower than infants 6 months to <1 year

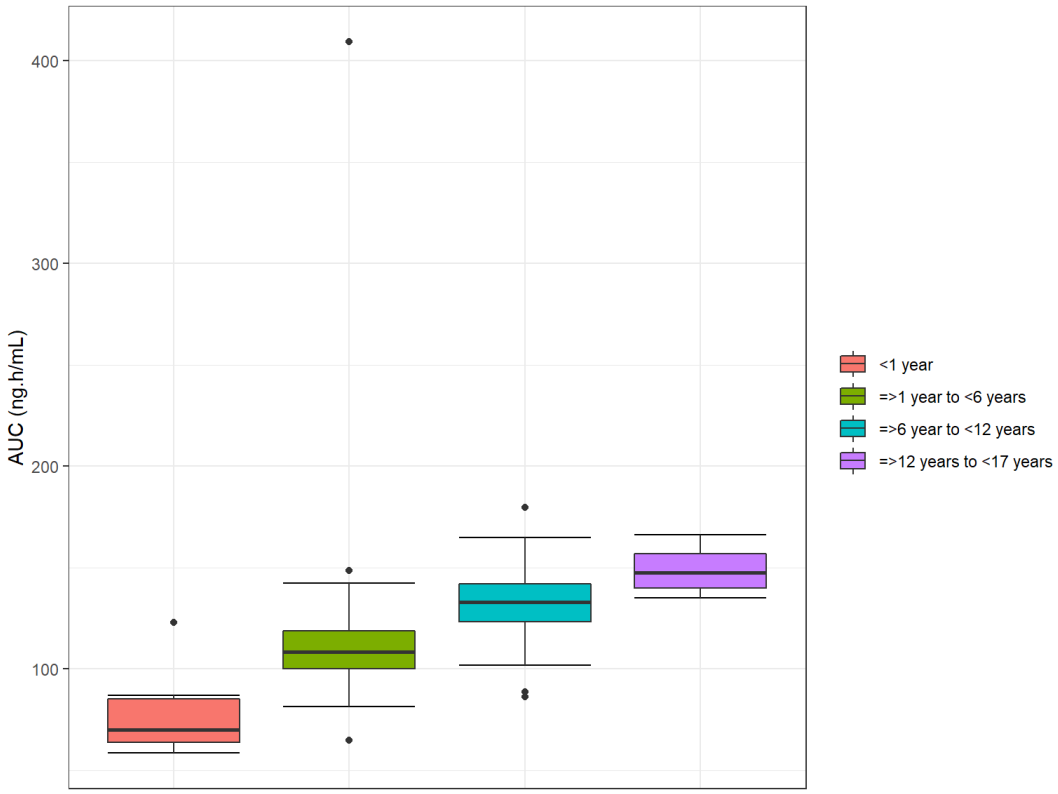
This suggests that the group of young paediatric patients in the target patient population aged 4 months to <1 year have a distribution of renal functions somewhere on the maturation curve including the steep slope and, perhaps, the late flattening part towards renal maturity.

This would normally call for the use of a maturation function in popPK modelling for extrapolation purposes. However, in the final popPK model the Applicant has used actual CrCl data from all patients without the addition of maturation function. This model proved to predicting the teduglutide concentrations rather well in the age-group 4 months to <1 year, and it was not improved in updated models.

Although including a factor accounting for kidney immaturity does not improve the population PK model, the exposure-response analysis considering the treatment time effect (longitudinal model) has reasonably described the relationship between actual PS reduction in L/Week and the exposure ($C_{max}$) across groups.

It is to be noted that the exposure is the same whether expressed as AUC, area under the curve from Time 0 to 24 h after dosing ($AUC_{0\text{-}24h}$) or area under the curve from Time 0 to infinity ($AUC_{0\text{-}\infty}$). This is due to the short half-life and lack of accumulation of teduglutide. As a result, the relationship between teduglutide AUC and age group in pediatric patients with SBS is presented as a single figure (**Figure 13**). The figure indicates that the lowest systemic exposure is in the youngest age group (infants 4 months to <1 year), following multiple doses at 0.05 mg/kg QD.

**Figure 13. Teduglutide AUC in Pediatric Patients with SBS by Age Group – Teduglutide 0.05 mg/kg**




Note: the AUC (=$AUC_{0\text{-}\infty}$) is the area under the curve from time 0 to 24 h after multiple doses.

From a safety perspective it is reassuring that lowest systemic exposure is seen in the youngest age group (infants 4 months to <1 year), following multiple doses at 0.05 mg/kg QD.

**Descriptive Statistics of PK Parameters in Pediatric Patients According to Formulation Strength**

Descriptive statistics of PK parameters of teduglutide in pediatric patients with SBS (0.05 mg/kg) according to formulation strength are presented in **Table 17**.

**Table 17. Descriptive Statistics of PK Parameters According to Formulation Strength in Paediatric Patients (0.05 mg/kg)**

| Formulation Strength | 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) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1.25 mg/vial (N=9) | Mean | 1.24 | 8.36 | 5.42 | 6.35 | 0.663 | 0.757 | 1.47 | 78.8 | 32.3 | 0.802 |
| | SD | 1.13 | 2.20 | 1.54 | 2.46 | 0.148 | 0.236 | 0.468 | 20.8 | 12.2 | 0.211 |
| | CV% | 91.0 | 26.3 | 28.5 | 38.8 | 22.3 | 31.2 | 31.9 | 26.3 | 37.9 | 26.3 |
| | Median | 0.880 | 7.79 | 5.36 | 6.55 | 0.714 | 0.737 | 1.37 | 70.0 | 29.1 | 0.801 |
| | Min | 0.380 | 5.15 | 3.04 | 2.98 | 0.390 | 0.397 | 0.828 | 58.7 | 23.0 | 0.484 |
| | Max | 4.00 | 11.8 | 8.84 | 9.40 | 0.828 | 1.17 | 2.15 | 123 | 62.7 | 1.13 |
| 5 mg/vial (N=22) | Mean | 4.31 | 15.3 | 7.28 | 9.90 | 0.478 | 0.651 | 0.874 | 104 | 31.2 | 0.940 |
| | SD | 1.63 | 2.18 | 1.47 | 2.58 | 0.0784 | 0.160 | 0.170 | 17.1 | 9.47 | 0.161 |
| | CV% | 37.7 | 14.2 | 20.2 | 26.1 | 16.4 | 24.5 | 19.5 | 16.4 | 30.3 | 17.1 |
| | Median | 4.11 | 15.7 | 7.13 | 10.4 | 0.457 | 0.666 | 0.831 | 104 | 27.9 | 0.906 |
| | Min | 1.67 | 10.5 | 4.92 | 5.11 | 0.347 | 0.351 | 0.653 | 81.4 | 21.8 | 0.701 |
| | Max | 8.43 | 18.5 | 9.83 | 13.3 | 0.607 | 0.961 | 1.32 | 140 | 54.2 | 1.26 |

CL/F = apparent clearance; CL/F/BW = body weight adjusted apparent clearance; CV = coefficient of variability; N = number of subjects; Vc/F = apparent central volume of distribution; Vc/F/BW = body weight adjusted apparent central volume of distribution; Ka = rate constant of absorption. Note: only pediatric patients < 20 kg were included in the descriptive statistics for the 5 mg/vial strength.

The mean body weight adjusted CL/F in pediatric patients who received the 1.25 mg/vial formulation was approximately 39% higher than that observed in patients who received the 5 mg/vial formulation (0.663 and 0.478 L/h/kg, respectively). The higher body weight adjusted CL/F in pediatric patients who received the 1.25 mg/vial formulation resulted in a 24% lower $AUC_{ss}$ relative to those who received the 5 mg/vial formulation (78.8 and 104 ng.h/mL, respectively). The mean body weight adjusted Vc/F values in pediatric patients with 1.25 mg/vial formulation was approximately 16% higher than that observed in patients with 5 mg/vial formulation (0.757 vs 0.651 L/kg, respectively). The mean $C_{max,ss}$ in pediatric patients who received the 1.25 mg/vial formulation was within 4% of those who received the 5 mg/vial formulation (32.3 and 31.2 ng/mL respectively). Based on the above results, the formulation strength had a low impact on the $C_{max}$ of teduglutide.

## 2.3.5. Discussion on clinical pharmacology

Four clinical studies with teduglutide enrolled infants aged 4 months to <1 year corrected gestational age were submitted for this extension of indication variation: 2 completed core studies, 1 completed long-term extension study, and 1 ongoing long-term extension study with an expected completion dated of 31 Dec 2021.

The MAH did not submit a Summary of Pharmacology during the ongoing procedure. The assessment is therefore based on data and results presented in the overview, Population PK/PD models, and clinical study reports.

The population estimate of Vc/F of teduglutide was 33.9 L. CL/F was 16.0 L/h and the typical half-life of teduglutide was 1.47 h.

The mean elimination half-life ($t_{1/2}$) in paediatric (4 months to <18 years) and adult subjects with SBS were 0.977 h and 1.22 h, respectively.

CL / F for teduglutide was dependent on body weight and creatinine clearance (CrCL) at baseline, suggesting lower CL/F values in lighter subject and in subjects with lower CrCL. Vc/F for teduglutide was dependent on body weight and age, suggesting lower Vc/F values in lighter subject and in younger subjects.

The relative bioavailability of teduglutide following SC administration in the thigh and arm was 6.5% lower than that observed following SC administration in the abdomen. The difference in bioavailability can be explained by differences in local absorption. The method of administration in infants is

consistent with the adult and pediatric administration, which is to administer teduglutide through subcutaneous injection alternating between 1 of the 4 quadrants of the abdomen with a shift to a thigh site in cases where injection into the abdomen is hampered by pain, scarring or hardening of the tissue. Due to the chronic dosing requirement, alternating sites of injection are expected and unavoidable. However, these variations are not expected to yield a difference in the PS volume reduction, due to chronic daily administration and alteration of injection sites over the course of treatment.

The mean CL/F of teduglutide in paediatric subjects (4 months to <18 years) was approximately 45% lower than that observed in adult subjects. The mean Vc/F of teduglutide in paediatric subjects (4 months to <18 years) was approximately 55% lower than that observed in adult subjects. Conversely, the mean Ka of teduglutide in paediatric subjects was approximately 2-fold higher than that observed in adult subjects. As a result, the mean $C_{max,ss}$ of teduglutide in paediatric and adult subjects with SBS were similar (33.9 ng/mL and 39.6 ng/mL, respectively).

Given the sparse data from only 7 patients on teduglutide in the target age group 4 months to <1 year a reliable PK-bridging is essential. The Applicant provided updated models as requested, yet, none improved the description of data from infants and young children compared to the original model. It is acknowledged that data collected in <1 year are limited to 7 infants, and the original model could not be optimised.

Additional boxplots were requested and overall, it is accepted that these box plots suggest a similar exposure in terms of observed concentrations in the time window of ≤3 h (representing the time window for Cmax) across the age-groups.

Overall, a PK/PD and exposure-response relation was found in paediatric subjects with SBS in the age span 4 months to <18 years) when evaluated by $C_{max}$.

No PK interaction studies have been presented. This is considered acceptable because PK and pharmacodynamics related drug-drug interactions (if there are any) in infants are expected to be the same as that indicated in the SmPC for adult and paediatric (>1 year) subjects with SBS, and caution should be used in infants when used concurrently with drugs that are also cleared through the kidneys.

Data collected in the 2 additional paediatric patients 4 months to < 1 year after the completion of study SHP633-301 did not impact the population estimates. Since the updated dataset included only one new concentration in a patient with ADA positive, ADA was not re-tested in the current analysis. This is accepted.

## 2.3.6. Conclusions on clinical pharmacology

A total of 7 paediatric subjects 4 months to <1 year of age with PK information were available from the core studies: SHP633-301 (5 subjects) and from Study SHP633-302 (2 subjects).

The limitations of the popPK model presented was discussed extensively in the previous sections and acknowledged that it could not be further optimised. The descriptive plots of observed $C_{max}$ across the age-groups to evaluate similar exposure across age-groups rounded the evidence to support similar exposure across age groups.

## 2.4. Clinical efficacy

The efficacy of teduglutide was evaluated in 2 completed core studies, SHP633-301 and SHP633-302, 1 completed long-term extension study, SHP633 304, and 1 ongoing long-term extension study, SHP633-305.

**Core studies**

The **SHP633-301 study** included 2 treatment arms, one where subjects received teduglutide doses of 0.05 mg/kg/day for 24 weeks plus standard of care (n=5) and the other where subjects received only the standard of care therapy for SBS (no teduglutide, n=5). It was an open-label study where non-Japanese pediatric subjects 4 months through <1 year corrected gestational age were randomized into either the teduglutide or standard of care arm.

The **SHP633-302** was an open-label Japanese study where all subjects enrolled received teduglutide doses of 0.05 mg/kg/day for 24 weeks. The pediatric study consisted of 2 cohorts: subjects 4 months through <1 year corrected gestational age (infants cohort, n=2) and subjects 1 through 15 years of age (children cohort). Changes to the ancillary kits used to prepare and administer the investigational product, including the introduction of a vial adaptor, occurred with Protocol Amendment 3. In addition, a process for training the parents/guardians and measures to provide oversight on study drug administration was implemented in Protocol Amendment 3. For these reasons, the children enrolled after Protocol Amendment 3 were analyzed separately.

Subjects in both studies participated in a 2-week minimum screening period, a 24-week treatment period, and a 4-week follow-up period. Subjects in the teduglutide treatment arm(s) (both studies) and the standard of care arm (SHP633-301) followed the same visit schedule. At all site visits and telephone contacts, safety was monitored, and nutritional support was reviewed and adjusted as needed.

In both studies, the efficacy parameters evaluated were related to changes in PS (namely PS volume, calories, hours per day, and days per week). The efficacy endpoint of reduction in PS volume of ≥20% at Week 24 (or end of treatment [EOT]) compared with baseline was used in both studies (primary endpoint in SHP633-301). In both studies, changes in PS were assessed.

**Extension studies**

Subjects who completed a core study, SHP633-301 and SHP633-302, were able to continue into ongoing open-label, long-term extension studies, **SHP633-304** and **SHP633-305**, respectively, to evaluate the long-term efficacy of teduglutide. The primary difference in study design between the SHP633-301 and SHP633-302 core studies is that there was no standard of care arm in SHP633-302 so that all subjects were treated with teduglutide at 0.05 mg/kg.

Enrolment into SHP633-304 was also open to subjects who had completed core study TED-C14-006, titled "A 24-week Double-blind, Safety, Efficacy, and Pharmacodynamic Study Investigating 2 Doses of Teduglutide in Paediatric Subjects through 17 Years of Age, with Short Bowel Syndrome who are Dependent on Parenteral Support." However, no paediatric subjects <1 year of age were enrolled in TED-C14-006.

The SHP633-304 and SHP633-305 study designs are similar. Subjects could participate in multiple no-teduglutide treatment (NTT) periods and/or multiple 28-week treatment cycles depending on the disease course and responses to teduglutide. Subjects not receiving teduglutide treatment (ie, in an NTT period), were seen every 12 weeks. Subjects who met ≥1 of the teduglutide treatment inclusion criteria at any point after screening, including during an NTT period, could proceed directly to a pre-

treatment visit if the investigator, subject, and parent or legal guardian agreed to proceed with teduglutide therapy. A 28-week teduglutide treatment cycle consisted of a 24-week teduglutide treatment duration followed by a 4-week follow-up (no treatment) period. To ensure sufficient safety monitoring and opportunities to reduce PS, the visit schedules during the 28-week teduglutide treatment cycles in the extension studies were similar to those of the core studies. During NTT periods, visits occur every 12 weeks, a frequency that is consistent with standard medical practice.

One of the goals of the extension studies was to determine whether paediatric subjects could receive long-lasting benefit from short-term (24 weeks) treatment with teduglutide. To address this question, teduglutide treatment in the extension studies was provided in 28-week cycles, consisting of 24 weeks of teduglutide treatment and 4 weeks of follow up. If a subject deteriorated during the follow-up period, the subject may have been evaluated immediately for additional teduglutide treatment. Subjects who clinically deteriorated or stopped improving at any time after the end of the follow-up period were also assessed for additional treatment eligibility.

Long-term efficacy is measured as sustained reduction in PS requirements. A reduction in PS volume of ≥20% at EOT was used as the primary endpoint in pivotal Phase 3 adult clinical trials and paediatric studies TED-C14-006 and SHP633-301 and was thus also used as an endpoint in the extension studies. Due to the flexible design of the extension studies, individual subjects had variable gaps between treatment cycles. There were also variable gaps in treatment between the core and extension studies. The baseline for assessing efficacy is last non-missing measurement taken prior to the first exposure to teduglutide. The baseline for subjects who never received teduglutide is the baseline of the respective core study.

### 2.4.1. Dose response studies

In both core and extension studies, teduglutide was dosed subcutaneously at 0.05 mg/kg/day. This dose was approved for adult use in the US and EU, and for paediatric use in the EU. A completed Phase 3 study (TED-C14-006) with teduglutide treatment of paediatric subjects with SBS resulted in clinically meaningful reductions in PS volume, calories, days per week, and hours per day, compared with the standard of care arm. A total 10% of subjects who received teduglutide achieved enteral autonomy within 24 weeks despite prior dependence on PS for several years. Teduglutide treatment also resulted in increases in enteral nutrition (EN) volume and caloric intake as well as plasma citrulline. Although the differences in efficacy between the 0.025 mg/kg/day and 0.05 mg/kg/day dose groups were small, a consistently greater effect was seen in the 0.05 mg/kg/day dose in all efficacy parameters (Kocoshis et al. 2020). A completed 12-week dose finding study (TED-C13-003) with teduglutide dosing at 0.025 mg/kg/day and 0.05 mg/kg/day showed a greater percentage of subjects achieving enteral autonomy at the 0.05 mg/kg/day dose (Carter et al. 2017). Population pharmacokinetic (PK) modeling and simulations suggested that the dose in paediatric subjects was likely to be same as the dose in adults. Further population PK and PK/pharmacodynamic (PD) modeling and simulation were performed to support the 0.05 mg/kg/day dose in paediatric subjects 4 months through <1 year.

Upon CHMP's request to justify that 0.05 mg/kg once daily is the optimal dose for infants 4 months through <1 year, the Applicant presented descriptive statistics of PK and PD parameters used in the longitudinal exposure-response analysis to determine the optimal dose (**Table 18**).

**Table 18. Descriptive statistics – Change from Baseline Prescribed PS (PN/IV) Volume in Paediatric Patients (0.05 mg/kg) by Age Groups Exposure Derived Based on PK Model**

**Model 009**

| 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] |

Longitudinal exposure-response analyses integrating data from all patients with SBS were performed to optimally assess the change from baseline diary PS (PN/IV) volume over time. As part of the model development, the effect of teduglutide AUC and $C_{max}$ were evaluated. The exposure-response model with $C_{max}$ was associated with a better goodness-of-fit relative to a model with AUC.

Descriptive statistics of PK and pharmacodynamic (PD) parameters (change from baseline prescribed PS [PN/IV] volume) in paediatric patients (0.05 mg/kg) by age groups are presented in **Table 18**.

At steady state, the median $C_{max}$ of teduglutide in the 4 months to <1 year, 1 to <6 years, 6 to <12 years, and 12 to 17 years age groups were 27.8, 31.5, 34.5 and 26.7 ng/mL, respectively. Overall, the median $C_{max}$ in median $C_{max}$ of teduglutide in the 4 months to <1 year was similar to those observed in other age groups.

At steady state, the median change from baseline PS (PN/IV) 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, -2.02, -5.76 and -8.63 L/Week, or -34%, -30%, -84% and -74%, respectively.

Based on the above results, a 0.05 mg/kg once daily dose was deemed to be the optimal dose for infants 4 months through <1 year. A dose reduction to 0.025 mg/kg would be expected to result in a 50% reduction in Cmax which would translate into a lower efficacy.

## 2.4.2. Main studies

The subject diary data were considered a more representative measure of efficacy than the prescription data; therefore, the efficacy summary focused on the subject diary data when available. The investigator prescribed data are presented when subject diary data are missing.

## Summary of Results of Individual Studies

A tabular summary of all efficacy studies is provided in **Table 19**. Narrative descriptions of the design and results of the efficacy studies are discussed below.

### Table 19. Clinical Efficacy Paediatric Studies of Teduglutide

| Study ID/ Status (CSR Module) | Number of Study Centers Location(s) | Study Start Enrollment status, date Total enrollment/ Enrollment goal | Design Control type | Study and Control Drugs Dose, Route & Regimen | Study Objectives | # Subjects by Arm Entered/ Completed | Duration | Gender (M/F) Median Age (Range) | Diagnosis Inclusion Criteria | Efficacy Endpoint(s) |
|---|---|---|---|---|---|---|---|---|---|---|
| SHP633-301/ Complete (Module 5.3.5.2) | 7 sites in Finland, France, and UK | Started: 31 Aug 2018<br>Completed: 24 Sep 2020<br>10/10 | Randomized open-label | TED: 0.05 mg/kg/day SC QD (abdomen, thigh, arm)<br>SOC | Safety, efficacy/PD, PK | TED: 5/4<br>SOC: 5/4 | 2- to 4-week screening period, 24-week treatment period, and 4-week follow-up period | 7/3<br>8.6 (5-12) months[a] | Pediatric subjects 4-12 months corrected gestational age with SBS who are dependent on PS | Change in PS and EN |
| SHP633-302/ Complete (Module 5.3.5.2) | 6 sites in Japan | Started: 13 Jan 2017<br>Completed: 21 Jan 2020<br>1-15 yrs: 8/5<br>4-<12 months[a]: 2/2 | Open-label | TED: 0.05 mg/kg/day SC QD (abdomen, thigh, upper arm) | Safety, efficacy, PD, PK | 1-15 yrs: 8/8 (6/6[b])<br>4-<12 months[a]: 2/2 | 2- to 4-week screening period, 24-week treatment period, and 4-week follow-up period | 1-15 yrs: 7/1 (5/1[b]) 5.90 (2.7-12.0) yrs<br>4-<12 months[a]: 1/1 9.95 (9.1-10.8) months[a] | Pediatric subjects 1-15 yrs and 4-<12 months (corrected gestational age) with SBS who are dependent on PS | Change in PS |
| SHP633-304/ Complete (Module 5.3.5.2) | 23 sites in US, UK, Canada, Belgium, Finland, and Italy | Started: 09 Jan2017<br>Completed: 05 Nov 2020<br>61/61 | Open-label extension | TED: 0.05 mg/kg/day SC QD (abdomen, thigh, arm) | Efficacy and safety | Overall:<br>TED/TED: 50<br>TED/NTT: 1<br>NTT/NTT: 7<br>NTT/TED: 3<br>Infants:<br>TED/TED: 4 | Multiple NTT periods and/or 28-week TED treatment cycles. Each TED treatment cycle consisted of | Overall:<br>41/20<br>5 (0-17) yrs<br>Infants:<br>4/2<br>0.6 (0-1) yr | Pediatric subjects who completed TED-C14-006[c] and SHP633-301 | Change in PS |

| Study ID/ Status (CSR Module) | Number of Study Centers Location(s) | Study Start Enrollment status, date Total enrollment/ Enrollment goal | Design Control type | Study and Control Drugs Dose, Route & Regimen | Study Objectives | # Subjects by Arm Entered/ Completed | Duration | Gender (M/F) Median Age (Range) | Diagnosis Inclusion Criteria | Efficacy Endpoint(s) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | NTT/NTT: 1<br>NTT/TED: 1 | 24 weeks of TED treatment followed by 4-week follow-up period (no treatment) | | | |
| SHP633-305/ Ongoing (Module 5.3.5.2) | 6 sites in Japan | 1-15 yrs: Started 31 Oct 2018 Interim 15 Apr 2020 7/8<br>4-<12 months[a]: Started 12 Sep 2019 Interim 14 Jul 2020 2/2 | Open-label extension | TED: 0.05 mg/kg/day SC QD (abdomen, thigh, upper arm) | Efficacy and safety | 1-15 yrs: TED 6/ongoing (5/ongoing[b]) NTT 1/ongoing (1/ongoing[b])<br>4-<12 months[a]: TED 2/ongoing NTT 0 | Multiple NTT periods and/or 28-week TED treatment cycles. Each TED treatment cycle consisted of 24 weeks of TED treatment followed by 4-week follow-up period (no treatment) | 1-15 yrs: 6/1 (5/1[b]) 5.70 (2.7-12.0) yrs (5.90 [2.7-12.0] yrs[b])<br>4-<12 months[a]: 1/1 9.95 (9.1-10.8) months[a] | Pediatric subjects who completed SHP633-302 | Change in PS |

**Table 1. Clinical Efficacy Pediatric Studies of Teduglutide**

| Study ID/ Status (CSR Module) | Number of Study Centers Location(s) | Study Start Enrollment status, date Total enrollment/ Enrollment goal | Design Control type | Study and Control Drugs Dose, Route & Regimen | Study Objectives | # Subjects by Arm Entered/ Completed | Duration | Gender (M/F) Median Age (Range) | Diagnosis Inclusion Criteria | Efficacy Endpoint(s) |
|---|---|---|---|---|---|---|---|---|---|---|

CSR=clinical study report; EN=enteral nutrition; F=female; M=male; min=minimum; NTT=no-teduglutide treatment; PD=pharmacodynamic; PK=pharmacokinetic; PS=parenteral support; QD=once daily; SC=subcutaneous; SOC=standard of care; TED=teduglutide; UK=United Kingdom; US=United States; yr=year

NTT/NTT-Subjects in the SOC arms of the core studies who never received teduglutide treatment in the prospective portions of the extension studies

NTT/TED-Subjects in the SOC arms of the core studies who then received teduglutide treatment in the prospective portions of the extension studies

TED/NTT-Subjects who received teduglutide treatment in the core studies but not in the prospective portions of the extension studies

TED/TED-Subjects who received teduglutide treatment in both the core and prospective portions of the extension studies.

[a] Corrected gestational age.

[b] Post-amendment 3 (SHP633-302 study).

[c] No pediatric subjects <1 year of age were enrolled in TED-C14-006. Section 2.1.3 presents a short summary of the study and see TED-C14-006 CSR for detailed information on the study.

***Core Studies***

## SHP633-301

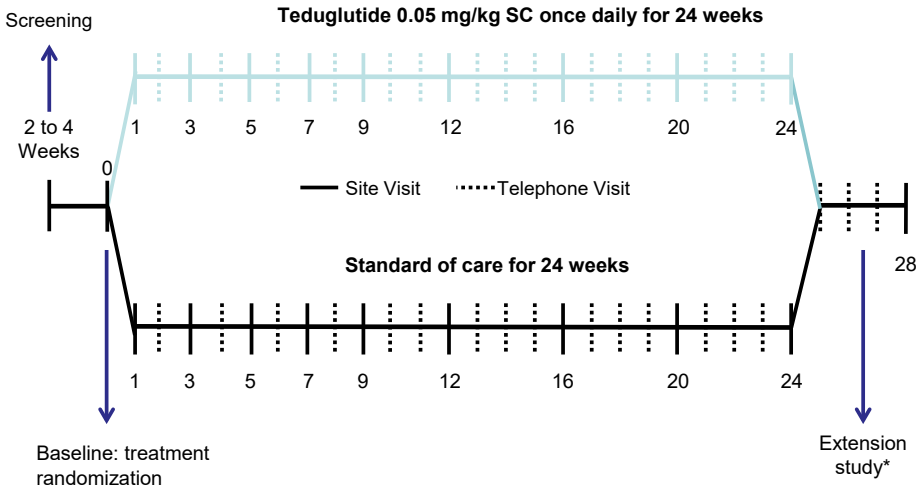
**Objectives:**

The objectives of this clinical study were to evaluate the safety, efficacy/PD and PK of teduglutide treatment in infants 4 to 12 months corrected gestational age with SBS dependent on PS.

**Methodology:**

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 (**Figure 14**). 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 treatment arm at the baseline visit (Week 0). Randomization was stratified according to the presence of a small bowel ostomy (eg, end jejunostomy or ileostomy). During the 24-week treatment period, subjects received either standard medical therapy for SBS (standard of care arm) or 0.05 mg/kg/day teduglutide subcutaneously in addition to standard medical therapy (teduglutide treatment arm). In both treatment arms, SOC therapy in the form of parenteral support is administered. To maintain consistency across centres, guidance and training was 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.

**Figure 14. 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.

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 centres, 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 PK analysis were collected in the teduglutide treatment arm at baseline (pre-dose, and 1 hour and 4 hours post-dose) and at Week 7 (2 hours post-dose).

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 may have proceeded immediately to the EOS visit if at least 1 "escape" criteria was met.

## Results

*Disposition*

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 standard of care 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 adverse events were caused by the study drug; teduglutide treatment never resumed and the subject completed the study.

*Demographic and baseline characteristics*

The mean corrected gestational age was 8.4±2.71 months. All but 1 subject in the teduglutide arm and 2 subjects in the standard of care 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 1 subject in the standard of care arm had baseline weight and weight/length ratio Z-scores of -2.8 and -2.2, respectively.

The main underlying causes of SBS were gastroschisis and necrotizing enterocolitis. One subject in the standard of care arm had a colostomy. All subjects had at least some remaining colon and the mean percentage 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*

Efficacy/PD analyses of PS and 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 and Change from Baseline in Parenteral Support Volume

The primary efficacy endpoint is the reduction in weight-normalized PS volume of ≥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 standard of care arm experienced ≥20% reduction in PS volume at EOT from baseline (2 subjects in the standard of care arm had missing data). Based on prescribed data, 3 (60.0%) subjects enrolled in each treatment arm experienced ≥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 standard of care 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 standard of care 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%.

Two patients between 4 and 6 months of age at baseline were enrolled in study SHP633-301. Rich measurements of prescribed PS (PN/IV) volume were collected over approximately 6 months in Longitudinal profiles of change from baseline prescribed PS in the 2 patients between 4 and 6 months of age who received 0.05 mg/kg QD are presented in **Figure 15**.

**Figure 15. Longitudinal Profiles of Change from Baseline Prescribed PS in Study SHP633-301 - Infants Between 4 and 6 Months**

Both infants between 4 and <6 months of age treated with 0.05 mg/kg QD had a marked reduction of prescribed PS (PN/IV) volume in study SHP633-301.

Moreover, both infants between 4 to <6 months of age treated with 0.05 mg/kg QD had similar $C_{max}$ values as those observed in infants between 6 months and <1 year.

In addition, longitudinal exposure-response analyses confirmed that the disease and its' manifestations are similar across age groups since infants (4 months to < 1 year) responded to teduglutide in a similar manner as paediatric patients (1 to 11 years).

As described in the exposure-response report, at Week 24, the median change from baseline PS (PN/IV) 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, -1.01, -2.88, and -4.31 L/Week, or -17%, -15%, -42% and -37%, respectively.

At steady state, the change from baseline PS (PN/IV) 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, -2.02, -5.76 and -8.63 L/Week, or -34%, -30%, -84% and -74%, respectively.

Reduction and Change from Baseline in Parenteral Support Caloric Intake

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

C Complete Weaning off Parenteral Support

No subject achieved enteral autonomy.

Change from Baseline in Enteral Nutrition Volume

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 standard of care arm experienced ≥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 standard of care 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 standard of care arm experienced ≥20% increase in EN volume at EOT from baseline (4 and 1 subjects had missing data in the teduglutide and standard of care 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 standard of care 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%.

Change from Baseline in Enteral Nutrition Caloric Intake

Based on subject diary data, 2 (40.0%) subjects enrolled in the teduglutide treatment arm and no subject in the standard of care arm experienced ≥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 standard of care 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%) subjects in the standard of care arm experienced ≥20% increase in EN caloric intake at EOT from baseline (4 and 1 subjects had missing data in the teduglutide and standard of care 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 standard of care 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%.

Change from Baseline in Days per Week and Hours per Day in Parenteral Support Usage

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 standard of care arm. There was no change in mean daily PS observed at EOT from baseline in the standard of care 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 standard of care 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%.

## SHP633-302

**Objectives:**

The objective of this clinical study was to evaluate the safety, tolerability, efficacy and PD and PK of teduglutide in paediatric subjects (4 months through 15 years of age) with SBS who are dependent on PS.

**Methodology:**

SHP633-302 was an open-label study consisting of a 2-week screening period and a 24-week treatment period in which subjects received 0.05 mg/kg/day of teduglutide (**Figure 16**). The study consisted of 2 cohorts: infants 4 through <12 months corrected gestational age and children 1 through 15 years of age.

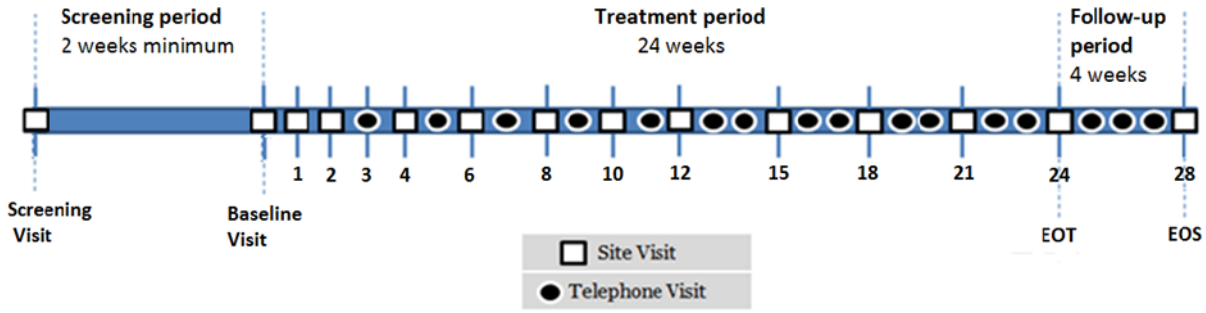
All subjects were screened for a minimum of 2 weeks prior to start of treatment to verify the requirements for nutritional support for each subject and to ensure adherence to eligibility parameters.

After screening, subjects eligible for the study progressed to the 24-week treatment period, during which all subjects received teduglutide 0.05 mg/kg subcutaneously once daily. At each site visit during the treatment phase, efficacy (adjustments to PS) and safety were monitored.

Subjects had blood samples taken for teduglutide PK analysis at pre-dose, and at 1- and 6-hours post-dose at the baseline visit. Subjects also had blood samples taken for teduglutide PK analysis at pre-dose, 2- and 4-hours post-dose at Week 4.

All subjects who completed the study could participate in a long-term extension study, SHP633-305, in which eligible subjects would continue to receive teduglutide. Subjects who were not enrolled in the treatment extension study or who discontinued prematurely at any time during the study participated in a follow-up visit 4 weeks (Week 28) after the last dose.

**Figure 16. SHP633-302 Study Schematic**




EOS=end of study; EOT=end of treatment

**Results**

*Disposition*

Two Japanese infants 4 months through <1 year corrected gestational age were enrolled after protocol amendment 3 and received teduglutide. Both infants completed a 28-week study.

*Demographic and baseline characteristics*

In the infants, the mean corrected gestation age was 10.0±1.20 months, with 1 infant of each sex.

In infants, the mean duration of SBS was 10.7±1.93 months. The main underlying cause of SBS was midgut volvulus for 1 infant and congenital absence of midgut for the other. Neither infant had a stoma. The mean remaining small intestine was 6.0±5.66 cm. Both infants had some remaining colon with a mean percentage of 75.0±35.36%. One infant had a distal or terminal ileum and had the ileocecal valve.

*Efficacy*

Analyses on weekly PS and EN volume, and caloric intake were based on 2 data sources: the subject diary data and the investigator prescribed data. The diary weekly PS and EN volume and caloric intake were calculated based on the daily volumes recorded in subjects' diaries within 7 days prior to each scheduled visit ("diary" is referred to as "actual" in the CSR source tables, figures, and listings). Investigator-prescribed data were captured from eCRFs. Generally, no remarkable discrepancy between the diary and prescribed-based data was found in efficacy endpoints. The subject diary data was considered a more representative measure of efficacy than the investigator prescribed data; therefore, the efficacy summary focuses on the subject diary data results.

Because the ancillary kits and subject training process implemented with Amendment 3 were designed to represent the planned commercial configuration and training methodology, the efficacy analysis focuses on data from children who enrolled after Protocol Amendment 3.

Reduction in Parenteral Support Volume

In infants, a ≥20% reduction in PS volume was recorded in 1 infant during the teduglutide treatment.

Change from Baseline in Parenteral Support Volume

Clinically meaningful reductions in PS volume were observed in 1 of the 2 infants. The mean change in PS volume at EOT was -26.2±13.61 mL/kg/day from the baseline value of 99.7±5.56 mL/kg/day, corresponding to a mean percentage change of -26.7±15.14%.

In infants, PS volume decreased during the 4-week follow-up period. The change of PS volume at EOS from EOT was -3.8±0.67 mL/kg/day, corresponding to a mean percentage change of -5.5±2.35%.

Change from Baseline in Parenteral Support Caloric Intake

Overall, the change in PS caloric intake was similar to that of PS volume for both post-amendment children and infants.

In infants, the mean PS caloric intake at baseline was 53.4±6.68 kcal/kg/day. The mean change in PS caloric intake at EOT from baseline was -13.8±3.17 kcal/kg/day, corresponding to a mean percentage change of -25.7±2.73%.

In infants, PS caloric intake decreased during follow-up period. The mean change in PS caloric intake at EOS from EOT was -4.0±1.38 kcal/kg/day, corresponding to a mean percentage change of -10.3±4.40%.

Complete Weaning off Parenteral Support

No infant subjects reached complete weaning.

Change from Baseline in Days per Week in Parenteral Support Usage

In infants, the number of days per week in PS usage was not reduced; they required PS 7 days/week both at baseline and EOT.

Change from Baseline in Hours per Day in Parenteral Support Usage

There was no change in daily PS usage hours in the 2 infants during the study.

Change from Baseline in Enteral Nutrition Volume and Caloric Intake

For the purpose of this study, EN was defined as specialized formula, and did not include table foods. In infants, the EN volume was essentially unchanged. In infants, the EN calories were essentially unchanged.

**Extension Studies**

## SHP633-304

**Objectives**

The objectives of this clinical study were to evaluate the long-term safety and efficacy of teduglutide treatment in paediatric subjects with SBS who completed TED-C14-006 (not discussed in efficacy section since not including infants below 12 months) or SHP633-301.

**Methodology**

**SHP633-304** was a Phase 3, prospective, open-label, long-term extension study to evaluate the safety and efficacy of teduglutide in paediatric subjects, including infants, with SBS who completed their core study, TED-C14-006 or SHP633-301, and who were dependent on PS. Children enrolled in TED-C14-006 were 1 through 17 years of age (no infants were enrolled); infants enrolled in SHP633-301 were 4 months to <1 year corrected gestational age. This extension study evaluated the long-term safety and durability of efficacy in subjects who had received 24 weeks of teduglutide treatment in their core study, as well as the need for additional teduglutide treatment in those subjects, and allowed for first-time treatment of teduglutide-naïve subjects who had participated in the standard of care arm in their core study (**Figure 17**)

For subjects who received teduglutide, clinic visits were to occur at Weeks 1, 2, 4, 6, 9, 12, 16, 20, 24, and 28. Subjects not receiving teduglutide treatment (ie, during a no-teduglutide treatment [NTT] period) were to be seen approximately every 12 weeks. Phone visits were to occur as needed following any adjustment in PS. Safety, efficacy, and quality of life data were collected throughout the study.

**Figure 17. SHP633-304 Study Schematic**

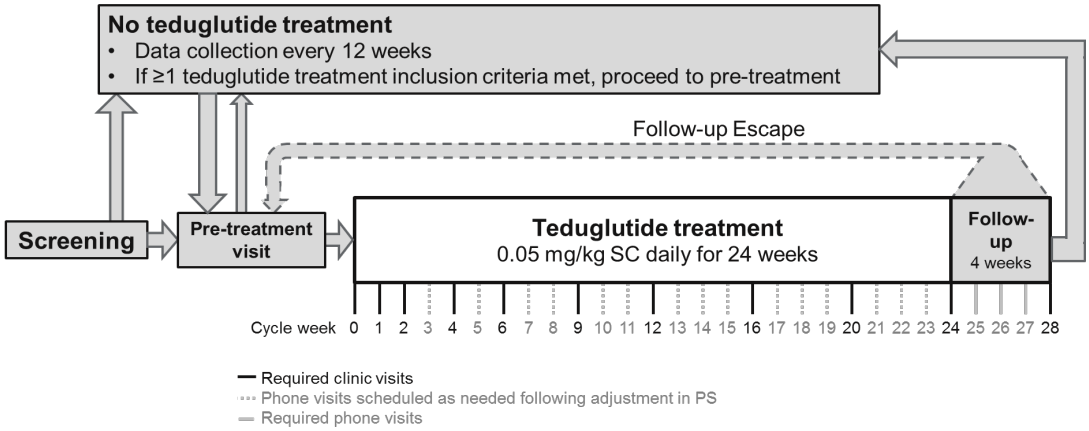



Figure legend: Safety and efficacy data for subjects not receiving teduglutide treatment were captured approximately every 12 weeks, but subjects could proceed to a pretreatment visit at any time to assess eligibility for teduglutide therapy. Eligible subjects entered a 28-week teduglutide cycle. During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

**Results**

In SHP633-304, subject data were analyzed by treatment and treatment cycle for the core study and the extension study. Specifically, subjects enrolled in this extension study were classified into treatment groups based on whether they received teduglutide in their core study and/or during this extension study at the time of analysis:

- NTT/NTT: Subjects in the standard of care arms of the core study who never received teduglutide treatment in the prospective portions of the extension study.
- NTT/TED: Subjects in the standard of care arm of the core study who then received teduglutide treatment in the prospective portions of the extension study.
- TED/NTT: Subjects who received teduglutide treatment in the core study but not in the prospective portions of the extension study.

- TED/TED: Subjects who received teduglutide treatment in both the core study and prospective portion of the extension study.
- ANY TED: Subjects who received teduglutide treatment in either their core study or the extension study.

In addition to the planned analyses, an analysis was conducted of a subset of subjects enrolled from the SHP633-301 core study (infant subjects). The disposition, demographic and baseline characteristics, and efficacy results of the infant subset analysis are presented in this Summary of Clinical Efficacy along the results from the planned analyses. The infant subset efficacy tables present results for the TED/TED and NTT/TED treatment groups.

**Disposition**

*Overall*

A total of 61 subjects, children 1 to 18 years of age at core Study TED-C14-006 baseline and infants 4 months to <1 year of age at core Study SHP633-301 baseline participated in SHP633-304 from 23 sites in the United States, Belgium, Canada, the United Kingdom, Finland, and Italy.

Most subjects (77.0%) completed the study. Overall, 19 subjects (31.1%) discontinued treatment early due to adverse events (3 subjects), physician decision (3 subjects), withdrawal by parent/guardian (1 subject), lost to follow-up (1 subject), and transition to commercial product (11 subjects); all were in the TED/TED group. Fourteen subjects (23.0%) discontinued from the study early.

*Infant Subset*

Six infant subjects 4 months to <1 year of age at core Study SHP633-301 baseline enrolled in SHP633-304. Of these, 5 (83.3%) subjects completed the study (SHP633-304 CSR) and 1 subject in the TED/TED group discontinued treatment and from the study due to adverse events. Of the 5 infant subjects who received teduglutide during the study, 4 had received teduglutide in the core study. One infant subject enrolled in the NTT/NTT group.

**Demographic and baseline characteristics**

*Overall*

The mean age at core study baseline of all subjects who received any teduglutide (ANY TED group) was 5.5±3.86 years, and the majority of subjects were in the 1 to less than 12 years age group (83.6%).

The majority of subjects were male (41/61 [67.2%]), white (42/61[68.9%]), and not Hispanic or Latino (40/61 [65.6%]. Baseline growth parameters for the ANY TED group showed below average weight and height, but the mean BMI Z-score was near 0, suggesting that some subjects were stunted due to chronic nutritional deficiency or illness.

In the ANY TED group, the mean small intestine length was 41.8±33.13 cm. A total of 92.6% (50/54) of subjects had at least some remaining colon, and the estimated mean percentage of colon remaining was 63.2±31.90%. For the NTT/NTT group, the mean small intestine length was 39.1±32.13 cm. All subjects had at least some remaining colon, and the estimated percent of colon remaining was 54.6±34.13%.

*Infant Subset*

The mean age at core study baseline of the 5 infant subjects in the ANY TED group was 0.6±0.21 years. The majority of infant subjects enrolled in the study were male (4/6 subjects), white (5/6 subjects), and not Hispanic or Latino (6/6 subjects); 1 infant subject was Asian (NTT/TED group). Baseline growth parameters for infants in the ANY TED group showed below average mean weight, height, and BMI Z-scores, suggesting that some subjects were stunted due to chronic nutritional deficiency or illness.

**Efficacy**

Overall, of the 61 subjects enrolled in the study, 50 were classified in the TED/TED group. Of these, all 50 subjects received teduglutide treatment in Cycle 1, 41 in Cycle 2, 33 in Cycle 3, 27 in Cycle 4, 20 in Cycle 5, and 3 in Cycle 6 (SHP633-304 CSR). Of the 7 subjects in the NTT/NTT group, 5 entered the NT1 through NT3 visits, 4 entered NT4 and NT5, 5 entered NT6 through NT9, and 1 entered NT10 through NT14 (SHP633-304 CSR).

Overall efficacy data from all cycles are presented in the CSR appendix tables. However, since Cycle 4 marks the end of 2 years of dosing in this study, the Cycle 1 Day 1 (or Cycle 1 EOT) and Cycle 4 Week 24/EOT results are preferentially reported for subjects in the TED/TED group in the text discussions of clinical efficacy results. Correspondingly for the NTT/NTT group, data at interval Visit 8 (NT8) is described in detail as a comparison. Baseline is defined as the core study baseline for subjects in the NTT/NTT, TED/NTT, and TED/TED groups and as the extension study baseline for the NTT/TED group; diary data are presented.

Efficacy data in the infant subset are presented for the NTT/TED and TED/TED groups, 1 subject and 4 subjects, respectively. All infant subjects treated received teduglutide treatment Cycle 1 except 1 subject in the TED/TED group who discontinued treatment and from the study at Cycle 1 Week 14. In the TED/TED group, 3 of the 4 infant subjects had missing diary data at Cycle 1 Day 1 and EOT while all 4 infant subjects had prescribed data; therefore, reductions in PS volume and mean changes from baseline in PS volume are presented for diary and prescription data.

Reduction and Change from Baseline in Parenteral Support Volume

*Overall*

Overall, clinically meaningful reductions in PS volume were achieved in the TED/TED group, whereas less change was observed in the NTT/NTT group.

For the TED/TED group, 23/50 (46.0%) subjects at Cycle 1 Day 1 and 20/27 (74.1%) subjects at cycle 4 EOT achieved ≥20% reduction from core study baseline in PS volume. For the NTT/NTT group, 1/6 (16.7%) subjects at NT1 and 2/5 (40.0%) subjects at NT8 achieved ≥20% reduction from core study baseline in PS volume.

For the TED/TED group, the mean change in diary PS volume at Cycle 1 Day 1 from core study baseline was -19.36±18.343 mL/kg/day (-35.22±31.724%); at Cycle 4 EOT the reduction was -32.61±24.639 mL/kg/day (-51.28±36.364%). For the NTT/NTT group, the mean change at Visit 1 (NT1) from core study baseline was -5.48±7.277 mL/kg/day (-13.08±21.323%); at NT8, the reduction was -13.04±13.280 mL/kg/day (-28.35±41.860%).

Overall, the mean reduction in PS volume increased progressively over teduglutide treatment cycles in the TED/TED group, while the untreated NTT/NTT group had less mean reduction of PS volume over time than the TED/TED group.

*Infant Subset*

Reductions in PS volume and mean changes from baseline in PS volume in infant subjects are presented for diary and prescription data.

Infant subjects experienced reductions in diary or prescribed PS volume during teduglutide treatment Cycle 1 in addition to the efficacy achievement following teduglutide treatment in the core studies.

Three (75.0%) infant subjects in the TED/TED group had missing diary data at Cycle 1 Day 1 and Cycle 1 EOT. Of the infant subjects in the TED/TED group, 1 (25.0%) subject at Cycle 1 Day 1 and no subject at Cycle 1 EOT achieved ≥20% reduction from core study baseline in PS volume based on diary data. The infant subject in the NTT/TED group did not achieve ≥20% reduction from baseline in PS volume at Cycle 1 EOT based on diary data.

Only 2 infant subjects, one in each treatment group, had diary PS volume recorded at Cycle 1 Day 1 and Cycle 1 EOT.

In the TED/TED group, the change in diary PS volume from core study baseline was -57.58 mL/kg/day (-39.28%) at Cycle 1 Day 1 and -28.94 mL/kg/day (-19.74%) at Cycle 1 EOT.

In the NTT/TED group, the change in diary PS volume from baseline was -10.15 mL/kg/day (-15.58%) at Cycle 1 EOT.

For 4 infant subjects in the TED/TED group based on prescribed data, 1 (25.0%) subject at Cycle 1 Day 1 and 3 (75.0%) subjects at Cycle 1 EOT achieved ≥20% reduction from core study baseline in PS volume. The infant subject in the NTT/TED group did not achieve ≥20% reduction from baseline in prescribed PS volume at Cycle 1 EOT.

For 4 infant subjects in the TED/TED group, the mean change in prescribed PS volume from core study baseline was -5.65±29.345 mL/kg/day (-10.34±52.091%) at Cycle 1 Day 1 and -19.98±34.998 mL/kg/day (-20.81±51.829%) at Cycle 1 EOT. For the infant subject in the NTT/TED group, the change in prescribed PS volume at Cycle 1 EOT from baseline was -10.26 mL/kg/day (-15.49%).

Two infant subjects, one in each treatment group, had a change in diary PS volume from baseline recorded at Cycle 2 and Cycle 3 EOT. Results show continuing reductions in PS volume from baseline in subjects receiving multiple additional teduglutide treatment cycles.

In the TED/TED group, the change in diary PS volume from core study baseline was -69.00 mL/kg/day (-47.07%) at Cycle 2 EOT and -107.54 mL/kg/day (-73.36%) at Cycle 3 EOT.

In the NTT/TED group, the change in diary PS volume from baseline was -16.40 mL/kg/day (-25.18%) at Cycle 2 EOT and -23.98 mL/kg/day (-36.82%) at Cycle 3 EOT.

Three infant subjects (2 in the TED/TED and 1 in the NTT/TED groups) and 2 infant subjects (one in each treatment group) had a change in prescribed PS volume from baseline recorded at Cycle 2 EOT and Cycle 3 EOT, respectively.

In the TED/TED group, the change in prescribed PS volume from core study baseline was -21.31±69.428 mL/kg/day (-2.91±64.214%) at Cycle 2 EOT and -87.14 mL/kg/day (-59.80%) at Cycle 3 EOT.

In the NTT/TED group, the change in prescribed PS volume from baseline was -56.95 mL/kg/day (-85.97%) at Cycle 2 EOT and -55.97 mL/kg/day (-84.50%) at Cycle 3 EOT.

Change from Baseline in Parenteral Support Caloric Intake

*Overall*

Similar to the change in PS volume, clinically meaningful reductions in PS caloric intake were achieved in the TED/TED group, whereas less change was observed in the NTT/NTT group.

For the TED/TED group, the mean change in PS caloric intake at Cycle 1 Day 1 from core study baseline was -15.90±12.556 kcal/kg/day (-39.62±31.155%); that at Cycle 4 EOT was -24.67±18.859 kcal/kg/day (-53.23±37.611%). For the NTT/NTT group, the mean change in PS caloric intake at NT1 from core study baseline was 0.28±6.193 kcal/kg/day (0.15±23.888%); at NT8, the reduction was -12.32±9.542 kcal/kg/day (-32.06±38.806%).

*Infant Subset*

The changes in weekly PS caloric intake from baseline based on subject diary and prescribed data for infant subjects are presented in SHP633-304 CSR, respectively.

Consistent with that observed with PS volume, reductions in PS caloric intake from baseline observed during treatment Cycle 1 in SHP633-304 are consistent with findings in the core studies (NTT/TED group) and show a continuing effect in subjects receiving additional teduglutide treatment (TED/TED group).

Only 2 infant subjects (one in each treatment group) had diary PS caloric intake recorded at Cycle 1 Day 1 and Cycle 1 EOT:

In the TED/TED group, the change in diary PS caloric intake from core study baseline was -28.10 kcal/kg/day (-39.24%) at Cycle 1 Day 1 and -4.66 kcal/kg/day (-6.50%) at Cycle 1 EOT.

In the NTT/TED group, the change in diary PS caloric intake from baseline was -0.40 kcal/kg/day (-0.53%) at Cycle 1 EOT.

For 4 infant subjects in the TED/TED group, the mean change in prescribed PS caloric intake from core study baseline was -0.60±31.625 kcal/kg/day (-2.18±61.662%) at Cycle 1 Day 1 and -4.59±35.205 kcal/kg/day (-7.17±66.995%) at Cycle 1 EOT. For the infant subject in the NTT/TED group, the change in prescribed PS caloric intake from baseline was -0.20 kcal/kg/day (-0.26%) at Cycle 1 EOT.

Two infant subjects, one in each treatment group, had change in diary PS caloric intake from baseline recorded at Cycle 2 and Cycle 3 EOT. Results show continuing reductions in PS caloric intake from baseline in subjects receiving multiple additional teduglutide treatment cycles.

In the TED/TED group, the change in diary PS caloric intake from core study baseline was -27.48 kcal/kg/day (-38.37%) at Cycle 2 EOT and -44.45 kcal/kg/day (-62.06%) at Cycle 3 EOT.

In the NTT/TED group, the change in diary PS caloric intake from baseline was -10.48 kcal/kg/day (-13.81%) at Cycle 2 EOT and -20.91 kcal/kg/day (-27.56%) at Cycle 3 EOT.

Three infant subjects (2 in the TED/TED and 1 in the NTT/TED groups) and 2 infant subjects (one in each treatment group) had a change in prescribed PS caloric intake from baseline recorded at Cycle 2 EOT and Cycle 3 EOT, respectively.

In the TED/TED group, the mean change in prescribed PS caloric intake from core study baseline was 6.40±49.143 kcal/kg/day (18.36±82.269%) at Cycle 2 EOT and -30.44 kcal/kg/day (-42.75%) at Cycle 3 EOT.

In the NTT/TED group, the change in prescribed PS caloric intake from baseline was -64.78 kcal/kg/day (-83.90%) at Cycle 2 EOT and -63.48 kcal/kg/day (-82.21%) at Cycle 3 EOT.

Complete Weaning off Parenteral Support

No infant subjects achieved enteral autonomy at any time during the study.

Change from Baseline in Hours per Day and Days per Week in Parenteral Support Usage

*Overall*

Teduglutide treatment was associated with clinically meaningful reductions in PS infusion days hours per day and days per week, whereas less change was observed in the NTT/NTT group.

For the TED/TED group, the mean change in PS from core study baseline at Cycle 1 Day 1 was -2.53±3.070 hours/day (-24.14±35.951%) and -1.05±1.897 days/week (-18.44±33.726%); at Cycle 4 EOT, the mean change was -4.83±5.069 hours/day (-40.68±42.255%) and -2.36±2.956 days/week (-34.66±44.475%).

For the NTT/NTT group, the mean change in PS from core study baseline at NT1 was -0.23±0.329 hours/day (-3.31±4.527%) and 0 days/week (0%); at NT8, the mean change was -0.77±2.645 hours/day (-17.64±47.200%) and -0.60±1.342 days/week, (-20.00±44.721%).

An examination of the relationship between reduction in PS volume and reduction in hours per day of PS in the TED/TED group showed that mean PS volume reductions of ≥20%, ≥50%, and ≥75% at Cycle 4 EOT corresponded with mean reductions of -5.49±5.413 hours/day (-47.23 ±44.573%), -7.24±5.719 hours/day (-64.73±45.682%), and -10.73±1.928 hours/day (-95.92±10.799%), respectively. Mean PS volume reductions of ≥20%, ≥50%, and ≥75% at Cycle 4 EOT also corresponded with mean reductions of -2.95±3.034 days/week (-43.32±45.863%), -4.61±2.369 days/week (-68.63±34.722%), and -6.43±0.976 days/week (-95.92±10.799%), respectively.

*Infant Subset*

The changes in weekly PS from baseline in hours per day and days per week are presented based on subject diary data in SHP633-304 CSR and based on prescribed data in SHP633-304 CSR.

Only 2 infant subjects (one in each treatment group) had diary PS infusion time recorded at Cycle 1 Day 1 and Cycle 1 EOT:

In the TED/TED group, the change in diary PS infusion time from core study baseline at Cycle 1 Day 1 was -4.80 hours/day (-40.00%) and -2.80 days/week (-40.00%); no change from core study baseline was observed at Cycle 1 EOT.

In the NTT/TED group, the change in diary PS infusion time from baseline at Cycle 1 EOT was -1.71 hours/day (-14.29%) and -1.00 days/week (-14.29%).

For the 4 infant subjects in the TED/TED group, the mean change in prescribed PS infusion time from core study baseline at Cycle 1 Day 1 was -0.13±0.250 hours/day (-1.19±2.381%) and -2.25±2.062 days/week (-35.00±29.543%); at Cycle 1 EOT, the mean change was -0.13±0.250 hours/day (-1.19±2.381%) and -2.00±2.160 days/week (-30.00±30.102%). For the infant subject in the NTT/TED group, the change in prescribed PS infusion time from baseline at Cycle 1 EOT was 0 hours/day and -1.00 days/week (-14.29%).

Two infant subjects, one in each treatment group, had changes in diary PS infusion time from baseline in days per week recorded at Cycle 2 and Cycle 3 EOT. Results show continuing reductions in diary PS from baseline in days per week in subjects receiving multiple additional teduglutide treatment cycles.

In the TED/TED group, the change in diary PS infusion time from core study baseline in days per week was 0 days/week at Cycle 2 EOT and -2.33 days/week (-33.33%) at Cycle 3 EOT.

In the NTT/TED group, the change in diary PS infusion time from baseline in days per week was -2.00 days/week (-28.57%) at Cycle 2 EOT and -3.00 days/week (-42.86%) at Cycle 3 EOT.

Three infant subjects (2 in the TED/TED and 1 in the NTT/TED groups) and 2 infant subjects (one in each treatment group) had a change in prescribed PS infusion time from baseline in days per week recorded at Cycle 2 EOT and Cycle 3 EOT, respectively. Results show continuing reductions in prescribed PS from baseline in days per week in subjects receiving multiple additional teduglutide treatment cycles.

In the TED/TED group, the change in prescribed PS infusion time from baseline in days per week was -0.50±0.707 days/week (-10.00±14.142%) at Cycle 2 EOT and -2.00 days/week (-28.57%) at Cycle 3 EOT.

In the NTT/TED group, the change in prescribed PS infusion time from baseline in days per week was -2.00 days/week (-28.57%) at Cycle 2 EOT and -3.00 days/week (-42.86%) at Cycle 3 EOT.

Quality of Life Findings

From parent reports, the Paediatric Quality of Life Generic Core Scale (PedsQL) Generic Core Subscale Scores total score and the PedsQL Gastrointestinal Symptoms Module diarrhea subscale score showed improvement (positive changes) from baseline to Cycle 4 EOT for the teduglutide treatment (TED/TED) group compared with slight decreases in scores from baseline to NT8 for the no teduglutide NTT group. Self-reported data showed improvement in the PedsQL Gastrointestinal Symptoms Module food and drink limits subscale score for the TED/TED group compared with the NTT/NTT group. Self-reported data also showed improvement in the total score for the TED/TED group, however similar improvement was shown in the NTT/NTT group.

PedsQL Generic Core Subscale Scores total score and the PedsQL Gastrointestinal Symptoms Module diarrhea subscale score were not included in the infant subset analysis.

**SHP633-305**

SHP633-305 is ongoing and the data cutoff date for the interim CSR is 15 April 2020 (paediatric subjects 1 to 15 years of age) and 14 Jul 2020 (paediatric subjects 4 months to <1 year corrected gestational age). Interim data included at least 6 months of treatment for 7 paediatric subjects 1 to 15 years (children cohort) and 2 paediatric subjects from 4 months to <1 year (infant cohort).

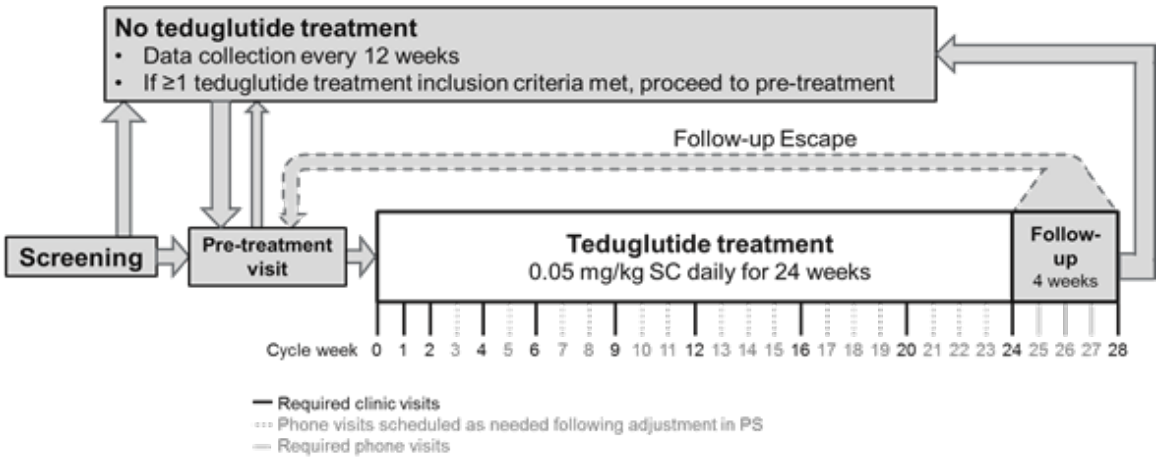
**Objectives**

The objectives of this clinical study were to evaluate the long-term safety and efficacy of teduglutide treatment in Japanese paediatric subjects with SBS who completed SHP633-302. This narrative summary only addresses the efficacy objective.

**Methodology**

SHP633-305 is a Phase 3, prospective, open-label, long-term extension study to evaluate the safety and efficacy of teduglutide in Japanese paediatric subjects who completed the core study SHP633-302. Eligibility for teduglutide treatment was assessed separately. Subjects might participate in multiple NTT periods and/or multiple 28-week teduglutide treatment cycles depending on the disease course (**Figure 18**). Subjects not receiving teduglutide treatment (ie, in an NTT period), are seen every 12 weeks. Subjects who meet ≥1 of the teduglutide treatment inclusion at any point after screening, including during an NTT period, start a 28-week cycle, consisting of 24 weeks of teduglutide treatment at 0.05 mg/kg SC once daily, followed by a 4-week follow-up (no treatment) period. At all site visits and telephone contacts, safety is monitored, and nutritional support is reviewed and adjusted as needed.

**Figure 18. SHP633-305 Study Schematic**




PS=parenteral support; SC=subcutaneous Safety and efficacy data for subjects not receiving teduglutide treatment are captured approximately every 12 weeks, but subjects may proceed to the pretreatment visit at any time in order to assess eligibility for teduglutide therapy. Subjects eligible for teduglutide will enter a 28-week treatment cycle. During this cycle, subjects will return to the site for safety and efficacy assessments at Day 1 (Week 0) and Weeks 1, 2, 4, 6, 9, 12, 16, 20, 24, and 28 (**solid black lines**). Phone visits are required approximately 1 week after adjustments in PS during the intervening weeks between Weeks 2 and 24 (**dashed grey lines**). At Week 24, subjects enter a 4-week follow-up period, where teduglutide is not received, during which phone visits will be performed weekly (**solid grey lines**). If at least 1 escape criterion is met at Week 24 or during the follow-up period, subjects may proceed directly to another pretreatment visit.

**Results**

*Disposition*

At the time of data cutoff, 7 children and 2 infants were enrolled and all received teduglutide in the core study (SHP633-302) and this extension study. Changes to the ancillary kits used to prepare and administer teduglutide, including the introduction of a vial adaptor, a process for training the parents/guardians, and measures to provide oversight of teduglutide administration were implemented in the core study SHP633-302 by protocol amendment 3 to provide assurance that all children were receiving prescribed and properly administered doses of teduglutide. Of 7 children enrolled, 1 child was

enrolled pre-amendment in the core study. Both infants were enrolled after the amendment. The efficacy results for the 6 post-amendment children were judged preferentially and are presented here; the safety analysis included all subjects regardless of the amendment under which they were enrolled.

Of the 9 subjects enrolled, 1 child participated in the study but selected not to receive teduglutide treatment due to ongoing enteral autonomy. The remaining 8 treated subjects, 6 children and 2 infants, had at least 24 weeks of treatment in this extension study. At the time of data cutoff, no subjects had discontinued; however, just after data cutoff, 1 infant subject discontinued from the study due to the risk of severe acute pancreatitis. Therefore, this discontinuation is not reflected in the interim data results.

*Demographic and baseline characteristics*

The mean corrected gestational age of the infant cohort enrolled at the beginning of the core study was 9.95±1.202 months, with one infant of each sex.

Baseline growth parameters both in post-amendment children and infants showed low weight, height, and BMI for age Z-score, suggesting that these subjects were stunted due to chronic illness or nutritional deficiency.

In the 2 infants, the mean duration of SBS was 10.66±1.928 months (approximately since birth). The main underlying cause of SBS was midgut volvulus for 1 infant and congenital absence of the midgut for the other. Neither infant had a stoma. The mean remaining small intestine was 6.00±5.657 cm. One infant had 50% of the colon remaining, and the other had 100%. One infant had a distal or terminal ileum and retained an ileocecal valve.

*Efficacy*

Clinically significant reductions in PS volume were observed during the 24-week treatment periods.

In the 5 post-amendment children, 2 (40.0%) subjects were recorded at Day 1 (initiation of this study) in the diary and prescribed data who achieved ≥20% reduction (compared with baseline in the core study) in weight-normalized PS volume and increased to 3 (60.0%) subjects in diary data and 4 (80.0%) subjects in prescribed data at the end of Cycle 1 as the visits progressed. These subjects maintained their status during the 4-week untreated follow-up period.

In post-amendment children, the mean diary PS volume at core study baseline was 52.9±26.97 mL/kg/day. The mean percentage change from baseline at EOT of each cycle was -42.1±38.37% for Cycle 1, -56.4±31.84% for Cycle 2, and -46.7% for Cycle 3, suggesting durability of efficacy across cycles; note that n=6 at baseline, n=5 at EOT of Cycle 1, n=4 at EOT of Cycle 2, n=1 at EOT of Cycle 3. The Week 28 mean change from baseline for Cycle 1 of -39.8% suggests that the percentage reduction was mostly maintained during the 4-week untreated follow-up period from EOT to Week 28.

In the 2 infants, both subjects (100%) achieved ≥20% reduction from core study baseline in weight-normalized PS volume in diary data at Cycle 1 Day 1 and 1 (50.0%) subject in prescribed data, and ≥20% reduction was maintained to Cycle 1 EOT by 1 infant in the diary and prescribed data.

In infants, the mean diary PS volume at core study baseline was 99.7±5.56 mL/kg/day. The mean change from baseline at EOT of Cycle 1 was -31.9±16.24 mL/kg/day (median=-31.9 mL/kg/day) or -32.5±18.10% (median=-32.5%).

In post-amendment children, the mean PS infusion days per week at core study baseline was 7.0 day/week. The mean percentage change from baseline at EOT of each cycle was -20.0±44.72% for

Cycle 1, -25.0±50.0% for Cycle 2; note that n=6 at baseline, n=5 at EOT of Cycle 1, n=4 at EOT of Cycle 2. In infants, the number of days per week in PS usage was not reduced; they required PS 7 days/week both at baseline and throughout the study.

There were 2 subjects in the children cohort that achieved enteral autonomy: 1 subject achieved enteral autonomy at Cycle 1 Week 4, which was sustained through Cycle 2 Week 12, while 1 subject achieved enteral autonomy at Week 12 in the core study, chose not to receive teduglutide in this extension study due to ongoing enteral autonomy, and maintained enteral autonomy during NTT periods. While both infants achieved the milestone of ≥20% reduction in PS volume, neither achieved enteral autonomy.

## *Analysis performed across trials (pooled analyses and meta-analysis)*

**Comparison and Analyses of Results Across Studies**

Due to differences in design among the paediatric studies, including differences in duration of treatment and intervals between treatments, the efficacy results from individual studies are presented side by side to support the effectiveness of teduglutide in infant subjects with SBS. The results are presented in this section by core studies (SHP633-301 and SHP633-302) and extension studies (SHP633-304 and SPH633-305).

**Core Studies**

**Subject Disposition, Demographics, and Baseline Characteristics**

**Subject Disposition**

The disposition of infant subjects in SHP633-301 and SHP633-302 is presented in **Table 20**. Overall, the majority of subjects who enrolled in the core studies completed treatment and completed the studies.

In SHP633-301, 8 subjects completed the study and 2 subjects discontinued from the study: 1 subject in the teduglutide arm met escape criteria during the follow-up period and 1 subject in the standard of care arm discontinued early from the study during the treatment period. In addition, 1 subject interrupted teduglutide treatment following the Week 10 visit and never resumed treatment.

In SHP633-302, 2 Japanese infant subjects were enrolled and received teduglutide. Both infants completed the 28-week study.

**Table 20. Subject Disposition – Infant Subjects in SHP633-301 and SHP633-302**

| | SHP633-301 | | SHP633-302 |
|---|---|---|---|
| Category | Teduglutide 0.05 mg/kg/day (N=5) n (%) | Standard of care (N=5) n (%) | Teduglutide 0.05 mg/kg/day (N=2) n (%) |
| Randomized/Enrolled Subjects | 5 | 5 | 2 |
| Treated with Teduglutide | 5 (100.0) | 0 | 2 (100.0) |
| Completed Treatment (Week 24) | 4 (80.0) | 4 (80.0) | 2 (100.0) |
| Early Treatment Discontinuation | 1 ( 20.0)[a] | 1 ( 20.0) | 0 |
| Adverse Event | 0 | 0 | 0 |
| Withdrawal by Parent/Guardian | 0 | 1 ( 20.0) | 0 |
| Completed Study (Week 28) | 4 ( 80.0) | 4 ( 80.0) | 2 (100.0) |
| Early Study Discontinuation | 1 (20.0) | 1 (20.0) | 0 |
| Withdrawal by Parent/Guardian | 0 | 1 (20.0) | 0 |
| Other | 1 (20.0)[b] | 0 | 0 |

[a] Subject 424-0022 had his teduglutide treatment interrupted on 15 May 2020 (Day 75) following Week 10 visit due to the parents' decision to interrupt teduglutide administration as they considered several AEs to be caused by the study drug (it was not the investigator's decision in the interest of safety but he was informed). The teduglutide treatment never resumed. The subject was undergoing routine visits up to Week 22 but the Week 24/EOT visit was not performed due to the COVID-19 pandemic. The subject's EOS visit was performed on 24 Sep 2020. Because Week 24/EOT visit was not performed, the subject was handled as early discontinued from treatment period after Week 22 visit. However, no reason for early termination was presented since no early termination eCRF page was filled out at any time for the subject as the subject attempted to complete Week 24 visit.

[b] Subject 419-0020 met several follow-up period escape criteria (increased PS requirements following discontinuation of teduglutide; deteriorating nutritional status despite maximal tolerated enteral nutrition following teduglutide discontinuation; and severe diarrhoea related to teduglutide discontinuation).

Note: For SHP633-301, percentages are based on the number of subjects randomized to each treatment group.
For SHP633-302, percentages were based on the intention-to-treat population.

**Demographics**

Demographic and baseline characteristics of infant subjects in SHP633-301 and SHP633-302 are presented in **Table 21**.

The subjects in SHP633-301 were slightly younger than the infant subjects in SHP633-302. The mean corrected gestational age of infant subjects treated with teduglutide was 8.5±3.09 months in SHP633-301 and 10.0±1.20 months in SHP633-302. The mean corrected gestational age of infant subjects in the standard of care arm in SHP633-301 was 8.3±2.65 months. As expected, the majority of infant subjects in both studies were 6 months to 12 months corrected gestational age.

The majority of subjects were male, the majority of subjects were white; no subjects were Hispanic or Latino. Among infant subjects treated with teduglutide in SHP633-301, 4 (80%) were male, and 4 (80.0%) were white and 1 (20.0%) Asian. Among infant subjects treated with teduglutide in SHP633-302, 1 (50.0%) was male and 2 (100.0%) were Asian. Among infant subjects in the standard of care arm in SHP633-301, 3 (60.0%) were male, and 4 (80.0%) were white and 1 (20.0%) Asian.

Baseline growth parameters for infant subjects in both studies showed below-average weight and weight for length Z-scores. Among the subjects treated with teduglutide, infant subjects in SHP633-302 showed lower average length, weight, and weight for length Z-scores, suggesting a more severe growth delay with SBS.

**Table 21. Demographics – Infant Subjects in SHP633-301 and SHP633-302**

| | SHP633-301 | | SHP633-302 |
|---|---|---|---|
| | Teduglutide 0.05 mg/kg/day | Standard of care | Teduglutide 0.05 mg/kg/day |
| Category | (N=5) | (N=5) | (N=2) |
| Corrected gestational age (months), Mean (SD) | 8.5 (3.09) | 8.3 (2.65) | 10.0 (1.20) |
| Corrected gestational age category (months), n (%) | | | |
| 4 - <6 months | 2 (40.0) | 1 (20.0) | 0 |
| 6 - 12 months | 3 (60.0) | 4 (80.0) | 2 (100.0) |
| Sex, n (%) | | | |
| Male | 4 (80.0) | 3 (60.0) | 1 (50.0) |
| Female | 1 (20.0) | 2 (40.0) | 1 (50.0) |
| Race, n (%) | | | |
| White | 4 (80.0) | 4 (80.0) | 0 |
| Asian | 1 (20.0) | 1 (20.0) | 2 (100.0) |
| Ethnicity, n (%) | | | |
| Not Hispanic or Latino | 5 (100.0) | 5 (100.0) | 2 (100.0) |
| Length for Age Z-Score at Baseline, Mean (SD) | -0.56 (2.034) | 0.11 (1.263) | -3.65 (1.14) |
| Weight for Age Z-Score at Baseline, Mean (SD) | -0.87 (1.681) | -0.58 (1.314) | -2.92 (2.67) |
| Weight for Length Z-Score at Baseline, Mean (SD) | -0.73 (1.288) | -0.75 (1.088) | -1.35 (4.91) |
| Head Circumference for Age Z-Score at Baseline, Mean (SD) | n=4<br>0.78 (1.138) | n=5<br>-0.07 (1.681) | 0.04 (2.81) |

SD=standard deviation

Note: Z-score is calculated as (observed value - median value of the reference population) / standard deviation value of reference population. World Health Organization Z-score calculation charts are used for calculation. Z-Scores are based on gestational age.

**Short Bowel History**

The SBS history of infant subjects in SHP633-301 and SHP633-302 is presented in **Table 22**.

The primary underlying causes of SBS were different in each study. The causes of SBS in infant subjects treated with teduglutide were gastroschisis (3 [60.0%] subjects), necrotizing enterocolitis and intestinal atresia (1 [20.0%] subject each) in SHP633-301, and midgut volvulus and congenital absence of midgut (1 [50.0%] subject each) in SHP633-302. The mean small intestine length was different in both studies and between treatment groups. In SHP633-301, the mean small intestine length was 23.4±10.69 cm in subjects treated with teduglutide and 35.0±34.92 cm in subjects in the standard of care arm. In SHP633-302, the mean small intestine length was 6.00±5.66 cm in infant subjects. Shorter remaining small intestine length also suggested a more severe status of SBS in SHP633-302 infant subjects. None of the infant subjects treated with teduglutide had a stoma and the remnant colon was in continuity in all subjects. One infant treated with teduglutide in each study had a distal or terminal ileum and had the ileocecal valve.

**Table 22. Short Bowel History – Infant Subjects in SHP633-301 and SHP633-302**

| | SHP633-301 | | SHP633-302 |
|---|---|---|---|
| **Category** | **Teduglutide 0.05 mg/kg/day (N=5)** | **Standard of care (N=5)** | **Teduglutide 0.05 mg/kg/day (N=2)** |
| Primary reason for the diagnosis of SBS, n (%) | | | |
| Necrotizing enterocolitis | 1 (20.0) | 2 (40.0) | 0 |
| Midgut volvulus | 0 | 0 | 1 (50.0) |
| Intestinal atresia | 1 (20.0) | 0 | 0 |
| Gastroschisis | 3 (60.0) | 2 (40.0) | 0 |
| Other | 0 | 1 (20.0) | 1 (50.0) |
| No of subjects with stoma, n (%) | 0 | 1 (20.0) | 0 |
| No of subjects with remaining colon, n (%) | 5 (100.0) | 5 (100.0) | 2 (100.0) |
| Estimated percent of colon remaining (%), Mean (SD) | 74.0 (18.51) | 51.7 (27.54) | 75.0 (35.36) |
| Colon is in continuity[a], n (%) | 5 (100.0) | 4 (80.0) | 2 (100.0) |
| Total estimated remaining small intestinal length (cm), Mean (SD) | 23.4 (10.69) | 35.0 (34.92) | 6.00 (5.66) |
| Distal/terminal ileum present, n (%) | 1 (20.0) | 0 | 1 (50.0) |
| Ileocecal valve present[b], n (%) | 1 (100.0) | 0 | 1 (100.0) |

SD=standard deviation

[a] Percentages are based on the number of subjects who have remaining colon in each treatment group.

[b] Percentages are based on the number of subjects with distal/terminal ileum present in each treatment group.

**Comparison of Efficacy Results of Core Studies**

**Reduction in Parenteral Support Volume**

A summary of ≥20% reduction in PS volume at EOT based on diary data for infant subjects in SHP633-301 and SHP633-302 is presented in **Table 23**.

The primary efficacy variable in SHP633-301 was reduction in weight-normalized PS volume of ≥20% at EOT compared with baseline. Although this endpoint was assessed in SHP633-302, no primary efficacy endpoint was specified in this study. In SHP633-302, PS volume was also analyzed with normalization for weight.

The responder rates (those who achieved ≥20% reduction in PS volume) in SHP633-301 infant subjects treated with teduglutide based on diary data were consistent with SHP633-302 infant subjects. In SHP633-301, 3 (60.0%) subjects treated with teduglutide had achieved a ≥20% reduction at EOT in diary PS volume compared with 1 (20.0%) subjects in the standard of care arm (2 subjects in the standard of care arm had missing diary data). In SHP633-302, 1 (50.0%) infant subject had achieved a ≥20% reduction in diary PS volume at EOT; the other infant did not achieve a ≥20% reduction in PS volume during the treatment period but did achieve ≥20% reduction for 2 weeks during the follow-up period based on the diary data (SHP633-302 CSR).

**Table 23. Summary of ≥20% Reduction in Parenteral Support Volume at End of Treatment Based on Subject Diary Data – Infant Subjects in SHP633-301 and SHP633-302**

| | SHP633-301 | | SHP633-302 |
|---|---|---|---|
| | Teduglutide 0.05 mg/kg/day | Standard of care | Teduglutide 0.05 mg/kg/day |
| **Intent-to-treat Population** | **(N=5)** | **(N=5)** | **(N=2)** |
| ≥20% PS Reduction at EOT Visit, n (%) | 3 (60.0) | 1 (20.0) | 1 (50.0) |
| **Per-protocol Population** | **(N=4)** | **(N=3)** | **(N=1)** |
| ≥20% PS Reduction at EOT Visit, n (%) | 3 (75.0) | 1 (33.3) | 1 (100.0) |

EOT=end of treatment; PS=parenteral support
Note: End of Treatment is defined as the last available visit after the date of first dose (or randomization in standard of care treatment group for SHP633-301) during the 24-week treatment period.

**Change from Baseline in Parenteral Support Volume**

A summary of change from baseline in PS volume at EOT based on subject diary data for infant subjects in SHP633-301 and SHP633-302 is presented in **Table 24**.

In SHP633-301 and SHP633-302, infant subjects treated with teduglutide experienced consistent reductions in mean percentage PS volume from baseline to EOT.

In SHP633-301 teduglutide treatment arm, the mean change in diary PS volume from baseline to EOT was -21.5±28.91 mL/kg/day (-24.8±34.72%) from a baseline of 95.3±45.93 mL/kg/day. In SHP633-301 standard of care arm, the mean change in diary PS volume from baseline to EOT was -9.5±7.50 mL/kg/day (-16.8±16.39%) from a baseline of 70.9±14.44 mL/kg/day. The mean percentage change of diary PS volume from baseline by visit is presented for SHP633-301 in **Figure 19**.

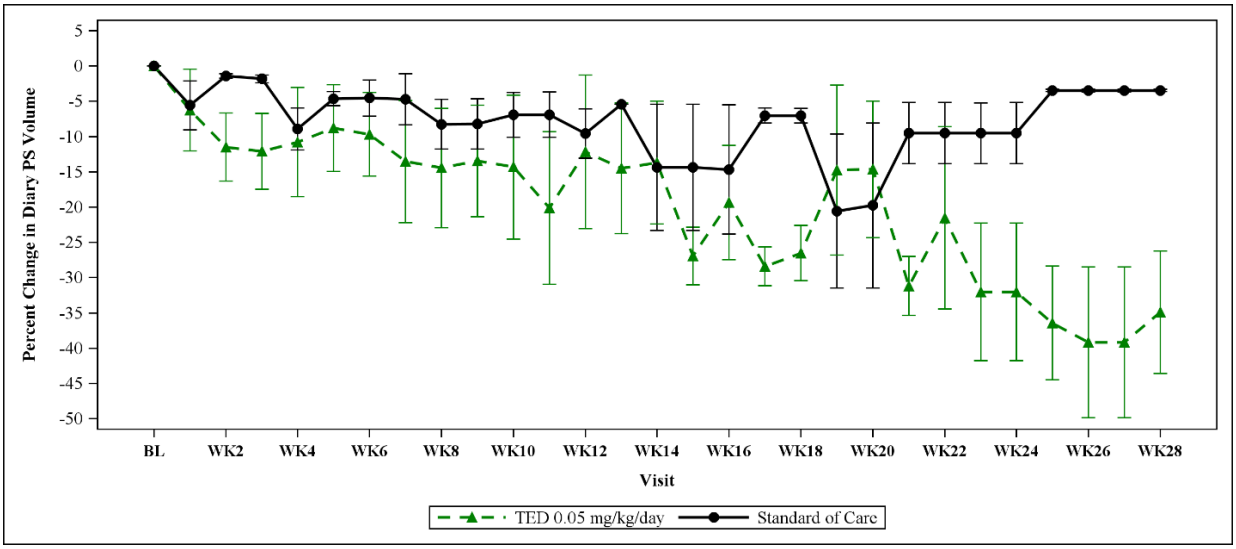
In SHP633-302 infant subjects, the mean change in diary PS volume from baseline to EOT was -26.2±13.61 mL/kg/day (-26.7±15.14%) from a baseline of 99.7±5.56 mL/kg/day. The mean percentage change of diary PS volume from baseline by visit is presented for SHP633-302 infants in **Figure 20**.

**Table 24. Summary of Change from Baseline in Parenteral Support Volume at End of Treatment based on Diary Data (Intent-to-treat Set) – Infant Subjects in SHP633-301 and SHP633-302**

| | SHP633-301 | | SHP633-302 |
|---|---|---|---|
| Visit/ PS Volume (mL/kg/day) | Teduglutide 0.05 mg/kg/day (N=5) | Standard of care (N=5) | Teduglutide 0.05 mg/kg/day (N=2) |
| Baseline | | | |
| n | 5 | 5 | 2 |
| Mean (SD) | 95.3 (45.93) | 70.9 (14.44) | 99.7 (5.56) |
| End of Treatment | | | |
| n | 5 | 3 | 2 |
| Change from Baseline, Mean (SD) | -21.5 (28.91) | -9.5 (7.50) | -26.2 (13.61) |
| Percent Change from Baseline, Mean (SD) | -24.8 (34.72) | -16.8 (16.39) | -26.7 (15.14) |

PS=parenteral support; SD=standard deviation
Note: End of Treatment is defined as the last available visit after the date of first dose (or randomization in standard of care treatment group for SHP633-301) during the 24-week treatment period.
Percent change is calculated as (change from baseline at the week / baseline value) * 100.
Average daily value based on subject diary data 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.
Average daily value based on prescribed data is calculated as (prescribed weekly PS parameter/ 7) / last available weight prior to or on the date of visit.
For the teduglutide treatment group, baseline is defined as the last available value prior to teduglutide administration.
For the standard of care treatment group (SHP633-301), baseline is defined as the last available value on or prior to the baseline visit.

**Figure 19. Mean ±SE Plot of Percent Change in Parenteral Support Volume by Visit Based on Diary Data (Intent-to-treat Set) – SHP633-301**




PS=parenteral support; SE=standard error

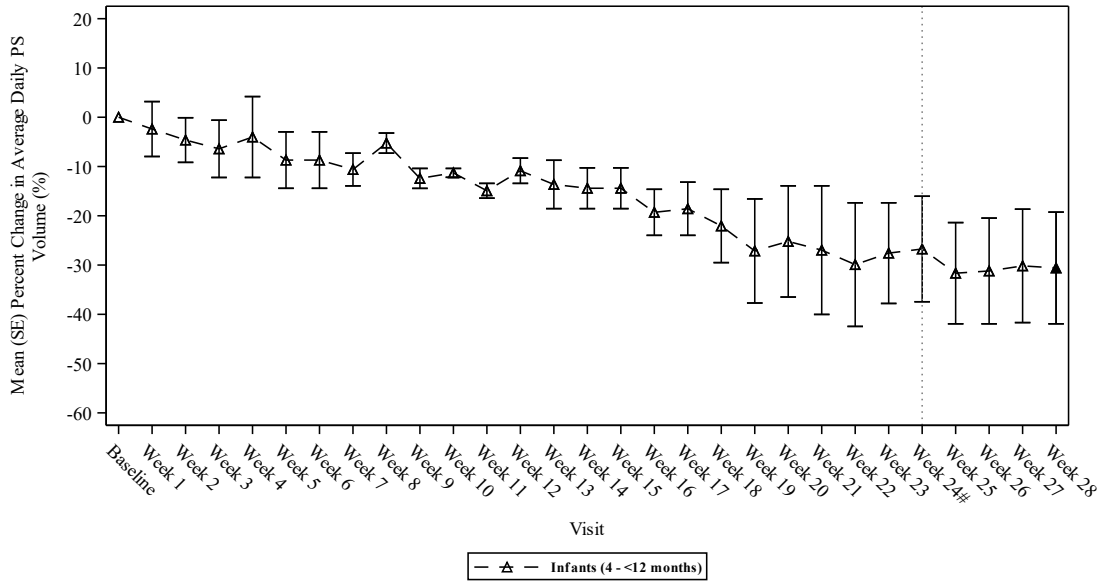
Note: Percent change is calculated as (change from baseline at the week / baseline value) * 100, using average daily values normalized by weight at the interval.

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.

**Figure 20. Mean ±SE Percent Change of Parenteral Support Volume from Baseline by Visit Based on Diary Data – Infants (Intent-to-treat Set) - SHP633-302**




# = End of Treatment Visit

Note: Infants were of 4 - <12 months corrected gestational age.

Note: Teduglutide treatment was up to 24 weeks. The Week 28 visit is 4 weeks after end of treatment (marked with a filled symbol).

Note: Percent change at baseline was presented as 0 in the figure.

Previous studies have demonstrated that the response to teduglutide is heterogenous in patients with SBS, primarily due to differences in short bowel history, remnant bowel anatomy, the presence or absence of a stoma, and PS volume requirements (Jeppesen et al. 2017; Jeppesen et al. 2011; O'Keefe et al. 2013). In infants, there is less physiologic need for "absolute" PS volume than adult and older pediatric patients (and therefore, no need for the same PS reduction volumes). This is confirmed by the observed baseline values: the median baseline prescribed PS volume in infant patients was 3.61 L/week as compared to older age groups with >6 L/week. In addition, PS volumes are adjusted conservatively in infants to minimize the risk of potential dehydration and electrolyte imbalances and medical needs. Further, it is expected that changes in the prescribed PS while on the treatment are much lower compared to older children, given that SBS in infants are much more dependent on the nutrition provided to them and they are not able to feed on their own. Therefore, management of parental nutrition in infants with SBS is much more conservative than that for older children.

Overall, the extent of reduction in PS volume (L/week) increased as a function of age and thereby body weight. These results are consistent with the greater PS volume required for SBS patients with greater body weight. Further, the 20% reduction in PS volume was the primary endpoint of the 2 core studies (SHP633-301 and SHP633-302) in infants. Efficacy was demonstrated in both studies (**Figure 21** and **Figure 22**) following 24 weeks of treatment:

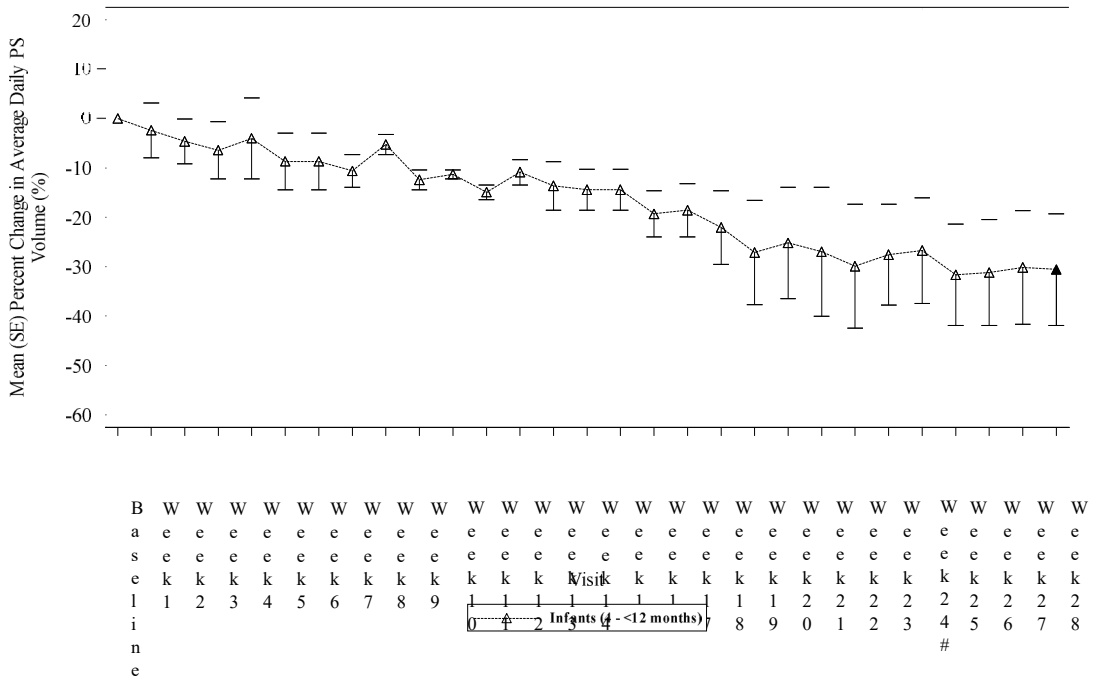
(1) Study SHP633-301 showed a mean percentage change from baseline of -27.3±33.52% in the teduglutide treated infants based on prescribed PS volume; and (2) in Study SHP633-302,

2 infants had PS reductions from baseline of 36% and 17%, respectively, (ref: Study SHP633-301 and SHP633-302 CSRs). In addition, consistency in the proportion of subjects achieving ≥20% PS reduction

following 24 weeks of treatment between age populations was demonstrated: 60% (3/5 subjects) in the infants aged 4 month to <1 year (Study SHP633-301), 62.0% (31/50 subjects) in children aged 1-17 years older (Study TED-C14-006) and 62.8% (27/43 subjects) in adults (Study CL0600-020).

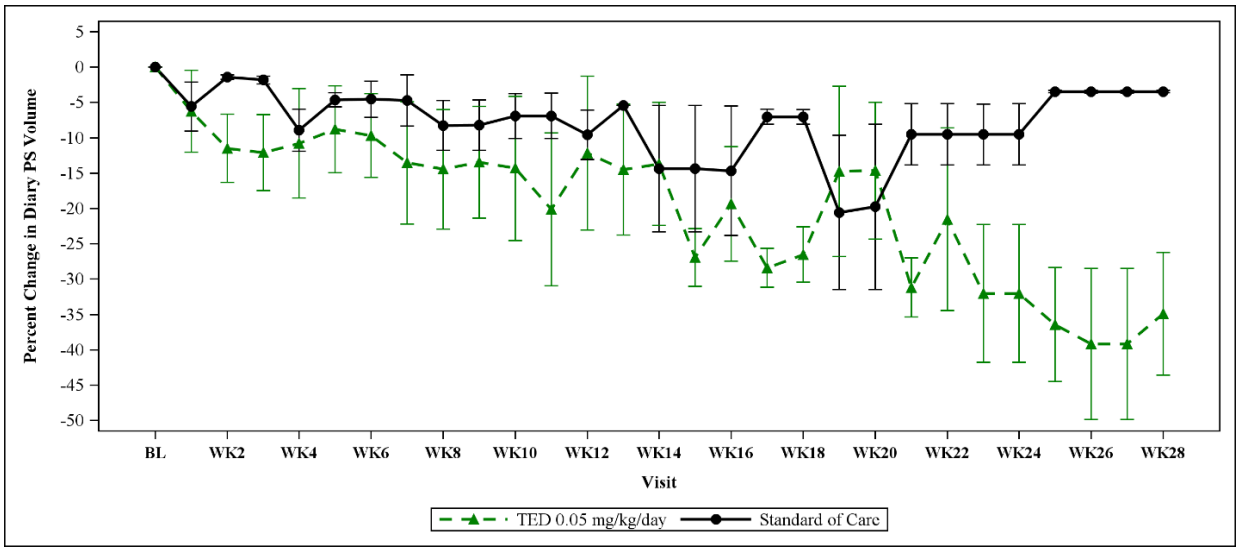
These observations have confirmed the teduglutide treatment effects in infant patients, which are supported by similar $C_{max}$ values across age groups, receiving 0.05 mg/kg daily treatment, resulting in a beneficial reduction in prescribed PS volume as presented in **Figure 21** and **Figure 22**.

**Figure 21. Mean ±SE Plot of Percent Change from Baseline in PS Volume by Visit Based on Diary Data (Intent-to-treat Set, Study SHP633-302)**




CSR=clinical study report; PS=parenteral support; SE=standard error

**Figure 22. Mean ±SE Plot of Percent Change from Baseline in PS Volume by Visit Based on Diary Data (Intent-to-treat Set, Study SHP633-30 Data)**




CSR=clinical study report; PS=parenteral support; SE=standard error

For the treatment response, complete weaning is not expected to be the same across age groups, as individual response is driven by their small intestine length due to SBS, receptor responses and expressions, physiological requirements, and clinical pharmacology properties (PK and pharmacodynamics [PD]).

**Change from Baseline in Parenteral Support Caloric Intake**

A summary of change from baseline in PS caloric intake at EOT based on subject diary data for infant subjects in SHP633-301 and SHP633-302 is presented in **Table 25**.

In SHP633-301 and SHP633-302, infant subjects treated with teduglutide experienced consistent reductions in mean percentage PS caloric intake from baseline to EOT.

In SHP633-301 teduglutide treatment arm, the mean change in diary PS caloric intake from baseline to EOT was -16.1±17.55 kcal/kg/day (-27.0±29.47%) from a baseline of 67.3±11.50 kcal/kg/day. In SHP633-301 standard of care arm, the mean change in diary PS caloric intake from baseline to EOT was -6.1±10.39 kcal/kg/day (-13.7±21.87%) from a baseline of 65.1±18.20 kcal/kg/day. The mean percentage change of diary PS caloric intake from baseline by visit is presented for SHP633-301 in **Figure 23**.

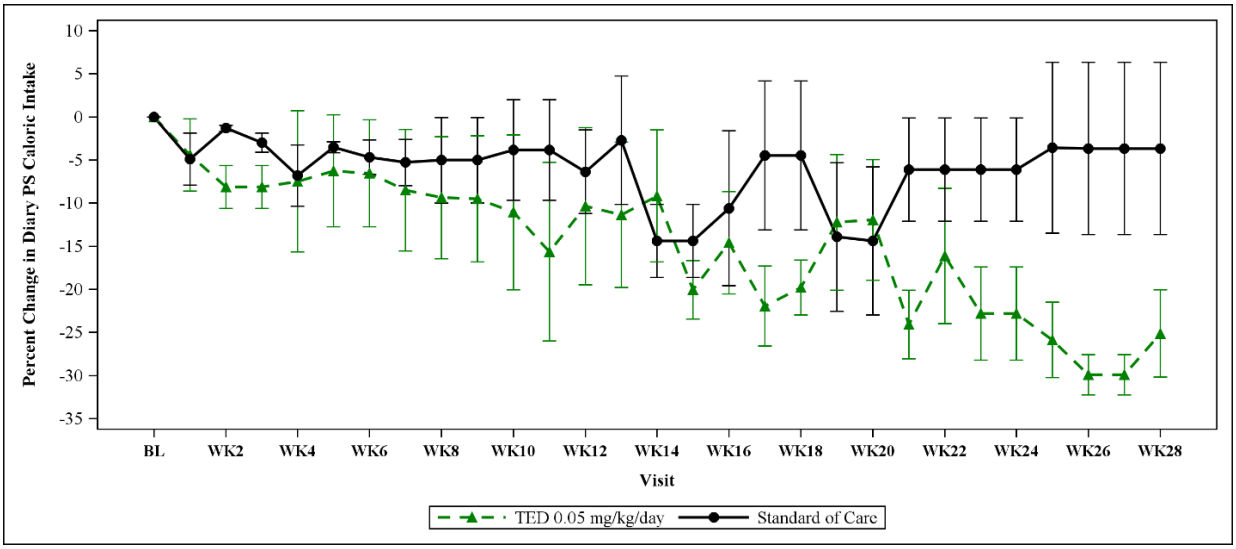
In SHP633-302 infant subjects, the mean change in diary PS caloric intake from baseline to EOT was -13.8±3.17 kcal/kg/day (-25.7±2.73%) from a baseline of 53.4±6.68 kcal/kg/day. The mean percentage change of diary PS caloric intake from baseline by visit is presented for SHP633-302 infants in **Figure 24**.

**Table 25. Summary of Change from Baseline in Parenteral Support Caloric Intake at End of Treatment based on Diary Data (Intent-to-treat Set) – SHP633-301 and SHP633-302**

| | SHP633-301 | | SHP633-302 |
|---|---|---|---|
| | Teduglutide 0.05 mg/kg/day | Standard of care | Teduglutide 0.05 mg/kg/day |
| Visit/ PS Caloric Intake (kcal/kg/day) | (N=5) | (N=5) | (N=2) |
| Baseline | | | |
| n | 5 | 5 | 2 |
| Mean (SD) | 67.3 (11.50) | 65.1 (18.20) | 53.4 (6.68) |
| End of Treatment | | | |
| n | 5 | 3 | 2 |
| Change from Baseline, Mean (SD) | -16.1 (17.55) | -6.1 (10.39) | -13.8 (3.17) |
| Percent Change from Baseline, Mean (SD) | -27.0 (29.47) | -13.7 (21.87) | -25.7 (2.73) |

PS=parenteral support; SD=standard deviation
Note: End of Treatment is defined as the last available visit after the date of first dose (or randomization in standard of care treatment group for SHP633-301) during the 24-week treatment period.
Percent change is calculated as (change from baseline at the week / baseline value) * 100.
Average daily value based on subject diary data 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.
Average daily value based on prescribed data is calculated as (prescribed weekly PS parameter/ 7) / last available weight prior to or on the date of visit.
For the teduglutide treatment group, baseline is defined as the last available value prior to teduglutide administration.
For the standard of care treatment group (SHP633-301), baseline is defined as the last available value on or prior to the baseline visit.

## Figure 23. Mean ±SE Plot of Percent Change in Parenteral Support Caloric Intake by Visit Based on Diary Data (Intent-to-treat Set) – SHP633-301




PS=parenteral support; SE=standard error

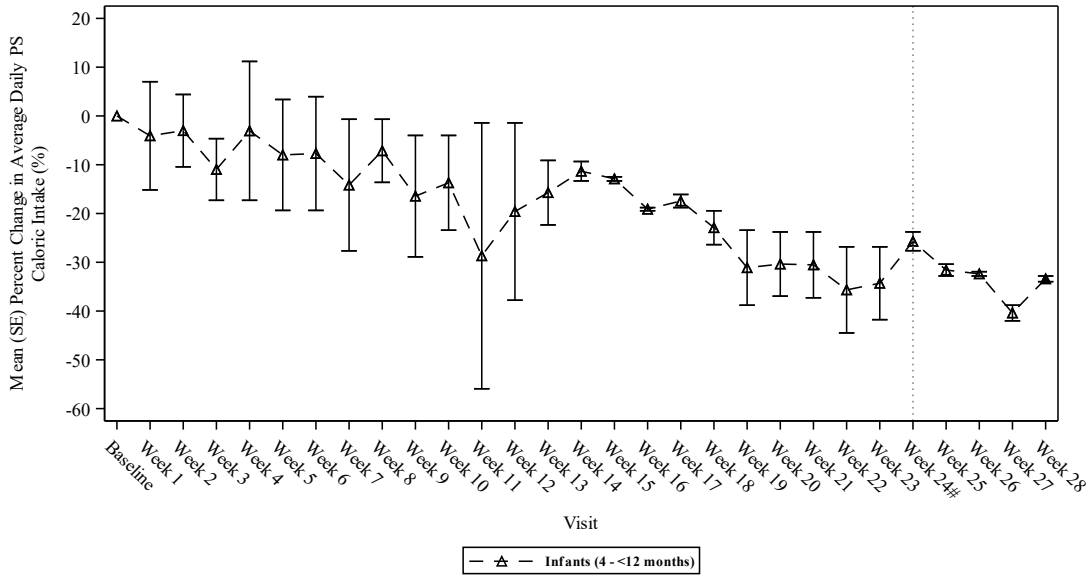
Note: Percent change is calculated as (change from baseline at the week / baseline value) * 100, using average daily values normalized by weight at the interval.

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.

**Figure 24. Mean ±SE Percent Change of Parenteral Support Caloric Intake from Baseline by Visit Based on Diary Data – Infants (Intent-to-treat Set) – SHP633-302**




# = End of Treatment Visit

Note: Infants were of 4 - <12 months corrected gestational age.

Note: Teduglutide treatment was up to 24 weeks. The Week 28 visit is 4 weeks after end of treatment (marked with a filled symbol).

Note: Percent change at baseline was presented as 0 in the figure.

**Complete Weaning Off Parenteral Support**

No infant subject enrolled in SHP633-301 and SHP633-302 achieved enteral autonomy, i.e., complete weaning off PS during the study.

**Reduction in Parenteral Support Infusion Time**

A reduction of 28.5% in mean change from baseline in number of days per week of diary PS usage at EOT was observed in SPH633-301 infants who received teduglutide, however, no consistent change was observed in SHP633-302 infants.

**Change and Percent Change from Baseline in Days per Week of PS (Diary data)**

In SHP633-301 teduglutide treatment arm, the mean change in number of days per week in diary PS usage at EOT from baseline was -1.9±2.01 days/week (-28.5±30.05%) from a baseline of 6.7±0.45 days/week. In SHP633-301 standard of care arm, there was no mean change in daily diary PS observed at EOT from a baseline of 7.0±0.00 days/week.

In SHP633-302 infant subjects, the number of days per week in diary PS usage was not reduced; infants required PS 7 days/week both at baseline and EOT.

**Change and Percent Change from Baseline in Hours per Day of PS (Diary data)**

In SHP633-301 teduglutide treatment arm, the mean change in daily PS usage at EOT from baseline was -3.1±3.31 hours (-28.9±30.61%) from a baseline of 11.2±0.79 hours. In SHP633-301 standard of care arm, the mean change in daily PS usage at EOT from baseline was -0.3±0.63 hours (-1.9±4.59%) from a baseline of 13.0±1.47 hours.

In SHP633-302 infant subjects, there was no change observed in daily PS usage hours during the study.

**Extension Studies**

**Subject Disposition, Demographics, and Baseline Characteristics**

**Subject Disposition**

The disposition of infant subjects in SHP633-304 and SHP633-305 is presented in **Table 26**.

In SHP633-304, 4 of the 6 infant subjects enrolled had previously received teduglutide treatment during the core study and received teduglutide treatment during the extension study (TED/TED group). Of the 2 infants subjects who did not received teduglutide in the core study, 1 received teduglutide in the extension study (NTT/TED group) and the other not (NTT/NTT group). Of the 6 infant subjects enrolled in SHP633-304, 1 subject discontinued teduglutide treatment and from the study (TED/TED group).

In SHP633-305, both infants subjects enrolled previously received teduglutide treatment in the core study and received teduglutide treatment during the extension study. Both subjects were still ongoing at the time of data cutoff.

**Table 26. Subject Disposition (Safety Population) – Infant Subjects in SHP633-304 and SHP633-305**

| | SHP633-304 | | | | SHP633-305[a] |
|---|---|---|---|---|---|
| Category | NTT/NTT | NTT/TED | TED/TED | Any TED | |
| Enrolled subjects, n | 1 | 1 | 4 | 5 | 2 |
| Completed treatment, n (%) | 0 | 1 (100.0) | 3 ( 75.0) | 4 ( 80.0) | - |
| Treated, n (%) | - | - | - | - | 2 (100.0) |
| Completed study, n (%) | 1 (100.0) | 1 (100.0) | 3 ( 75.0) | 4 ( 80.0) | 0 |
| Ongoing | - | - | - | - | 2 (100.0) |
| Early treatment discontinuation, n (%) | 0 | 0 | 1 ( 25.0) | 1 ( 20.0) | 0 |
| Adverse event, n (%) | 0 | 0 | 1 ( 25.0) | 1 ( 20.0) | 0 |
| Withdrawal by parent/guardian, n (%) | 0 | 0 | 0 | 0 | 0 |
| Physician decision, n (%) | 0 | 0 | 0 | 0 | 0 |
| Lost to follow-up, n (%) | 0 | 0 | 0 | 0 | 0 |
| Other, n (%) | 0 | 0 | 0 | 0 | 0 |
| Early study discontinuation, n (%) | 0 | 0 | 1 ( 25.0) | 1 ( 20.0) | 0 |
| Adverse event, n (%) | 0 | 0 | 1 ( 25.0) | 1 ( 20.0) | 0 |
| Withdrawal by subject | 0 | 0 | 0 | 0 | 0 |
| Physician decision, n (%) | 0 | 0 | 0 | 0 | 0 |
| Lost to follow-up, n (%) | 0 | 0 | 0 | 0 | 0 |
| Death, n (%) | 0 | 0 | 0 | 0 | 0 |
| Other, n (%) | 0 | 0 | 0 | 0 | 0 |

[a] Both infant subjects enrolled in SHP633-305 took teduglutide in their core study and in the extension study.
Note: The safety population contains all enrolled subjects who provided informed consent and met all the inclusion criteria.
Note: NTT/NTT=Subjects who participated in the standard of care arm in their core study and did not receive any teduglutide treatment in the extension study.
NTT/TED=Subjects who participated in the standard of care arm in their core study but subsequently received teduglutide treatment in the extension study.
TED/TED=Subjects who took teduglutide in their core study and in the extension study.
ANY TED=Subjects who took teduglutide in either their core study or in the extension study.
Note: Percentages are based on the number of subjects in the safety population for the defined treatment groups.

In SHP633-304, 1 (25.0%) infant subject in the TED/TED group and 1 (100.0%) infant subject in the NTT/TED group had at least 80% compliance for the study overall and Cycle 1 at the time of data cutoff.

In SHP633-305, all infant subjects had at least 80% treatment compliance.

**Demographics**

Demographic and baseline characteristics of infant subjects in SHP633-304 and SHP633-305 are presented in **Table 27**.

The infant subjects treated with teduglutide in SHP633-304 and SHP633-305 were of similar corrected gestational age at baseline of the core study. The mean age of infant subjects in SHP633-304 TED/TED and NTT/TED groups was 0.6±0.24 years and 0.6 (-) year, respectively, and the mean age of infant subjects in SHP633-305 was 9.95±1.202 months. Among infant subjects treated with teduglutide in SHP633-304, 4 (80.0%) were male, 4 (80.0%) were white (TED/TED group), 1 (20.0%) Asian (NTT/TED group), and 5 (100.0%) were not Hispanic or Latino. Among all subjects treated with teduglutide in SHP633-305, 1 (50.0%) was male, 2 (100.0%) were Asian, and 2 (100.0%) were not Hispanic or Latino.

In both extension studies, baseline growth parameters for subjects treated with teduglutide showed below-average weight, and height Z-scores. Body mass index Z-scores were near 0, suggesting that some subjects were stunted due to chronic nutritional deficiency. Among subjects treated with

teduglutide, infant subjects in SHP633-305 showed lower average length, weight, and weight for length Z-scores, suggesting a more severe growth delay with SBS. Improved mean weight Z-score after teduglutide treatment, when compared with core study baseline Z-score, was observed in SHP633-305 infant subjects in both the core study.

The corrected gestational age of the white female infant subject who never received teduglutide (NTT/NTT group in SHP633-304) was 0.4 years. This subject did not fulfill teduglutide treatment criteria, also reflecting on the better nutritional status at baseline, as indicated by near average weight and height Z-scores.

**Table 27. Demographics (Safety Set) – Infant Subjects in SHP633-304 and SHP633-305**

| | SHP633-304 | | | | SHP633-305[a] |
|---|---|---|---|---|---|
| **Category** | **NTT/NTT (N=1)** | **NTT/TED (N=1)** | **TED/TED (N=4)** | **Any TED (N=5)** | **(N=2)** |
| Age at core study baseline (years), mean (SD) | 0.4 (-) | 0.6 (-) | 0.6 (0.24) | 0.6 (0.21) | 9.95 (1.202)[b] |
| Age Group, n (%) | | | | | |
| Less than 1 year | 1 (100.0) | 1 (100.0) | 4 (100.0) | 5 (100.0) | 2 (100.0) |
| Sex, n (%) | | | | | |
| Male | 0 | 1 (100.0) | 3 ( 75.0) | 4 ( 80.0) | 1 (50.0) |
| Female | 1 (100.0) | 0 | 1 ( 25.0) | 1 ( 20.0) | 1 (50.0) |
| Race, n (%) | | | | | |
| White | 1 (100.0) | 0 | 4 (100.0) | 4 ( 80.0) | 0 |
| Asian | 0 | 1 (100.0) | 0 | 1 ( 20.0) | 2 (100.0) |
| Ethnicity | | | | | |
| Not Hispanic or Latino | 1 (100.0) | 1 (100.0) | 4 (100.0) | 5 (100.0) | 2 (100.0) |
| Weight z-score at core study baseline, mean (SD) | 0.26 (-) | -2.80 (-) | -0.17 (0.665) | -0.69 (1.309) | -2.916 (2.6705) |
| Weight for length Z-score at baseline, mean (SD) | - | - | - | - | -1.349 (3.4688) |
| Height z-score at core study baseline, mean (SD) | 0.35 (-) | -2.08 (-) | 0.24 (1.073) | -0.22 (1.393) | -3.652 (1.1428) |
| BMI Z-Score at core study baseline, mean (SD) | 0.08 (-) | -2.19 (-) | -0.41 (1.040) | -0.77 (1.202) | - |
| Head circumference Z-score at core study baseline, mean (SD) | -0.75 (-) | -1.70 (-) | 0.78 (1.138) | 0.29 (1.487) | 0.040 (1.9902) |

SD=standard deviation

[a] Both infant subjects enrolled in SHP633-305 took teduglutide in their core study and in the extension study.

[b] In corrected gestational age (months).

Note: The safety population contains all enrolled subjects who provided informed consent and met all the inclusion criteria.

Note: NTT/NTT=Subjects who participated in the standard of care arm in their core study and did not receive any teduglutide treatment in the extension study.

NTT/TED=Subjects who participated in the standard of care arm in their core study but subsequently received teduglutide treatment in the extension study.

TED/TED=Subjects who took teduglutide in their core study and in the extension study.

ANY TED=Subjects who took teduglutide in either their core study or in the extension study.

Note: Percentages are based on the number of subjects in the safety population for the defined treatment groups.

**Comparison of Efficacy Results of Extension Studies**

At completion of SHP633-304 and at time of data cutoff of SHP633-305 interim analysis, only 2 infant subjects in the TED/TED group (SHP633-304) and none in SHP633-305 had completed Cycle 2 EOT; therefore efficacy results are presented for teduglutide treatment Cycle 1. In SHP633-304, the infant subset efficacy analysis focused on the TED/TED (4 subjects) and NTT/TED (1 subject) treatment groups. One infant subject in the TED/TED group (SHP633-304) discontinued treatment and from the study at Cycle 1 Week 14.

The analyses of weekly PS volume were based on 2 data sources: each subject's diary data and the investigator prescribed data. The diary data are considered a more representative measure of efficacy than the investigator prescribed data and therefore the efficacy summary generally focuses on the diary data results. In SHP633-305, generally, no remarkable discrepancy between the diary and prescribed-based data was found in efficacy endpoints. In SHP633-304, of the 4 infant subjects in the TED/TED group, 3 subjects had missing diary data at Cycle 1 Day 1 and Cycle 1 EOT while all 4 infant subjects had prescribed data; therefore, reductions in PS volume and mean changes from baseline in PS volume in both extension studies are presented for diary and prescription data in **Table 28** and **Table 29**, respectively.

**Reduction in Parenteral Support Volume**

A summary of ≥20% reduction in weight-normalized PS volume based on subject diary and prescribed data for infant subjects in SHP633-304 and SHP633-305 is presented in **Table 28**.

Data from SHP633-304 and SHP633-305 show that ≥20% reduction in PS volume was sustained or improved at Cycle 1 EOT in some infant subjects who received teduglutide treatment during the core and extension studies based on diary data or prescribed data.

In SHP633-304, of the infant subjects in the TED/TED group based on diary data, 1 (25.0%) subject at Cycle 1 Day 1 and no subject at Cycle 1 EOT achieved ≥20% reduction from core study baseline in PS volume (3 [75.0%] infant subjects in the TED/TED group had missing diary data at Cycle 1 Day 1 and Cycle 1 EOT). The infant subject in the NTT/TED group did not achieve ≥20% reduction from baseline in PS volume at Cycle 1 EOT based on diary data.

In SHP633-304, of the infant subjects in the TED/TED group based on prescribed data, 1 (25.0%) subject at Cycle 1 Day 1 and 3 (75.0%) subjects at Cycle 1 EOT achieved ≥20% reduction from core study baseline in PS volume. The infant subject in the NTT/TED group did not achieve ≥20% reduction from baseline in PS volume at Cycle 1 EOT based on prescribed data.

In SHP633-305, both infant subjects achieved ≥20% reduction in PS volume at Cycle 1 Day 1 (initiation of this study) based on diary data and 1 subject based in prescribed data, and ≥20% reduction was maintained to EOT by 1 infant in the diary and prescribed data.

**Table 28. Summary of ≥20% Reduction in Parenteral Support Volume at End of Treatment Based on Subject Diary and Prescribed Data (Safety Set) – Infant Subjects in SHP633-304 and SHP633-305**

| Reductions in Diary PS Volume (mL/kg/day), n (%) /Visits | SHP633-304 | | | | SHP633-305[a] | |
|---|---|---|---|---|---|---|
| | NTT/TED (N=1) | | TED/TED (N=4) | | (N=2) | |
| | Diary | Prescribed | Diary | Prescribed | Diary | Prescribed |
| **At Least 20%** | | | | | | |
| Cycle 1 Day 1 | 0 | 0 | 1 ( 25.0) | 1 ( 25.0) | 2 (100) | 1 (50.0) |
| Missing | 0 | 1 (100) | 3 ( 75.0) | 0 | 0 | 0 |
| Cycle 1 EOT | 0 | 0 | 0 | 3 ( 75.0) | 1 (50.0) | 1 (50.0) |
| Missing | 0 | 0 | 3 ( 75.0) | 0 | 0 | 0 |

EOT=end of treatment; PS=parenteral support
[a] Both infant subjects enrolled in SHP633-305 took teduglutide in their core study and in the extension study.
TED/TED=subjects who received teduglutide in their core study and this extension study.
NTT/TED=Subjects who participated in the standard of care arm in their core study but subsequently received teduglutide treatment in the extension study.
Note: For SHP633-304, baseline is defined as the core study baseline for subjects in the NTT/NTT, TED/NTT, and TED/TED groups and as the extension study baseline for the NTT/TED group. For SHP633-305, baseline is defined as the core study baseline.
End of Treatment is defined as the last available visit after the date of first dose during the 24-week treatment period.

**Change from Baseline in Parenteral Support Volume**

A summary of mean and percentage changes from baseline in weight-normalized PS volume based on subject diary and prescribed data for infant subjects in SHP633-304 and SHP633-305 is presented in **Table 29**.

Reductions in diary and prescribed PS volume from baseline observed during treatment Cycle 1 in infant subjects are consistent with findings in the core studies (SHP633-304 NTT/TED group) and show a continuing effect in subjects receiving additional teduglutide treatment (SHP633-304 TED/TED group and SHP633-305 subjects). Greater reductions in PS volume were observed in SHP633-305 infant subjects during treatment Cycle 1 as they presented a more severe SBS history with growth delay and greater PS need at baseline; these subjects could have a greater potential for PS reductions after teduglutide treatment.

In SHP633-304, 2 infant subjects, one in each treatment group, had diary PS volume recorded at Cycle 1 Day 1 and Cycle 1 EOT. In the TED/TED group, the change in diary PS volume from core study baseline was -57.58 mL/kg/day (-39.28%) at Cycle 1 Day 1 and -28.94 mL/kg/day (-19.74%) at Cycle 1 EOT. In the NTT/TED group, the change in diary PS volume from baseline was -10.15 mL/kg/day (-15.58%) at Cycle 1 EOT.

In SHP633-304 infant subjects in the TED/TED group, the mean change in prescribed PS volume from core study baseline was -5.65±29.345 mL/kg/day (-10.34±52.091%) at Cycle 1 Day 1 and -19.98±34.998 mL/kg/day (-20.81±51.829%) at Cycle 1 EOT. For the infant subject in the NTT/TED group, the change in prescribed PS volume at Cycle 1 EOT from baseline was -10.26 mL/kg/day (-15.49%).

In SHP633-305 two infant subjects, the mean diary PS volume at core study baseline was 99.7±5.56 mL/kg/day. The mean change from baseline was -34.1±14.99 mL/kg/day (-34.7±16.97%)

at Cycle 1 Day 1 and -31.9±16.24 mL/kg/day (-32.5±18.10%) at Cycle 1 EOT. The median change from baseline core study diary PS volume at Cycle 1 EOT was -31.9 mL/kg/day (-32.5%).

The details of characteristics and PS volume change at Cycle 1 EOT based on diary data for infant subjects in SHP633-304 and SHP633-305 are presented in **Table 30**.

**Table 29. Summary of Mean Percentage Change from Baseline in Parenteral Support Volume Based on Subject Diary and Prescribed Data (Safety Set) – Infant Subjects in SHP633-304 and SHP633-305**

| | SHP633-304 | | | | SHP633-305[a] | |
|---|---|---|---|---|---|---|
| | NTT/TED (N=1) | | TED/TED (N=4) | | (N=2) | |
| **Visit** | **Diary** | **Prescribed** | **Diary** | **Prescribed** | **Diary** | **Prescribed** |
| **Baseline** | | | | | | |
| n | 1 | 1 | 3 | 4 | 2 | 2 |
| Mean Baseline PS Volume (mL/kg/day) Percentage (SD) | 65.12 (-) | 66.25 (-) | 110.35 (58.054) | 97.47 (51.203) | 99.7 (5.56) | 95.5 (4.48) |
| **Cycle 1 Day 1** | | | | | | |
| n | 1 | 1 | 1 | 4 | 2 | 2 |
| Mean Change from Baseline in PS Volume (mL/kg/day) Mean (SD) | -0.02 (-) | 0 | -57.58 (-) | -5.65 (29.345) | -34.1 (14.99) | -29.0 (24.85) |
| Mean Percentage Change from Baseline in PS Volume (%) n, Percentage (SD) | -0.03 (-) | 0 | -39.28 (-) | -10.34 (52.091) | -34.7 (16.97) | -29.7 (24.62) |
| **Cycle 1 EOT** | | | | | | |
| n | 1 | 1 | 1 | 4 | 2 | 2 |
| Mean Change from Baseline in PS Volume (mL/kg/day) Mean (SD) | -10.15 (-) | -10.26 (-) | -28.94 (-) | -19.98 (34.998) | -31.9 (16.24) | -31.3 (26.77) |
| Mean Percentage Change from Baseline in PS Volume (%) n, Percentage (SD) | -15.58 (-) | -15.49 (-) | -19.74 (-) | -20.81 (51.829) | -32.5 (18.10) | -32.1 (26.51) |

EOT=end of treatment; PS=parenteral support; SD=standard deviation
[a] Both infant subjects enrolled in SHP633-305 took teduglutide in their core study and in the extension study.
TED/TED=Subjects who received teduglutide in their core study and this extension study.
NTT/TED=Subjects who participated in the standard of care arm in their core study but subsequently received teduglutide treatment in the extension study.
Note: For SHP633-304, baseline is defined as the core study baseline for subjects in the NTT/NTT, TED/NTT, and TED/TED groups and as the extension study baseline for the NTT/TED group. For SHP633-305, baseline is defined as the core study baseline.
End of Treatment is defined as the last available visit after the date of first dose during the 24-week treatment period.

## Table 30. Details of Characteristics and Parenteral Support Change at Cycle 1 End of Treatment (Diary Data) - Infant Subjects in SHP633-304 and SHP633-305

| Study/ Treatment Group | Corrected Gestational Age (months)/ Chronological Age (months) | Race/ Sex | Primary Reason for the Diagnosis of SBS | Total Estimated Remaining Small Intestinal Length (cm) | Presence of the Distal/ Terminal Ileum | Ileocecal Valve Present | Remaining Colon | Estimated Percentage of Colon Remaining | Change of PS Volume at Cycle 1 EOT mL/kg/d [a] | Percent Change of PS Volume at Cycle 1 EOT[a] | Percent Change in Days per Week of PS at Cycle 1 EOT[a] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **SHP633-304** | | | | | | | | | | | |
| TED/TED | 0.8[b]/ 11.8 | White/Female | Gastroschisis | 28 | No | No | Yes | 75% | -28.94 | -19.74 | 0 |
| TED/TED | 0.9[b]/ 11.6 | White/Male | Necrotizing enterocolitis | 40 | No | No | Yes | 80% | -27.55[c] | -63.49[c] | -57.14[c] |
| TED/TED | 0.4[b]/ 6.1 | White/Male | Gastroschisis | 15 | No | No | Yes | 65% | NA | NA | NA |
| TED/TED | 0.5[b]/ 7.7 | White/Male | Gastroschisis | 19 | No | No | Yes | 19%[d] | 7.56[e] | 5.36[e] | 0[e] |
| NTT/TED | 0.6[b]/ 9.8 | Asian/Male | Necrotizing enterocolitis | 5 | No | No | Yes | 70% | -10.15 | -15.58 | -14.29 |
| **SHP633-305[f]** | | | | | | | | | | | |
| | 10.8/ 12.1 | Asian/Female | Other: Congenital absence of midgut | 2 | No | No | Yes | 50% | -20.40 | -19.69 | 0 |
| | 9.1/ 9.5 | Asian/Male | Midgut volvulus | 10 | Yes | Yes | Yes | 100% | -43.37 | -45.29 | 0 |

EOT=End of treatment; PS=parenteral support; SBS=short bowel syndrome; NA=not available

[a] Based on diary data.

[b] Corrected gestational age in years.

[c] Value at Cycle Week 9.

[d] The value of the estimated percentage of colon remaining reported in the SHP633-304 CSR (19%) is inconsistent with the value reported in the SHP633-301 CSR (core study) (50%). This inconsistency is under investigation.

[e] Value at Cycle Week 1.

[f] Both infant subjects took teduglutide in the core study and in the extension study.

Note: End of Treatment was defined as the last available measurement after the date of first dose during the 24-week treatment period.

**Complete Weaning Off Parenteral Support**

In SHP633-304, none of the infant subjects achieved enteral autonomy during SHP633-304.

In SHP633-305, while the 2 infants achieved a 20% reduction in PS volume, neither achieved enteral autonomy.

## 2.4.3. Discussion on clinical efficacy

The Applicant presents data to support the benefit/risk assessment of teduglutide in infant subjects 4 months to <1 year corrected gestational age with short bowel syndrome (SBS) who are dependent on parenteral support (PS).

The efficacy of teduglutide was evaluated in 2 completed core studies, SHP633-301 and SHP633-302, 1 completed long-term extension study, SHP633 304, and 1 ongoing long-term extension study at the time of submission of this application, SHP633-305. In addition, TED-C14-006 was presented. However, the study did not enrol any infant subjects.

**Core studies:**

The primary efficacy variable in SHP633-301 was reduction in weight-normalized PS volume of ≥20% at EOT compared with baseline. Although this endpoint was assessed in SHP633-302, no primary efficacy endpoint was specified in this study.

**SHP633-301:** 10 infants were randomized to either teduglutide (n=5) or standard of care (n=5). Eight subjects completed the study. One infant in each arm discontinued study treatment and study. The mean corrected gestational age was 8.4±2.71 months. The primary efficacy endpoint was the reduction in weight-normalized PS volume of ≥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 standard of care arm experienced ≥20% reduction in PS volume at EOT from baseline (2 subjects in the standard of care arm had missing data). No subject achieved enteral autonomy during the study.

**SHP633-302:**

Two Japanese infants 4 months through <1 year corrected gestational age were enrolled and received teduglutide. Both infants completed a 28-week study. The mean corrected gestation age was 10.0±1.20 months A ≥20% reduction in PS volume was recorded in 1 infant (50%) during the teduglutide treatment.

**TED-C14-006:** the study did not enroll infant subjects.

**SHP633-304:**

Six infant subjects 4 months to <1 year of age at core Study SHP633-301 baseline were enrolled in SHP633-304 (4 from teduglutide arm and 2 from SoC arm). 5 (83.3%) subjects completed the study (one infant from the teduglutide arm in SHP633-301). The mean age at core study baseline of the 5 infant subjects in the ANY TED group was 0.6±0.21 years. Subject data were analyzed by treatment and treatment cycle for the core study and the extension study.

***Diary data***: 1 (25.0%) subject at Cycle 1 Day 1 and no subject at Cycle 1 EOT achieved ≥20% reduction from core study baseline in PS volume. The infant subject in the NTT/TED group did not achieved ≥20% reduction from baseline in PS volume at Cycle 1 EOT. ***Prescribed data***: For 4 infant subjects in the TED/TED group based on prescribed data, 1 (25.0%) subject at Cycle 1 Day 1 and 3 (75.0%) subjects at Cycle 1 EOT achieved ≥20% reduction from core study baseline in PS volume. The

infant subject in the NTT/TED group did not achieve ≥20% reduction from baseline in prescribed PS volume at Cycle 1 EOT.

**SHP633-305:** is ongoing and the data cut-off date for the interim CSR is 14 Jul 2020 (paediatric subjects 4 months to <1 year corrected gestational age). Interim data included at least 6 months of treatment for 2 paediatric subjects from 4 months to <1 year (infant cohort). The mean corrected gestational age of the infant cohort enrolled at the beginning of the core study was 9.95±1.202 months. In the 2 infants, both subjects (100%) achieved ≥20% reduction from core study baseline in weight normalized PS volume in diary data at Cycle 1 Day 1 and 1 (50.0%) subject in prescribed data, and ≥20% reduction was maintained to Cycle 1 EOT by 1 infant in the diary and prescribed data.

***Comparison of results across studies***

None of the infant subjects achieved enteral autonomy in any of the presented studies.

**Core studies:**

In total 3 infants were below 6 months of age, of these 2 infants received TED 0,5 mg/kg. Nine infants were 6-12 months of age, of these 5 infants received TED 0,5 mg/kg. Two infants were Asian and 8 were white of origin.

**Extension studies:**

Only 2 infant subjects in the TED/TED group (SHP633-304) and none in SHP633-305 had completed Cycle 2 EOT; therefore efficacy results are presented for teduglutide treatment Cycle 1. Based on diary data, totally 3/6 infants achieved ≥20% reduction in PS volume at Cycle 1. They all received teduglutide treatment in the core- and extension study (TED/TED). The MAH states that the results presented for infants were similar to the results observed in previous paediatric studies.

## 2.4.4. Conclusions on the clinical efficacy

The efficacy of teduglutide was evaluated in 2 completed core studies, SHP633-301 and SHP633-302, 1 completed long-term extension study, SHP633 304, and 1 ongoing long-term extension study at the time of submission of this application, SHP633-305.

In SHP633-301 10 infants were randomized to either teduglutide (n=5) or standard of care (n=5). Eight subjects completed the study. The primary efficacy endpoint was the reduction in weight-normalized PS volume of ≥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 standard of care arm experienced ≥20% reduction in PS volume at EOT from baseline (2 subjects in the standard of care arm had missing data). A number of secondary endpoints were evaluated and a reduction in caloric intake and change from baseline in daily PS usage hours compared to the SoC care arm was seen, however these results are only supportive and subject to uncertainty due to small numbers. No subject achieved enteral autonomy during the study.

In SHP633-302 two Japanese infants 4 months through <1 year corrected gestational age were enrolled and received teduglutide. Both infants completed a 28-week study. The mean corrected gestation age was 10.0±1.20 months A ≥20% reduction in PS volume was recorded in 1 infant (50%) during the teduglutide treatment.

In the extension studies, based on diary data, totally 3/6 infants achieved a ≥20% reduction in PS volume at Cycle 1. They all received teduglutide treatment in the core- and extension study (TED/TED).

No infant subject enrolled in any of the core- or extension studies achieved enteral autonomy, i.e. complete weaning off PS during the study.

## 2.5. Clinical safety

### Introduction

The current SmPc for Revestive summarizes the safety profile as follows:

*Adverse reactions were retrieved from 2 placebo-controlled clinical studies with Revestive in 109 patients with SBS treated with doses of 0.05 mg/kg/day and 0.10 mg/kg/day for up to 24 weeks. Approximately 52% of the patients treated with Revestive experienced adverse reactions (versus 36% of the patients given placebo).*

*The most commonly reported adverse reactions were abdominal pain and distension (49%), respiratory tract infections (28%), nausea (27%), injection site reactions (21%), headache (17%), vomiting (14%) and oedema peripheral (10%). Approximately 38% of the treated patients with a stoma experienced gastrointestinal stoma complications. The majority of these reactions were mild or moderate. No new safety signals have been identified in patients exposed to 0.05 mg/kg/day of Revestive for up to 30 months in a long-term open-label extension study.*

The MAH presents safety data from all 4 clinical studies of teduglutide in which infants were enrolled (core studies SHP633-301 and SHP633-302; extension studies SHP633-304 and SHP633-305) for the evaluation of safety of teduglutide in infant subjects 4 to 12 months corrected gestational age with Short Bowel Syndrome (SBS) who are dependent on parenteral support (PS), as shown in **Table 31**. All data presented are for infants; data are not pooled and are presented by study.

**Table 31. Clinical safety Studies of Teduglutide with Enrolled Infants**

| Type of Study | Study ID | Country | Status | Objectives of the Study | Study Design | Subjects In Treatment Group(s) (Safety Population) | Healthy subjects or Diagnosis of patients | Treatment Duration | Study Report Location |
|---|---|---|---|---|---|---|---|---|---|
| **Pediatric Phase 3 Studies** | | | | | | | | | |
| Safety, efficacy, PK | SHP633-301 | Finland, France, Italy, UK | Complete | Safety, efficacy/PD and PK in infants with SBS | A Randomized, Open-label, 24-Week Safety, Efficacy, and Pharmacokinetic Study of Teduglutide in Infants 4 to 12 Months of Age with Short Bowel Syndrome Who are Dependent on Parenteral Support | 5 teduglutide 0.05 mg/kg/day SC<br>5 standard of care<br>Infants (n)=10 | Infant patients with SBS | 24 weeks | Module 5.3.5.2 |
| Safety, efficacy and PK | SHP633-302 | Japan | Complete | Safety, efficacy and PK in pediatric patients with SBS | A 24-week Safety, Efficacy, Pharmacodynamic, and Pharmacokinetic Study of Teduglutide in Japanese Pediatric Subjects, Aged 4 Months through 15 Years, with Short Bowel Syndrome who are Dependent on Parenteral Support | 10 teduglutide 0.05 mg/kg/day SC<br>Children n=8, Infants n=2 | Pediatric patients with SBS | 24 weeks | Module 5.3.5.2 |

| Type of Study | Study ID | Country | Status | Objectives of the Study | Study Design | Subjects In Treatment Group(s) (Safety Population) | Healthy subjects or Diagnosis of patients | Treatment Duration | Study Report Location |
|---|---|---|---|---|---|---|---|---|---|
| **Pediatric Phase 3 Studies** | | | | | | | | | |
| Uncontrolled Clinical Study | SHP633-304 | Belgium, Canada, Finland, Italy, UK, US | Complete | Long-term safety and efficacy in pediatric patients with SBS | A Prospective, Open-label, Long-term Safety and Efficacy Study of Teduglutide in Pediatric Patients with Short Bowel Syndrome Who Completed TED-C14-006 or / SHP633-301 | 54 teduglutide 0.05 mg/kg/day SC<br>Children n=49<br>Infants n=6<br>NTT/NTT = 1<br>NTT/TED = 1<br>TED/TED = 4 | Pediatric patients with SBS | Long-term extension[b] | Module 5.3.5.2 |
| Uncontrolled Clinical Study | SHP633-305 | Japan | Ongoing[a] | Long-term safety and efficacy in pediatric patients with SBS | A Prospective, Open-label, Long-term Safety and Efficacy Study of Teduglutide in Japanese Pediatric Subjects with Short Bowel Syndrome Who Completed SHP633-302 | 9 [a] teduglutide 0.05 mg/kg/day SC<br>Children n=7<br>Infants n=2 | Pediatric patients with SBS | Long-term extension[b] | Module 5.3.5.2 |

NTT=no teduglutide treatment; PK=pharmacokinetics; SBS=short bowel syndrome; TED=teduglutide.

[a] Study SHP633-305 is ongoing; the data cutoff date for infants was 14 Jul 2020. The data presented in this document and the SHP633-305 Interim CSR include at least 6 months of data in the extensions study for the 2 subjects in the infant cohort.

[b] Extension Study SHP633-304 and Study SHP633-305 include multiple treatment cycles of 24 weeks each.

## *Patient exposure*

As of May 2021, a total of 718 subjects have been treated with teduglutide and 247 subjects have been treated with placebo/standard of care in the overall clinical development program for teduglutide. Of the 718 subjects treated with teduglutide in the clinical studies, 613 were adult subjects, 97 were paediatric subjects, and 8 were infant subjects. **Table 32** presents the total number of infant subjects for whom data are presented.

**Table 32. Enumeration of Infant Subjects in the Teduglutide Clinical Development Programme**

| Study Group | Placebo/Standard of Care N | Teduglutide N | Total N |
|---|---|---|---|
| ***Core Studies*** | | | |
| SHP633-301 | 5 | 5 | 10 |
| SHP633-302 | 0 | 2 | 2 |
| ***Extension Studies*** | | | |
| SHP633-304 | 1[a] | 5[a,b] | 6[a] |
| SHP633-305 | 0 | 2[c] | 2[c] |
| **Grand Total Subjects** | **4** | **8[d]** | **12** |

[a] All infant subjects in Study SHP633-304 rolled over from the Core Study SHP633-301.
[b, d] One subject in the Study SHP633-301 standard of care group rolled over to SHP633-304 and started teduglutide treatment and is therefore accounted for in both Standard of Care and teduglutide treatment groups.
[c] All infant subjects in Study SHP633-305 rolled over from the Core Study SHP633-302.

In **Study SHP633-301**, 5 infant subjects were treated with teduglutide, for whom the mean duration of exposure was 149.4±42.15 days (range 74 days to 169 days).

For Study **SHP633-302**, 2 infant subjects were treated with teduglutide, for whom the mean duration (±standard deviation [SD]) of exposure was 167.5±0.71 days.

For Study **SHP633-304**, 5 infant subjects were treated with teduglutide, all of whom rolled over from Study SHP633-301 (1 of whom rolled in from the standard of care group in SHP633-301); the mean duration (SD) of exposure was 54.49±26.981 weeks.

For Study **SHP633-305**, 2 infant subjects were treated with teduglutide, both of whom rolled over from Study SHP633-302; the mean duration (SD) of overall exposure was 42.93±7.374 weeks.

**Table 33** presents the summary of exposure to teduglutide for the safety population for Study SHP633-301. The mean duration of exposure to teduglutide was 149.4±42.15 days (range 74 days to 169 days). Four subjects received ≥24 weeks (168 days) of treatment and 1 subject received 4 weeks to <12 weeks (28 days to <84 days) of treatment.

**Table 33. Study SHP633-301 – Extent of Exposure – Safety Population**

| Parameter | 0.05 mg/kg/day Teduglutide (N=5) |
|---|---|
| Extent of Exposure (days) | |
| Mean (SD) | 149.4 (42.15) |
| Median | 168.0 |
| Min, Max | 74, 169 |
| n (%) | |
| <4 Weeks | 0 |
| 4 – <12 Weeks | 1 (20.0) |
| 12- <24 Weeks | 0 |
| ≥24 Weeks | 4 (80.0) |

Extent of exposure is calculated as last study dose date – first study dose date + 1.
Subjects in the standard of care group do not receive study drug.
Percentages are based on the number of subjects in the specified population who received teduglutide.

**Table 34** presents the summary of exposure to teduglutide for the safety population for Study SHP633-302. The mean duration (±SD) of exposure to teduglutide in infants (n=2) was 167.5±0.71 days (167 and 168 days), and both infants received the 24-week teduglutide treatment.

**Table 34. Study SHP633-302 – Extent of Exposure – Safety Population (Infants Only)**

| Parameter | 0.05 mg/kg/day Teduglutide (N=2) |
|---|---|
| Extent of Exposure (days) | |
| Mean (SD) | 167.5 (0.71) |
| Median | 167.5 |
| Min, Max | 167, 168 |
| Any Exposure, n (%) | 2 (100.0) |
| <4 weeks, n (%) | 0 |
| 4-<12 weeks, n (%) | 0 |
| 12-<24 weeks, n (%) | 1 (50.0)[a] |
| ≥24 weeks, n (%) | 1 (50.0) |

SD=standard deviation
a: One infant who received the 167 days teduglutide treatment was regarded as the 24-week treatment.
Note: Extent of Exposure was defined as (last dose date - first dose date +1).

**Table 35** presents the summary of exposure to teduglutide in infants for the safety population for Study SHP633-304. The mean duration (SD) of exposure to teduglutide in infants (n=5) was 54.49±26.981 weeks. One subject who participated in SHP633-304 was in the NTT/NTT treatment group and is not included in the table below due to no exposure to study drug.

**Table 35. Study SHP633-304 – Extent of Exposure – Safety Population (Infants Only)**

| Parameter | Statistics | NTT/TED (N=1) | TED/TED (N=4) | ANY TED (N=5) |
|---|---|---|---|---|
| Overall extent of exposure in the core study plus extension (weeks) | n | 1 | 4 | 5 |
| | Mean (SD) | 63.57 (-) | 52.22 (30.598) | 54.49 (26.981) |
| | Median | 63.57 | 41.72 | 50.43 |
| | Min, Max | 63.6, 63.6 | 29.4, 96.0 | 29.4, 96.0 |
| 0-<6 | n (%) | 0 | 0 | 0 |
| 6-<12 | n (%) | 0 | 0 | 0 |
| 12-<18 | n (%) | 0 | 0 | 0 |
| 18-<24 | n (%) | 0 | 0 | 0 |
| 24-<30 | n (%) | 0 | 1 (25.0) | 1 (20.0) |
| 30-<36 | n (%) | 0 | 1 (25.0) | 1 (20.0) |
| 36-<42 | n (%) | 0 | 0 | 0 |
| 42-<48 | n (%) | 0 | 0 | 0 |
| 48-<54 | n (%) | 0 | 1 (25.0) | 1 (20.0) |
| 54-<60 | n (%) | 0 | 0 | 0 |
| 60-<66 | n (%) | 1 (100.0) | 0 | 1 (20.0) |
| 66-<72 | n (%) | 0 | 0 | 0 |
| 72-<78 | n (%) | 0 | 0 | 0 |
| 78-<84 | n (%) | 0 | 0 | 0 |
| 84-<90 | n (%) | 0 | 0 | 0 |
| 90-<96 | n (%) | 0 | 0 | 0 |
| 96-<102 | n (%) | 0 | 1 (25.0) | 1 (20.0) |

SD=standard deviation

Note: Overall extent of exposure in weeks is calculated as [the exposure in days in the core SHP633-301 study (date of last dose - date of first dose + 1) + the sum of extent of exposure across all cycles in the SHP633-304 extension study]/7.

**Table 36** presents the summary of exposure to teduglutide for the safety population for Study SHP633-305. The mean duration of overall exposure to teduglutide in infants (n=2) was 42.93±7.374 weeks; 1 infant received teduglutide treatment for 37.7 weeks and the other received teduglutide treatment for 48.1 weeks.

**Table 36. Table 44. Study SHP633-305 – Extent of Exposure – Safety Population (Infants Only)**

| Parameter | Statistics | 0.05 mg/kg/day Teduglutide (N=2) |
|---|---|---|
| Overall extent of exposure in the core study plus extension (weeks) | Mean (SD)<br>Median<br>Min, Max | 42.93 (7.374)<br>42.93<br>37.7, 48.1 |
| Any Exposure | n (%) | 2 (100.0) |
| 0-<12 weeks | n (%) | 0 (0.0) |
| 12-<24 weeks | n (%) | 0 (0.0) |
| 24-<48 weeks | n (%) | 1 (50.0) |
| 48-<72 weeks | n (%) | 1 (50.0) |
| 72-<96 weeks | n (%) | 0 (0.0) |
| 96-<120 weeks | n (%) | 0 (0.0) |
| 120-<144 weeks | n (%) | 0 (0.0) |
| 144-<168 weeks | n (%) | 0 (0.0) |
| At least 168 weeks | n (%) | 0 (0.0) |

SD=standard deviation
Note: Overall extent of exposure in weeks is calculated as [the exposure in days in the core Study SHP633-302 (date of last dose - date of first dose + 1) + the sum of extent of exposure across all cycles in the SHP633-305 extension study]/7.

Upon CHMP's request, the Applicant provided pooled teduglutide exposure analyses in **Table 37**.

**Table 37. SHP633 Pooled Extent of Exposure by Gestational Age**

| | <6 Months | 6 - <12 Months | Total |
|---|---|---|---|
| Overall extent of exposure in the core study plus extension (weeks) | | | |
| Mean (SD) | 39.93 (14.849) | 45.09 (31.596) | 43.61 (26.620) |
| Median (Min, Max) | 39.93 (29.4, 50.4) | 37.71 (10.6, 96.0) | 37.71 (10.6, 96.0) |
| | | | |
| Any Exposure, n (%) | 2 (100.0) | 5 (100.0) | 7 (100.0) |
| 0-<12 weeks, n (%) | 0 | 1 (20.0) | 1 (14.3) |
| 12-<24 weeks, n (%) | 0 | 0 | 0 |
| 24-<48 weeks, n (%) | 1 (50.0) | 2 (40.0) | 3 (42.9) |
| 48-<72 weeks, n (%) | 1 (50.0) | 1 (20.0) | 2 (28.6) |
| 72-<96 weeks, n (%) | 0 | 0 | 0 |
| 96-<120 weeks, n (%) | 0 | 1 (20.0) | 1 (14.3) |
| 120-<144 weeks, n (%) | 0 | 0 | 0 |
| 144-<168 weeks, n (%) | 0 | 0 | 0 |
| At least 168 weeks, n (%) | 0 | 0 | 0 |

Max: maximum; Min: minimum.

In the two core studies SHP633-301 and SHP633-302 and the two extension studies SHP633-304 and SHP633-305, a total of 7 patients aged 4 months to <1 year were exposed to teduglutide for an overall mean duration of 43.61 weeks, median 37.71 weeks. The mean exposure duration in the patients <6 months vs. ≥6 months -<1 year was 39.93 vs. 45.09 weeks, median 39.93 vs. 37.71 weeks. All

patients except 1 were exposed for at least 24 weeks in the core studies. This is acceptable and in alignment with the agreed PIP.

### *Adverse events*

In Study **SHP633-301**, a total of 87 treatment emergent adverse events (TEAEs) were reported in 10 (100%) infant subjects in both treatment groups (5 in the placebo arm, 5 in the teduglutide treatment arm). The TEAEs reported by subjects during the study were mostly mild in severity. There were 9 TEAEs that were considered by the investigator to be related to study drug in 2 (40.0%) subjects in the teduglutide arm. The most frequent TEAEs by PT in teduglutide treatment arm were vomiting in 3 (60.0%) subjects, and diarrhea, frequent bowel movements, pyrexia, and nasopharyngitis in 2 (40.0%) subjects each. In Study SHP633-301, a summary of TEAEs is presented in **Table 38**.

**Table 38. Study SHP633-301 Overall Summary of Treatment-Emergent Adverse Events – Safety Population**

| | Teduglutide (N=5) | | Standard of Care (N=5) | | Total Infants (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 of special interest[c] | 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; for AEs with more than 1 degree of severity, they are counted for each row.
b. Subjects are counted once per row; for AEs with more than 1 causality, they are counted for each row.
c. TEAEs of special interest are discussed in Section 2.1.5.

In Study **SHP633-302**, a total of 19 TEAEs were reported in 2 (100%) infant subjects. Of those TEAEs, none were considered by the investigator to be related to study drug. All TEAEs in infants were mild or moderate in severity. Adverse events system organ classes (SOCs) reported in both infants (100.0%) were in the SOCs of General disorders and administration site reactions, and Infections and infestations. A summary of TEAEs is presented in **Table 39**.

**Table 39. Study SHP633-302 Overall Summary of Treatment-Emergent Adverse Events – Safety Population**

| Category | Total Infants (N=2) | |
|---|---|---|
| | n (%) | m |
| Number of subjects with | | |
| At least one TEAE | 2 (100.0) | 19 |
| At least one TEAE related to the IP | 0 | |
| At least one TESAE | 2 (100.0) | 9 |
| At least one TESAE related to the IP | 0 | |
| TEAE Severity | | |
| Mild | 1 (50.0) | 12 |
| Moderate | 2 (100.0) | |
| Severe | 0 | 7 |
| Number of subjects with TEAE highest severity | | |
| Mild | 0 | |
| Moderate | 2 (100.0) | |
| Severe | 0 | |
| TESAE severity | | |
| Mild | 1 (50.0) | 3 |
| Moderate | 2 (50.0) | 6 |
| Severe | 0 | |

In Study **SHP633-304**, a total of 63 TEAEs were reported in 5 (100%) infant subjects across treatment groups. Of these, 3 subjects (60%) reported severe TEAEs. Two TEAEs were considered by the investigator to be related to study drug in 2 (40%) subjects. There were 2 TEAEs that led to treatment discontinuation in 1 (20%) subject, 1 TEAE that led to study discontinuation in 1 subject (20%), and 1 TEAE that led to death in 1 subject (20%). The most frequent TEAEs by PT in the teduglutide treatment arms were device-related sepsis in 3 (60%) subjects. A summary of TEAEs for the infants only are presented in **Table 40**.

**Table 40. Study SHP633-302 Overall Summary of Treatment-Emergent Adverse Events – Safety Population**

| | NTT/NTT (N=1) | | NTT/TED (N=1) | | TED/TED (N=4) | | Any TED (N=5) | |
|---|---|---|---|---|---|---|---|---|
| **Category** | **n(%)** | **m** | **n(%)** | **m** | **n(%)** | **m** | **n(%)** | **m** |
| Any TEAE | 1 (100.0) | 11 | 1 (100.0) | 27 | 4 (100.0) | 36 | 5 (100.0) | 63 |
| TEAE highest severity[a] | | | | | | | | |
| Mild | 0 | | 1 (100.0) | | 0 | | 1 (20.0) | |
| Moderate | 1 (100.0) | | 0 | | 1(25.0) | | 1 (20.0) | |
| Severe | 0 | | 0 | | 3 (75.0) | | 3 (60.0) | |
| TEAE relationship[b] | | | | | | | | |
| Not related | - | - | 0 | 26 | 3 (75.0) | 35 | 3 (60.0) | 61 |
| Related | - | - | 1 (100.0) | 1 | 1 (25.0) | 1 | 2 (40.0) | 2 |
| Any TESAE | 1 (100.0) | 3 | 1 (100.0) | 1 | 4 (100.0) | 12 | 5 (100.0) | 13 |
| TESAE relationship[b] | | | | | | | | |
| Not related | - | - | 1 (100.0) | 1 | 4 (100.0) | 12 | 5 (100.0) | 13 |
| Related | - | - | 0 | 0 | 0 | 0 | 0 | 0 |
| AE leading to treatment discontinuation | - | - | 0 | 0 | 1 (25.0) | 2 | 1 (20.0) | 2 |
| AE leading to study discontinuation | 0 | 0 | 0 | 0 | 1 (25.0) | 1 | 1 (20.0) | 1 |
| TEAE leading to death | 0 | 0 | 0 | 0 | 1 (25.0) | 1 | 1 (20.0) | 1 |
| TEAE of special interest[c] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

In Study **SHP633-305**, a total of 12 TEAEs were reported in 2 infant subjects (100%), of which 4 were TESAEs. Most TEAEs were mild or moderate in severity. There were no TEAEs considered by the investigator to be related to study drug, and no TEAEs leading to discontinuation.

In Study **SHP633-305**, of the data cutoff date, a summary of TEAEs for infants only are presented in **Table 41**.

**Table 41. Study SHP633-302 Overall Summary of Treatment-Emergent Adverse Events – Safety Population**

| **Category** | **Infants (N=2) N (%)** |
|---|---|
| Number of TEAEs | 12 |
| Number of subjects with: | |
| At least one TEAE | 2 (100.0) |
| At least one TEAE related to the IP | 0 |
| At least one TESAE | 2 (100.0) |
| At least one TESAE related to the IP | 0 |
| TEAE severity (number of events): | |
| Mild | 9 |
| Moderate | 2 |
| Severe | 1 |
| TEAE worst severity (number of subjects [%]): | |
| Mild | 1 (50.0) |
| Moderate | 0 |
| Severe | 1 (50.0) |
| TESAE severity (number of events): | |
| Mild | 2 |
| Moderate | 1 |
| Severe | 1 |
| TEAEs leading to discontinuation | 0 |

| | |
|---|---|
| TEAEs leading to death | 0 |
| TEAEs of special interest[a] | 0 |

IP=investigational product; TEAE=treatment-emergent adverse event; TESAE=treatment-emergent serious adverse event
[a] TEAEs of special interest are discussed in Section 2.1.5.

***Analysis by System Organ Class or Syndrome***

Across all clinical studies with teduglutide, the SOCs with the highest percentage of subjects reporting TEAEs were typically Gastrointestinal disorders, Infections and infestations, and General disorders and administration site conditions. Across the clinical studies that enrolled infants, a review of the TEAEs in the infant studies within the SOCs of Gastrointestinal disorders, Infections and infestations, and General disorders and administration site conditions revealed no new or unexpected trends and appeared consistent with the known characteristics of the patient population, the known site of action of teduglutide, and/or the mode of administration.

In Study **SHP633-301**, the incidence of TEAEs by system organ class (SOC) and PT are presented in **Table 42**.

For the teduglutide arm, the SOCs with the highest percentage of subjects reporting TEAEs were Infections and infestations in 4 (80.0%) subjects and Gastrointestinal disorders in 3 (60.0%) subjects. The most frequent TEAEs by PT were vomiting in 3 (60.0%) subjects, and diarrhea, frequent bowel movements, pyrexia, and nasopharyngitis in 2 (40.0%) subjects each. There were 4 events in 3 (60.0%) subjects in the teduglutide arm in the SOC of Product issues. Note that all of the device-related TEAEs were considered to be complications of central venous catheters used to prepare and administer PS, not the device used to prepare or administer teduglutide.

One subject in the teduglutide arm reported 20 out of the 87 TEAEs, which is consistent with the subject's extensive medical and surgical history that included liver biopsy, revision of ileostomy, and mucous fistula and stoma reversal, and are expected AEs in this patient population and not related to subject's treatment with teduglutide. This subject presented out of range hematology parameters, and elevated aspartate transaminase (AST), alanine transaminase (ALT), gamma glutamyl transferase (GGT), and alkaline phosphatase values at baseline, which are consistent with pretreatment liver disease.

For the standard of care arm, the SOCs with the highest percentage of subjects reporting TEAEs were Gastrointestinal disorders, Infections and infestations, and Investigations in 3 (60.0%) subjects each. The most frequent TEAEs were teething and upper respiratory tract infection in 2 (40.0%) subjects each.

**Table 42. Study SHP633-301 Incidence of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term – Safety Population**

| System Organ Class<br>Preferred Term | Teduglutide (N=5) | | Standard of Care (N=5) | | Total Infants (N=10) | |
|---|---|---|---|---|---|---|
| | 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 |

| System Organ Class<br>Preferred Term | Teduglutide (N=5) | | Standard of Care (N=5) | | Total Infants (N=10) | |
|---|---|---|---|---|---|---|
| | n (%) | m | n (%) | m | n (%) | m |
| **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 |
| **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.

In Study **SHP633-302**, the incidence of TEAEs by SOC and PT are presented in **Table 43**. Overall, 2 (100.0%) infants reported 19 TEAEs. Adverse events SOCs reported in both infants (100.0%) were in the SOCs of General disorders and administration site reactions, and Infections and infestations. All TEAEs by PT, with the exception of pyrexia (4 events in 2 [100.0%] subjects) were reported by 1 infant. Note that all of the device-related TEAEs were considered to be complications of central venous catheters used to prepare and administer PS, not the device used to prepare or administer teduglutide.

**Table 43. Study SHP633-302 Incidence of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term – Safety Population**

| System Organ Class<br>Preferred Term | Infants[a] (N=2) | |
|---|---|---|
| | n (%) | m |
| **Any TEAEs** | **2 (100.0)** | **19** |
| **Gastrointestinal disorders** | **1 (50.0)** | **1** |
| Enterocolitis | 1 (50.0) | 1 |
| **General disorders and administration site conditions** | **2 (100.0)** | **4** |
| Pyrexia | 2 (100.0) | 4 |
| **Infections and infestations** | **2 (100.0)** | **6** |
| Viral upper respiratory tract infection | 1 (50.0) | 1 |
| Device related infection | 1 (50.0) | 2 |
| Otitis media | 1 (50.0) | 1 |
| Upper respiratory tract infection | 1 (50.0) | 2 |
| **Injury, poisoning and procedural complications** | **1 (50.0)** | **1** |
| Vaccination complication | 1 (50.0) | 1 |
| **Respiratory, thoracic and mediastinal disorders** | **1 (50.0)** | **3** |
| Upper respiratory tract inflammation | 1 (50.0) | 3 |
| **Skin and subcutaneous tissue disorders** | **1 (50.0)** | **4** |
| Dry skin | 1 (50.0) | 1 |
| Dermatitis contact | 1 (50.0) | 1 |
| Dermatitis diaper | 1 (50.0) | 2 |

PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event; m=number of events
a: Infants of 4 through <12 months corrected gestational age.
Note: TEAEs were defined as any adverse events whose onset occurred, severity worsens or intensity increases during or after receiving the study medication.
Note: Subjects were counted no more than once for incidence but counted multiple times for the number of events.
Note: SOCs and PTs were coded using MedDRA v.20.0.

In Study **SHP633-304**, the incidence of TEAEs by SOC and PT only for the infants are presented in **Table 44**.

In the ANY TED group, overall, 5 (100%) subjects reported 63 TEAEs. The SOCs with the highest percentage of subjects reporting TEAEs were Gastrointestinal disorders in 5 (100.0%) subjects, Infections and infestations in 4 (80.0%) subjects, and General disorders and administration site conditions in 3 (60%) subjects. The most frequent TEAEs by PT were device related sepsis in 3 (60%) subjects, and the following PTs in 2 (40%) subjects each: device breakage, diarrhea, frequent bowel movements, pyrexia, rhinorrhea, upper respiratory tract infection, and vomiting. The balance of the PTs were reported in 1 (20%) subject each. Note that all of the device-related TEAEs were considered to be complications of central venous catheters used to prepare and administer PS, not the device used to prepare or administer teduglutide.

In the NTT/NTT group, overall, 1 (100%) subject reported 11 TEAEs, 6 of which were in the SOC of Skin and subcutaneous tissue disorders: 2 TEAEs of rash and erythema, and 1 each of rash erythematous and rash papular.

**Table 44. Study SHP633-304 Incidence of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term – Safety Population**

| | NTT/NTT (N=1) | | NTT/TED (N=1) | | TED/TED (N=4) | | ANY TED (N=5) | |
|---|---|---|---|---|---|---|---|---|
| **System Organ Class** Preferred Term | **n (%)** | **m** | **n (%)** | **m** | **n (%)** | **m** | **n (%)** | **m** |
| **Any AE** | **1 (100.0)** | **11** | **1 (100.0)** | **27** | **4 (100.0)** | **36** | **5 (100.0)** | **63** |
| **Gastrointestinal disorders** | **1 (100.0)** | **1** | **1 (100.0)** | **10** | **4 (100.0)** | **7** | **5 (100.0)** | **17** |
| Diarrhoea | 0 | 0 | 1 (100.0) | 2 | 1 (25.0) | 3 | 2 (40.0) | 5 |
| Frequent bowel movements | 0 | 0 | 1 (100.0) | 1 | 1 (25.0) | 1 | 2 (40.0) | 2 |
| Vomiting | 1 (100.0) | 1 | 1 (100.0) | 6 | 1 (25.0) | 1 | 2 (40.0) | 7 |
| Abdominal distension | 0 | 0 | 0 | 0 | 1 (25.0) | 1 | 1 (20.0) | 1 |
| Abdominal pain | 0 | 0 | 0 | 0 | 1 (25.0) | 1 | 1 (20.0) | 1 |
| Toothache | 0 | 0 | 1 (100.0) | 1 | 0 | 0 | 1 (20.0) | 1 |
| **General disorders and administration site conditions** | **1 (100.0)** | **1** | **1 (100.0)** | **1** | **2 (50.0)** | **2** | **3 (60.0)** | **3** |
| Pyrexia | 1 (100.0) | 1 | 0 | 0 | 2 (50.0) | 2 | 2 (40.0) | 2 |
| Complication associated with device | 0 | 0 | 1 (100.0) | 1 | 0 | 0 | 1 (20.0) | 1 |
| **Infections and infestations** | **1 (100.0)** | **2** | **1 (100.0)** | **5** | **3 (75.0)** | **7** | **4 (80.0)** | **12** |
| Device related sepsis | 1 (100.0) | 1 | 0 | 0 | 3 (75.0) | 3 | 3 (60.0) | 3 |
| Upper respiratory tract infection | 0 | 0 | 1 (100.0) | 2 | 1 (25.0) | 1 | 2 (40.0) | 3 |
| Catheter site infection | 0 | 0 | 0 | 0 | 1 (25.0) | 1 | 1 (20.0) | 1 |
| Device related infection | 0 | 0 | 0 | 0 | 1 (25.0) | 2 | 1 (20.0) | 2 |
| Nasopharyngitis | 0 | 0 | 1 (100.0) | 1 | 0 | 0 | 1 (20.0) | 1 |
| Rhinitis | 0 | 0 | 1 (100.0) | 1 | 0 | 0 | 1 (20.0) | 1 |

| | NTT/NTT (N=1) | | NTT/TED (N=1) | | TED/TED (N=4) | | ANY TED (N=5) | |
|---|---|---|---|---|---|---|---|---|
| **System Organ Class** Preferred Term | **n (%)** | **m** | **n (%)** | **m** | **n (%)** | **m** | **n (%)** | **m** |
| Urinary tract infection | 0 | 0 | 1 (100.0) | 1 | 0 | 0 | 1 (20.0) | 1 |
| Lower respiratory tract infection | 1 (100.0) | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Injury, poisoning and procedural complications** | **0** | **0** | **1 (100.0)** | **1** | **1 (25.0)** | **1** | **2 (40.0)** | **2** |
| Anastomotic ulcer | 0 | 0 | 0 | 0 | 1 (25.0) | 1 | 1 (20.0) | 1 |
| Procedural pain | 0 | 0 | 1 (100.0) | 1 | 0 | 0 | 1 (20.0) | 1 |
| **Investigations** | **0** | **0** | **0** | **0** | **1 (25.0)** | **2** | **1 (20.0)** | **2** |
| Haemoglobin decreased | 0 | 0 | 0 | 0 | 1 (25.0) | 1 | 1 (20.0) | 1 |
| Serum ferritin decreased | 0 | 0 | 0 | 0 | 1 (25.0) | 1 | 1 (20.0) | 1 |
| **Metabolism and nutrition disorders** | **0** | **0** | **0** | **0** | **1 (25.0)** | **1** | **1 (20.0)** | **1** |
| Decreased appetite | 0 | 0 | 0 | 0 | 1 (25.0) | 1 | 1 (20.0) | 1 |
| **Nervous system disorders** | **0** | **0** | **0** | **0** | **2 (50.0)** | **5** | **2 (40.0)** | **5** |
| Cerebral ischaemia | 0 | 0 | 0 | 0 | 1 (25.0) | 1 | 1 (20.0) | 1 |
| Ischaemic stroke | 0 | 0 | 0 | 0 | 1 (25.0) | 2 | 1 (20.0) | 2 |
| Somnolence | 0 | 0 | 0 | 0 | 1 (25.0) | 1 | 1 (20.0) | 1 |
| Vasculitis cerebral | 0 | 0 | 0 | 0 | 1 (25.0) | 1 | 1 (20.0) | 1 |
| **Product issues** | **1 (100.0)** | **1** | **0** | **0** | **2 (50.0)** | **8** | **2 (40.0)** | **8** |
| Device breakage[a] | 1 (100.0) | 1 | 0 | 0 | 2 (50.0) | 8 | 2 (40.0) | 8 |
| **Respiratory, thoracic and mediastinal disorders** | **0** | **0** | **1 (100.0)** | **7** | **1 (25.0)** | **1** | **2 (40.0)** | **8** |
| Rhinorrhoea | 0 | 0 | 1 (100.0) | 2 | 1 (25.0) | 1 | 2 (40.0) | 3 |
| Cough | 0 | 0 | 1 (100.0) | 3 | 0 | 0 | 1 (20.0) | 3 |
| Epistaxis | 0 | 0 | 1 (100.0) | 2 | 0 | 0 | 1 (20.0) | 2 |
| **Skin and subcutaneous tissue disorders** | **1 (100.0)** | **6** | **1 (100.0)** | **3** | **1 (25.0)** | **2** | **2 (40.0)** | **5** |
| Dermatitis diaper | 0 | 0 | 0 | 0 | 1 (25.0) | 2 | 1 (20.0) | 2 |
| Pain of skin | 0 | 0 | 1 (100.0) | 1 | 0 | 0 | 1 (20.0) | 1 |
| Rash | 1 (100.0) | 2 | 1 (100.0) | 2 | 0 | 0 | 1 (20.0) | 2 |
| Erythema | 1 (100.0) | 2 | 0 | 0 | 0 | 0 | 0 | 0 |
| Rash erythematous | 1 (100.0) | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| Rash papular | 1 (100.0) | 1 | 0 | 0 | 0 | 0 | 0 | 0 |

In Study **SHP633-305**, as of the data cut-off date, the incidence of TEAEs by SOC and PT are presented in **Table 45**. In infants, the only SOC with AEs reported in both subjects was Infections and infestations. All TEAEs by PT were reported by 1 infant. Note that all of the device-related TEAEs were considered to be complications of central venous catheters used to prepare and administer PS, not the device used to prepare or administer teduglutide.

**Table 45. Study SHP633-305 Incidence of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term – Safety Population**

| System Organ Class<br>Preferred Term | Infants (N=2)<br>n (%) | <br>m |
|---|---|---|
| **Any TEAEs** | **2 (100.0)** | **12** |
| **Gastrointestinal disorders** | **1 (50.0)** | **1** |
| Pancreatitis acute | 1 (50.0) | 1 |
| **General disorders and administration site conditions** | **1 (50.0)** | **1** |
| Injection site reaction | 1 (50.0) | 1 |
| **Infections and infestations** | **2 (100.0)** | **6** |
| Viral upper respiratory tract infection | 1 (50.0) | 1 |
| Medical device site infection | 1 (50.0) | 1 |
| Gastroenteritis adenovirus | 1 (50.0) | 1 |
| Oral candidiasis | 1 (50.0) | 1 |
| Upper respiratory tract infection | 1 (50.0) | 2 |
| **Investigations** | **1 (50.0)** | **1** |
| Blood alkaline phosphatase increased | 1 (50.0) | 1 |
| **Nervous system disorders** | **1 (50.0)** | **1** |
| Seizure | 1 (50.0) | 1 |
| **Skin and subcutaneous tissue disorders** | **1 (50.0)** | **2** |
| Dermatitis | 1 (50.0) | 1 |
| Dermatitis diaper | 1 (50.0) | 1 |

PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event; m=events
[a] The number of children enrolled based upon Protocol Amendment 3.
Note: TEAEs were defined as any adverse events whose onset occurred, severity worsened or intensity increased during or after receiving the first IP dose in the core study. Only AEs recorded in the current study are summarized.
Note: Subjects were counted no more than once for incidence but counted multiple times for the number of events.
Note: SOCs and PTs were coded using MedDRA v.20.0.

## *Serious adverse event/deaths/other significant events*

**Treatment-Emergent Adverse Events by Maximum Severity**

In Study **SHP633-301**: Overall, the majority of TEAEs reported during the study were mild or moderate in severity.

A total of 3 severe TEAEs were reported during the study; 1 in the teduglutide treatment arm and 2 in the standard of care arm: 1 subject in the teduglutide arm reported the event of device leakage and 2 subjects in the standard of care arm each reported the event of device related infection.

All severe TEAEs were assessed as serious due to the subjects' hospitalization and considered by the investigators to be not related to study drug. Note that all of the device-related TEAEs were considered to be complications of central venous catheters used to prepare and administer PS, not the device used to prepare or administer teduglutide.

**SHP633-302**: In infants, all TEAEs were mild or moderate.

In Study **SHP633-304**: Overall, the majority of TEAEs reported during the study were mild or moderate in severity.

In the ANY TED group, 3 subjects reported severe TEAEs: device related sepsis in 2 (40%) subjects; catheter site infection, cerebral ischaemia, device related infection, ischemic stroke, and pyrexia in 1 (20%) subject each. In the NTT/NTT group, all TEAEs were mild or moderate. Note that all of the device-related TEAEs were considered to be complications of central venous catheters used to prepare and administer PS, not the device used to prepare or administer teduglutide.

Study **SHP633-305**: as of the data cutoff date, all TEAEs were mild or moderate in severity, except for a severe TESAE of acute pancreatitis in 1 infant which was considered by the investigator to be not related to teduglutide treatment.

**Treatment-Emergent Adverse Events by Relationship**

In Study **SHP633-301**, TEAEs by causal relationship are presented in **Table 46**. Overall, 9 TEAEs reported in 2 (20.0%) subjects were considered by the investigator to be related to study drug; both subjects were enrolled in the teduglutide arm.

One subject reported 8 of the 9 related TEAEs (abdominal distension, gastrointestinal sounds abnormal, vomiting [5 events], and fecal volume increased) as well as multiple non-related TEAEs all linked to the SOC of Gastrointestinal disorders. This subject's dosing with teduglutide on Day 75 per parents' decision (not the investigator's) and was never resumed, and the subject was last evaluated on Day 207. The other subject reported 2 TEAEs of alanine aminotransferase increased, and only the second event was considered by the investigator to be related to study drug. The investigator considered that event to be moderate in intensity. The subject's bilirubin remained in the normal range, and no action with study drug was taken. This subject later enrolled in the extension study.

**Table 46. Study SHP633-301 Summary of Treatment-Emergent Adverse Events by Causal Relationship by System Organ Class and Preferred Term – Safety Population**

| | Teduglutide (N=5) | | Standard of Care (N=5) | | Total Infants (N=10) | |
|---|---|---|---|---|---|---|
| **Category** | **n (%)** | **m** | **n (%)** | **m** | **n (%)** | **m** |
| **Any TEAE** | **2 (40.0)** | **9** | **0** | **0** | **2 (20.0)** | **9** |
| **Gastrointestinal Disorders** | **1 (20.0)** | **7** | **0** | **0** | **1 (10.0)** | **7** |
| Abdominal distension | 1 (20.0) | 1 | 0 | 0 | 1 (10.0) | 1 |
| Gastrointestinal sounds abnormal | 1 (20.0) | 1 | 0 | 0 | 1 (10.0) | 1 |
| Vomiting | 1 (20.0) | 5 | 0 | 0 | 1 (10.0) | 5 |
| **Investigations** | **2 (40.0)** | **2** | **0** | **0** | **2 (20.0)** | **2** |
| Alanine aminotransferase increased | 1 (20.0) | 1 | 0 | 0 | 1 (10.0) | 1 |
| Fecal volume increased | 1 (20.0) | 1 | 0 | 0 | 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.

In Study **SHP633-302**, no TEAEs considered by the investigator to be related to study drug were reported in either infant.

In Study **SHP633-304**, overall, 2 TEAEs reported in 2 (40.0%) subjects were considered by the investigator to be related to study drug; 1 subject was in the NTT/TED group reported 1 event of vomiting; the other subject was in the NTT/TED group and reported 1 event of abdominal pain.

In Study **SHP633-305**, as of the data cutoff date, no TEAEs considered by the investigator to be related to study drug were reported in either of the 2 infants.

**Deaths**

No deaths were reported in infants in any of the studies presented. However, in Study SHP633-304, 1 death was reported in an adolescent in this study and, for completeness, a mini-narrative is presented below.

In Study SHP633-304, the subject was an adolescent male subject with a medical history of SBS, midgut volvulus, cerebral palsy, hydrocephalus, and seizure disorder. The subject commenced treatment with teduglutide 0.05 mg/kg/day in Study TED-C14-006 and the last dose of teduglutide was administered in Study SHP633-304 approximately 11 months after treatment start. Per the investigator, the subject's family elected to pursue end-of-life care due to the inability of the subject to

wean off PS and impaired quality-of-life related to both SBS and comorbid conditions. For reasons unrelated to teduglutide, the subject died shortly thereafter due to worsening of SBS, which was assessed by the investigator as serious and severe in intensity.

**Other Serious Adverse Events**

In Study **SHP633-301**, TESAEs by SOC and by PT are presented in **Table 47**. Overall, 7 subjects reported 11 TESAEs: 4 (80.0%) subjects in the teduglutide treatment arm and 3 (60.0%) subjects in the standard of care arm.

For the teduglutide arm, SOCs with subjects reporting TESAEs are Product issues in 2 (40.0%) subjects, and General disorders and administration site conditions and Immune system disorder in 1 (20.0%) subject each. A total of 5 TESAEs were reported, all of which considered by the investigator to be not related to study drug. One subject reported 2 events of pyrexia, 1 subject reported the event of immunization reaction, 1 subject reported the event of device breakage, and another subject the event of device leakage. Note that all of the device-related TEAEs were considered to be complications of central venous catheters used to prepare and administer PS, not the device used to prepare or administer teduglutide.

For the standard of care arm, the SOCs with subjects reporting TESAEs are Infections and infestations in 2 (40.0%) subjects, and Investigations, Metabolism and nutrition disorders, Nervous system disorders, and Product issues in 1 (20.0%) subject each. A total of 6 TESAEs were reported, all of which were considered by the investigator to be not related to study drug: 2 (40.0%) subjects reported the events of device related infection, 1 (20%) subject reported the event of transaminases increased, and 1 (20%) subject reported all the events of metabolic acidosis, ataxia, and device occlusion.

**Table 47. SHP633-301—Summary of Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term—Safety Population**

| | Teduglutide (N=5) | | Standard of Care (N=5) | | Total Infants (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.

In Study **SHP633-302**, TESAEs by SOC and by PT are presented in **Table 48**.

Overall, 2 (100%) infant subjects reported 9 TESAEs, none of which were considered by the investigator to be related to study drug. The SOCs with infant subjects reporting TESAEs were General disorders and administration site conditions and Infections and infestations, 2 (100%) subjects; Respiratory, thoracic and mediastinal disorders, 1 subject (50%). Both infants reported TESAEs of pyrexia. In addition, device related infection, upper respiratory tract infection and upper respiratory tract inflammation reported were each also noted in 1 infant, respectively. Note that all of the device-related TEAEs were considered to be complications of central venous catheters used to prepare and administer PS, not the device used to prepare or administer teduglutide.

**Table 48. SHP633-302—Summary of Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term—Safety Population (Infants Only)**

| SOC<br>PT | Infants[b]<br>(N=2)<br>n (%) | Events |
|---|---|---|
| **Any TESAE** | **2 (100.0)** | **9** |
| **General disorders and administration site conditions** | **2 (100.0)** | **4** |
| Pyrexia | 2 (100.0) | 4 |
| **Immune system disorders** | **0** | **0** |
| Anaphylactic reaction | 0 | 0 |
| **Infections and infestations** | **2 (100.0)** | **4** |
| Device infection | 1 (50.0) | 2 |
| Adenovirus infection | 0 | 0 |
| Gastroenteritis | 0 | 0 |
| Medical device site infection | 0 | 0 |
| Hand-foot-and-mouth disease | 0 | 0 |
| Upper respiratory tract infection | 1 (50.0) | 2 |
| **Respiratory, thoracic and mediastinal disorders** | **1 (50.0)** | **1** |
| Upper respiratory tract inflammation | 1 (50.0) | 1 |

SOC=system organ class; PT=preferred term

a: Infants of 4 through <12 months corrected gestational age.

Note: Subjects were counted no more than once for incidence, but counted multiple times for the number of events.

Note: SOCs and PTs were coded using MedDRA v.20.0.

In Study **SHP633-304**, TESAEs by SOC and by PT for the infants are presented in **Table 49**.

Overall, in the ANY TED group, 5 (100%) infant subjects reported 13 TESAEs. The SOCs with infant subjects reporting TESAEs were Infections and infestations, 3 (60%) subjects; General disorders and administration site conditions, 2 (40%) subjects; Nervous system disorders and Product issues, 1 subject (50%) each. All of the device-related TEAEs were considered as complications of central venous catheters used to prepare and administer PS, not the device used to prepare or administer teduglutide. All TESAEs were considered by the investigator to not be related to study drug: 3 subjects (60%) reported 3 events of device related sepsis, 1 subject (20%) reported 2 events of ischemic stroke, and 1 subject (20%) reported 2 events of device breakage; the balance were single events in 1

(20%) subject each: catheter site infection, cerebral ischaemia, complication associated with device, device related infection, pyrexia, and upper respiratory tract infection. Note that all of the device-related TEAEs were considered to be complications of central venous catheters used to prepare and administer PS, not the device used to prepare or administer study drug.

Overall, in the NTT group, 1 infant subject reported 3 TESAEs. The SOCs with infant subject reporting TESAEs were Infections and infestations and Product issues in 1 subject (100%) each. The 3 TESAEs were device related sepsis, lower respiratory tract infection, and device breakage. Note that all of the device-related TEAEs were considered to be complications of central venous catheters.

**Table 49. SHP633-304—Summary of Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term—Safety Population (Infants Only)**

| | NTT/NTT (N=1) | | NTT/TED (N=1) | | TED/TED (N=4) | | Any TED (N=5) | |
|---|---|---|---|---|---|---|---|---|
| **Category** | **n (%)** | **m** | **n (%)** | **m** | **n (%)** | **m** | **n (%)** | **m** |
| **Any TESAE** | **1 (100.0)** | **3** | **1 (100.0)** | **1** | **4 (100.0)** | **12** | **5 (100.0)** | **13** |
| **General disorders and administration site conditions** | **0** | **0** | **1 (100.0)** | **1** | **1 (25.0)** | **1** | **2 (40.0)** | **2** |
| Complication associated with device | 0 | 0 | 1 (100.0) | 1 | 0 | 0 | 1 (20.0) | 1 |
| Pyrexia | 0 | 0 | 0 | 0 | 1 (25.0) | 1 | 1 (20.0) | 1 |
| **Infections and infestations** | **1 (100.0)** | **2** | **0** | **0** | **3 (75.0)** | **6** | **3 (60.0)** | **6** |
| Device related sepsis | 1 (100.0) | 1 | 0 | 0 | 3 (75.0) | 3 | 3 (60.0) | 3 |
| Catheter site infection | 0 | 0 | 0 | 0 | 1 (25.0) | 1 | 1 (20.0) | 1 |
| Device related infection | 0 | 0 | 0 | 0 | 1 (25.0) | 1 | 1 (20.0) | 1 |
| Upper respiratory tract infection | 0 | 0 | 0 | 0 | 1 (25.0) | 1 | 1 (20.0) | 1 |
| Lower respiratory tract infection | 1 (100.0) | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Nervous system disorders** | **0** | **0** | **0** | **0** | **1 (25.0)** | **3** | **1 (20.0)** | **3** |
| Cerebral ischaemia | 0 | 0 | 0 | 0 | 1 (25.0) | 1 | 1 (20.0) | 1 |
| Ischaemic stroke | 0 | 0 | 0 | 0 | 1 (25.0) | 2 | 1 (20.0) | 2 |
| **Product issues** | **1 (100.0)** | **1** | **0** | **0** | **1 (25.0)** | **2** | **1 (20.0)** | **2** |
| Device breakage | 1 (100.0) | 1 | 0 | 0 | 1 (25.0) | 2 | 1 (20.0) | 2 |

m=Number of events; n=Number of subjects experiencing the event, TESAE=Treatment-emergent serious adverse event
Note: TESAE, defined as serious treatment emergent events occurring from the time of the signing of the informed consent form (ICF) for this extension study through last study visit.
Note: Percentages are based on the number of subjects enrolled in each treatment group.
Note: Treatment-emergent adverse events are defined as adverse events that started or worsened on or after the date of first dose for treatment groups TED/TED, TED/NTT, NTT/TED and ANY TED and adverse events that started or worsened on or after the core study baseline visit for NTT/NTT.
Note: Subjects are counted no more than once for incidence, but can be counted multiple times for the number of events.
Note: Adverse events were coded to primary SOC and preferred term using the MedDRA v.19.1.

In Study **SHP633-305**, as of the data cutoff date, TESAEs by SOC and by PT are presented in **Table 50**.

Overall, in infants, 4 TESAEs were reported in 2 subjects (100.0%). The SOCs with infant subjects reporting TESAEs were Gastrointestinal disorders, Infections and infestations, and Nervous system disorders, all in 1 subject (50%) each. One infant reported a TESAE of acute severe pancreatitis; teduglutide treatment was interrupted, the event was treated, and considered). Other TESAEs included gastroenteritis adenovirus, seizure, and upper respiratory tract infection, all of which were reported by 1 infant. None of the TESAEs were considered by the investigator to be related to study drug.

**Table 50. SHP633-305—Summary of Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term—Safety Population (Infants Only)**

| System Organ Class<br>Preferred Term | Infants (N=2)<br>n (%) | <br>Events |
|---|---|---|
| **Any TESAEs** | **2 (100.0)** | **4** |
| **Gastrointestinal disorders** | **1 (50)** | **1** |
| Pancreatitis acute | 1 (50) | 1 |
| **Infections and infestations** | **1 (50.0)** | **2** |
| Gastroenteritis adenovirus | 1 (50.0) | 1 |
| Upper respiratory tract infection | 1 (50.0) | 1 |
| **Nervous system disorders** | **1 (50.0)** | **1** |
| Seizure | 1 (50.0) | 1 |

SOC=system organ class; PT=preferred term; m=events
Note: Subjects were counted no more than once for incidence, but counted multiple times for the number of events.
Note: SOCs and PTs were coded using MedDRA v.20.0.

**Other Significant Adverse Events**

**Adverse Events Leading to Discontinuation**

In Study **SHP633-301**, overall, 1 subject enrolled in the teduglutide arm reported 5 TEAEs that led to study drug discontinuation (vomiting [2 events], gastrointestinal sounds abnormal, irritability, and fecal volume increased; 1 event each). Teduglutide treatment was interrupted at Day 75 (after Week 10 visit) following the parents' 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 (Day 72 through Day 96 and Day 86 through Day 96), gastrointestinal sounds abnormal (Day 72 through Day 207), and fecal volume increased (Day 96 through Day 135) were considered by the investigator to be related to study drug and mild in severity (except for 1 event of vomiting of Day 72 through Day 96 deemed moderate in severity). The event of irritability (Day 72 through Day 207) was considered by the investigator to not be related to study drug and mild in severity. All events were considered recovered and resolved; teduglutide treatment was never resumed, although the subject did complete the study.

In Study **SHP633-302**, no infants discontinued due to AEs during the conduct of the study.

In Study **SHP633-304**, no infants discontinued due to AEs during the conduct of the study.

In Study **SHP633-305**, as of the data cutoff date, no TEAEs leading to discontinuation were reported. However, A 12.1-month old female infant reported a severe TESAE of acute pancreatitis on 30 Dec 2019, 88 days after initiating teduglutide, which was interrupted. The TESAE was considered by the investigator to not be related to study drug. At a point just after data cutoff, the subject discontinued from the study due to the risk of severe acute pancreatitis. Therefore, this discontinuation is not reflected in the current data outputs yet.

**Adverse Events of Special Interest**

Across studies SHP633-301, SHP633-302, SHP633-304, and SHP633-305, adverse events of special interest (AESI) were defined in each study protocol as:

- Growth of pre-existing polyps of the colon
- Benign neoplasia of the GI tract including the hepatobiliary system

- Tumor-promoting ability (eg, benign and/or malignant neoplasia of any kind, not limited to those of the GI or hepatobiliary system)

Following is a review of AESIs reported in these studies.

In Study **SHP633-301**, no AESIs were reported during the conduct of this study.

In Study **SHP633-302**, no AESIs were reported during the conduct of this study.

In Study **SHP633-304**, there was 1 unconfirmed AESI of cecal polyps reported in a non-infant subject.

In Study **SHP633-305**, no AESIs were reported during the conduct of this study.

**Analysis of Adverse Events by Organ System or Syndrome**

This section presents a review of TEAEs by SOC. Across all clinical studies, the SOCs with the highest percentage of subjects reporting TEAEs were typically Gastrointestinal disorders, Infections and infestations, and General disorders and administration site conditions.

The safety data observed in infant patients treated with teduglutide was consistent with that observed in the overall adult and paediatric patients with SBS treated with teduglutide. Across the clinical studies that enrolled infants, a review of the TEAEs within the SOCs of Gastrointestinal disorders, Infections and infestations, and General disorders and administration site conditions revealed no new or unexpected trends and appeared consistent with the known characteristics of the patient population, the known site of action of teduglutide, and/or the mode of administration.

Following is a brief review of the TEAEs by highest reporting SOC.

**Gastrointestinal Disorders**

Across all studies, Gastrointestinal disorders was consistently one of the most frequently reported SOC for TEAEs in teduglutide-treated adult, paediatric, and infant patients. For patients with SBS, TEAEs in the Gastrointestinal disorders SOC appear consistent with the underlying disease and therefore are not unexpected. A review of the TEAEs within the SOC of Gastrointestinal disorders in the infant studies revealed no new or unexpected results.

**Infections and Infestations**

Across all studies, Infections and infestations also was consistently one of the most frequently reported SOC for TEAEs in teduglutide-treated adult, paediatric, and infant patients. For patients with SBS, device-related infection events commonly result from the central venous catheters used to administer PS and are, therefore, not unexpected. Across the teduglutide development program, all device-related infection events were related to central venous catheters used to administer PS and not to the teduglutide injection device. A review of the TEAEs within the SOC of Infections and infestations in the infant studies revealed no new or unexpected results.

**General Disorders and Administration Site Conditions**

Across all studies, General disorders and administration site conditions was consistently one of the most frequently reported SOC for TEAEs in teduglutide-treated adult, paediatric, and infant patients. A review of the TEAEs within the SOC of General disorders and administration site conditions in the infant studies revealed no new or unexpected results.

## *Laboratory findings*

**Serum Chemistry**

In Study **SHP633-301**, no clinically meaningful change was observed in infants in chemistry measures during the study, other than increased ALT and increased transaminases values each in 1 subject in the standard of care arm and increased ALT in 1 subject in the teduglutide treatment arm.

In Study **SHP633-302**, no clinically meaningful change was observed in chemistry measurements in infants from baseline through Week 28.

In Study **SHP633-304**, no clinically meaningful change was observed in chemistry measurements in infants during the study.

In Study **SHP633-305**, as of the data cutoff date, out of range high or low chemistry values were observed in infants for various tests at various visits. These results were not remarkable during either period in any cycle.

**Hematology**

In Study **SHP633-301**, no clinically meaningful change was observed in infants in hematology measurements during the study.

In Study **SHP633-302**, no clinically meaningful change was observed in infants in hematology measurements from baseline through Week 28.

In Study **SHP633-304**, no clinically meaningful change was observed in infants in hematology measurements during the study.

In Study **SHP633-305**, as of the data cutoff date, out of range high or low hematology values were observed in infants for various hematology tests at various visits. These results were not remarkable during either period in any cycle.

**Urinalysis**

In Study **SHP633-301**, no clinically meaningful change was observed in urinalysis measurements during the study.

In Study **SHP633-302**, no clinically meaningful change was observed in urinalysis measurements from baseline through Week 28.

In **Study SHP633-304**, no clinically meaningful change was observed in infants in urinalysis measurements during the study.

In Study **SHP633-305**, as of the data cutoff date, as of the data cutoff date, out of range high or low values were observed for most subjects for various urinalysis tests at various visits. These results were not remarkable during either period in any cycle.

**Individual Clinically Significant Abnormalities**

**Serum Chemistry**

In Study **SHP633-302**, markedly abnormal findings in chemistry were reported in 1 infant: the infant had markedly elevated lipase (>3×ULN); the baseline value of lipase in this infant was 46 U/L and, after teduglutide treatment, this value increased over time, reaching the clinically abnormal range (>3×ULN) of 106 U/L at Week 2. Lipase value increased to 507 U/L at Week 6. After that, this value was gradually decreased; lipase value was 34 U/L at EOT and 36 U/L at EOS. Amylase was within the normal range (28 100 U/L) throughout the study with the exception of low values (22 and 23 U/L at Weeks 10 and 12, respectively). No AEs relating to the elevated lipase were reported.

***Vital Signs and Other Safety Evaluations***

Across the clinical studies that enrolled infants, no clinically meaningful vital sign changes in pulse rate, blood pressure, or body temperature in infants were reported. Electrocardiograms were not assessed in Study SHP633-301, Study SHP633-304, or Study SHP633-305; in Study SHP633-302, no clinically significant abnormalities in ECGs were reported. Antibody testing was performed across studies. In Study SHP633-301, no anti-drug antibodies (ADAs) were detected in tested subjects. In Study SHP633-302, ADA were detected in both infants at end of treatment and end of study; the infant with neutralizing ADA was not a responder. In Study SHP633-304, antibody positivity varied at different assessment points; at the end of study timepoint, 2 of 3 (66.7%) subjects tested ADA negative: 1 subject was positive for anti-teduglutide antibodies, with neutralizing antibodies present. In Study SHP633-305 (ongoing), 1 ADA was detected prior to teduglutide dosing in 1 infant and positive ADA with neutralizing antibodies were present at Week 12 for the other infant.

**Vital Signs**

In Study **SHP633-301**, no clinically meaningful vital sign changes in pulse rate, blood pressure, or body temperature in infants were reported.

In Study **SHP633-302,** no clinically meaningful vital sign changes in pulse rate, blood pressure, or body temperature were reported in infants.

In Study **SHP633-304**, no clinically meaningful vital sign changes in pulse rate, blood pressure, or body temperature were reported.

In Study **SHP633-305**, as of the data cutoff date, no clinically meaningful vital sign changes in pulse rate, blood pressure, or body temperature were reported.

**Electrocardiograms**

Electrocardiograms were not assessed Study SHP633-301, Study SHP633-304, or Study SHP633-305.

In Study **SHP633-302**, no clinically significant abnormalities in ECGs were reported.

**Antibodies**

In Study **SHP633-301**, none of the 3 subjects in the teduglutide arm who were tested at Week 12 and Week 28 (EOS) visits had ADAs detected.

In Study **SHP633-302,** ADA were detected in both infants at EOT and EOS. One infant had neutralizing ADA at EOT and EOS, and the other had non-neutralizing ADA at EOT and EOS. The infant with non-neutralizing ADA was a responder, ie, a ≥20% reduction in PS volume; whereas the infant with neutralizing ADA was not a responder.

In Study **SHP633-304**: Overall, of 49 subjects (children and infants) tested in the TED/TED group, the number with neutralizing antibodies varied over time between 0 and 5 subjects and a lack of effect of antibody positivity on response to teduglutide treatment was concluded. Specifically, a summary of antibody test results for the 4 infants in the TED/TED group at Day 1 and Week 28 of each treatment cycle is presented in **Table 51**. At Cycle 1 Day 1, 3 out of 4 subjects tested in the TED/TED group were negative for anti-teduglutide antibodies; 1 subject was positive with neutralizing antibodies present. At the end of study timepoint, 2 of 3 (66.7%) subjects tested negative; 1 subject was positive for anti-teduglutide antibodies, with neutralizing antibodies present.

**Table 51. SHP633-304—Summary of Antibody Results by Visit (Safety Population)—Infants Only**

| Visit<br>Results | TED/TED<br>(N=4) |
|---|---|
| **Cycle 1 Day 1** | |
| n | 4 |
| Negative n (%) | 3 (75.0) |
| Positive n (%) | 1 (25.0) |
| No neutralizing antibodies present n (%) | 0 |
| Neutralizing antibodies present n (%) | 1 (100.0) |
| **Cycle 1 Week 24** | |
| n | 1 |
| Negative n (%) | 1 (100.0) |
| Positive n (%) | 0 |
| No neutralizing antibodies present | 0 |
| Neutralizing antibodies present | 0 |
| **Cycle 2 Day 1** | |
| n | 1 |
| Negative n (%) | 0 |
| Positive n (%) | 1 (100.0) |
| No neutralizing antibodies present | 1 (100.0) |
| Neutralizing antibodies present | 0 |
| **End of Study** | |
| n | 3 |
| Negative n (%) | 2 (66.7) |
| Positive n (%) | 1 (33.3) |
| No neutralizing antibodies present | 0 |

**Table 51. SHP633-304—Summary of Antibody Results by Visit (Safety Population)—Infants Only**

| Visit<br>Results | TED/TED<br>(N=4) |
|---|---|
| Neutralizing antibodies present | 1 (100.0) |

Note: TED/TED - subjects who received teduglutide in their core study and in this study.

Note: Blood samples for antibodies were drawn for all the teduglutide-exposed subjects.

In Study **SHP633-305**, as of the data cutoff date, overall, in Cycle 1 on Day 1, 1 infant had ADA detected prior to teduglutide dosing which persisted through Week 24; this infant reported a TEAE of injection site reaction, which was considered by the investigator to not be related to study drug. The infant was ongoing at the time of data cutoff and had not yet reached Week 28. For subjects with no ADA detected prior to teduglutide dosing in Cycle 1 on Day 1, 1 infant had positive ADA with neutralizing antibodies present at Week 12. When treatment was stopped, the infant reported positive ADA results by Week 28). There were no reports of teduglutide-related hypersensitivity reaction in the subjects who tested ADA positive. There was no association of ADA with hypersensitivity or teduglutide efficacy. The CHMP requested exposure-safety data in infants who had ADA detected in study SHP633-302, SHP633-304 and SHP633-305.

Among the 11 subjects less than 6 months of age, anti-drug antibodies (ADA) were detected in 2 subjects from study SHP633-302 while 5 of 6 subjects, aged 6 to 12 months, had ADAs detected in study SHP633-302 (n=2) and study SHP633-304 (n=3). Two of the subjects from study SHP633-302 (SHP633-302-0005-0002, SHP633-302-0006-0001) continued to test positive in the extension study, study SHP633-305 (**Table 52**). Among the 7 subjects that are ADA positive, there were 17 TEAEs in 2 subjects all mild or moderate in intensity in the 0 to <6 months age group and 111 TEAEs in 5 subjects including 6 severe TEAEs in 3 subjects in the 6 to 12 months age group (Table 4.4.2i). In the 10 ADA negative subjects, there were 95 TEAEs in 9 subjects including 3 severe TEAEs in 3 subjects in the 0 to <6 months age group and 7 TEAEs in 1 subject including 3 severe TEAEs in 1 subject in the 6 to 12 months age group (Table 4.4.2k). The data shows that the frequency of TEAEs were not much different between the ADA positive and ADA negative subjects, and therefore suggests that ADA status does not have an association with overall safety.

**Table 52. ADA Positive Exposure Data -TAK633-302, TAK633-304, and TAK633-305**

| Age Category (Months) | Study | Visit Number |
|---|---|---|
| 0-<6 | SHP633-302 | Week 24<br>End of Treatment |
| | SHP633-302 | Week 28<br>End of Study |

| Age Category (Months) | Study | Visit Number |
|---|---|---|
| 6-12 | SHP633-302 | Week 24<br>Week 28<br>End of Treatment<br>End of Study |
| | SHP633-302 | Week 24<br>Week 28<br>End of Treatment<br>End of Study |
| | SHP633-304 | Cycle 1 Day 1<br>Cycle 1 Week 12<br>Cycle 2 Day 1<br>Cycle 2 Week 12<br>Pretreatment 2<br>Pretreatment 3<br>End of Study/Early Termination |
| | SHP633-304 | Cycle 2 Week 12<br>End of Study/Early Termination |
| | SHP633-304 | Cycle 1 Week 12 |
| 6-12 | SHP633-305 | NTT1<br>NTT1<br>Last NTx<br>Cycle 1 Week 12<br>Cycle 1 Week 28<br>End of Treatment of the Last Cycle |
| | SHP633-305 | Cycle 1 Day 1<br>Cycle 1 Week 12<br>Cycle 1 Week 24<br>End of Treatment of Cycle 1<br>Cycle 2 Day 1<br>Cycle 2 Week 12<br>Cycle 2 Week 24<br>End of Treatment of Cycle 2<br>Cycle 3 Day 1<br>Day 1 of the Last Cycle |

In a total of 17 infants <1 year in the 3 studies SHP633-302, SHP633-304 and SHP633-305, 7 patients were ADA positive, and 10 patients were ADA negative. All patients in both the ADA positive and ADA negative groups experienced one or more TEAS. While the number and severity of events in each patient varied, no clear trend related to ADA status seemed to emerge.

## *Safety in special populations*

**Safety in special populations**

**Body Weight and Body Mass Index**

In Study **SHP633-301**, changes in body weight, length, and weight/length ratio Z-scores were within the expected range for infants. The head circumference Z-scores observed in the standard of care arm seem to drop further over time compared with the teduglutide treatment arm.

In Study **SHP633-302**, In infants, dramatic weight gains were observed, indicating that reductions in calories delivered intravenously were more than compensated for by improvements in nutrient absorption by the small intestine.

In Study **SHP633-304**, In infants, no clinically meaningful changes in weight, height, BMI, or head circumference Z-scores were noted in the TED/TED and NTT/NTT groups Subjects in the NTT/TED group appeared to have improvements in weight and height Z-scores during teduglutide treatment.

In Study **SHP633-305**: As of the data cutoff date, improved mean weight Z-score after teduglutide treatment was observed in infants, when compared with core study Z-scores.

**Intrinsic Factors**

Subgroup analyses by age are the basis of this submission and no further analyses were performed. Of the 12 unique infant subjects evaluated in this document, 8 were males and 4 were females; analyses by sex were not performed. Two of the studies were completed entirely in Japanese populations (Study SHP633-302 and SHP633-305), and there appeared to be no clinically meaningful differences between the results in these studies and all of the other clinical studies in the teduglutide program.

Across studies, patients with hepatic or renal impairment were excluded from studies.

No further new information has been presented in the submission other than that presented for infants in the prior sections.

**Extrinsic Factors**

No relevant new information is available.

**Safety related to drug-drug interactions and other interactions**

No new information is available.

**Post marketing experience**

Teduglutide is currently approved in over 40 countries. Key product approvals include approval for the treatment of adults with SBS by the European Community (EC) on 30 Aug 2012, and the FDA on 21 Dec 2012. Teduglutide was further approved for the treatment of patients aged ≥1 year with SBS by the FDA on 16 May 2019 and the EC on 29 Jun 2016.

**Non-study Post-authorization Exposure**

Worldwide Periodic Safety Update Reports for teduglutide are submitted annually; the most recent safety and efficacy information received during the reporting period of 31 Aug 2019 through 30 Aug 2020 was evaluated, and the following are the key outcomes of that evaluation. Based on the

marketing data at the time of report, the estimated cumulative patient exposure to teduglutide is 8949 person-years of treatment. Overall, the results indicated that teduglutide demonstrates clinically significant benefits in the treatment of patients with SBS, where longer term use of the drug results in persistent and durability of effect. The benefit risk profile for teduglutide in the treatment of SBS for patients aged 1 year and older remains positive.

**Non-interventional Study**

As of the time of this submission, there is 1 company-sponsored, ongoing non-interventional study: TED-R13-002: A Prospective, Multicenter Registry for Patients with Short Bowel Syndrome. No treatment is provided by the Sponsor in this observational registry. Analyses of data reported from adult and paediatric patients with SBS enrolled in this registry are performed and submitted annually to the Food and Drug Administration (FDA) and every second year to European Medicines Agency (EMA); for the latter, 4 interim reports are to be provided 6 months after the data lock points (ie., Q4 2016, Q4 2018, Q4 2020, and Q4 2022). To date, no data for infant patients (ie., patients under 1 year of age) with SBS treated with teduglutide have been reported in this registry.

Upon CHMP's request, the MAH provided data supporting that the data is strong enough to support safety in infants 4-12 months.

In studies that enrolled infants, most treatment emergent adverse events (TEAEs) in the core and extension studies were mild to moderate and not related to treatment with teduglutide. In infants, no adverse events of special interest were reported, and a total of 3 TEAEs led to treatment discontinuation in 2 infants. There appeared to be no differentiating trends in the frequency, severity, distribution in System Organ Class or relationship of TEAEs or treatment emergent serious adverse events, and the results appear similar to the overall evaluation of safety of teduglutide in all patients with SBS. With continuing exposure, the rate of TEAEs does not appear to increase, suggesting teduglutide is well tolerated over time. The evaluation of safety in the studies that enrolled infants revealed no new or unexpected trends or concerns and therefore confirms that the safety profile of teduglutide in infant patients with SBS is consistent with the previous experience from adults and children with SBS. No new safety issues were observed.

The current EMA-approved post-authorization safety study (PASS), Study TED-R13-002, already allows enrollment of "Male and female patients, of any age, with a diagnosis of SBS" as the first inclusion criteria.

The current study began enrolling patients more than 8 years ago and closed enrolment in late June 2022, around the same time as the cut-off date for the latest interim report and this data analysis (ie, 30 Jun 2022). This registry had been planned for 8 years of enrolment with at least 10 years of follow-up for each patient with SBS. Patients were enrolled in the study worldwide. The Applicant has been sending interim reports to EMA every 2 years, the latest of which submitted on 19 Dec 2022. The final study report is expected to be submitted in Q2 2033.

Over the last 8 years, 1403 adults (734 never-treated and 669 ever treated) and 397 paediatric (273 never treated and 124 ever treated) patients entered the study. In the same period of open enrolment, 43 infants under 1 year of age (33 never treated and 10 ever treated) entered in this study. The relatively low number of infants enrolled in the study compared with adults and paediatric population older than 1 year of age is consistent with the prevalence of SBS as a rare disease in the infant population.

The analysis of infant safety data presented in this response did not show any new safety signal or concern. The overall safety profile observed in the infant population of this study is consistent with those observed in children above 1 year of age and adults.

Each of the patients, including infants, enrolled in this study will be followed up for a period of at least 10 years and their safety data will be collected, analysed and reported as per regulatory guidelines. A robust pharmacovigilance system, including monthly signal detection is in place and closely monitors all sources of safety data in patients, including infants aged 4 months and above, receiving teduglutide. This pharmacovigilance system is described in the European RMP. Furthermore, "Limited long-term safety data over 1 year of exposure" is currently one of the missing information in the RMP and is closely monitored on a monthly basis during the signal detection activities. Re-opening the recruitment to enrol infants of any age will not lead to a significant number of new patients or a considerable amount of safety data, and would extensively delay the completion of the study beyond the current agreed timelines.

In light of the above, it is considered that the current Risk Management Plan and planned pharmacovigilance activities are adequate and neither re-opening of recruitment of infants =>4 months to <1 year in PASS TED-R13-002, nor initiating a new study in this age-group alone is recommended.

### 2.5.1. Discussion on clinical safety

The MAH presents safety data from all 4 clinical studies of teduglutide in which infants were enrolled (core studies SHP633-301 and SHP633 302; extension studies SHP633-304 and SHP633-305 [ongoing]) for the evaluation of safety of teduglutide in infant subjects 4 to 12 months corrected gestational age with Short Bowel Syndrome (SBS) who are dependent on parenteral support (PS).

As of May 2021, a total of 718 subjects have been treated with teduglutide, of these only 8 subjects were infants (4-12 months of age). Exposure data was provided for the individual studies only. Upon CHMP 's request, overall pooled exposure data for infants 4 to 12 months corrected gestational age as well as for those infants 4-6 months and 6-12 months were also provided.

The adverse event profile is consistent with that observed in the overall adult and paediatric population with SBS.

One infant in study SHP633-301 discontinued teduglutide due to adverse events (parents' decision, not investigator), mainly related to the gastrointestinal system (vomiting and GI sounds and fecal volume increased, all mild or moderate in severity and found related to teduglutide by investigator).

In study SHP633-301, 4 (80%) teduglutide treated infants reported one or more serious adverse events compared with 3 (60%) in the Standard of Care arm. The SAEs were pyrexia, immune reactions in the teduglutide arm and device related infection in the SoC arm. Also, device problems were reported as SAE (parenteral device). None of the SAEs were judged to be related to teduglutide treatment as evaluated by the investigator.

Adverse events of special interest (AESI) were defined in the study protocols as growth of pre-existing polyps of the colon, benign neoplasia of the GI tract including the hepatobiliary system, and tumour-promoting ability (eg, benign and/or malignant neoplasia of any kind, not limited to those of the gastrointestinal or hepatobiliary system). No confirmed AESIs were reported during the conduct of these studies.

One death occurred in study SHP633-304, 11 months after treatment start. Due to severe co-morbidities, including SBS, midgut volvulus, cerebral palsy, hydrocephalus, and seizure disorder the patient were according to the investigator elected to pursue end-of-life care and home-hospice. No relation to teduglutide for this death.

ADA was detected in infants in study SHP633-302, SHP633-304 and SHP633-305. The data shows that the frequency of TEAEs were not much different between the ADA positive and ADA negative subjects, and therefore suggests that ADA status does not have an association with overall safety.

Overall, it appears that the safety evaluation of teduglutide in infant patients with SBS is consistent with the previous experience from adults and children with SBS and that no new safety issues were observed. However, only 8 infants of 718 subjects have been treated with teduglutide, therefore uncertainty remains whether there is strong enough data to support the extension of indication in infant subjects 4 to 12 months corrected gestational age.

The limited tissue expression of the GLP-2 receptor is the basis for the general safety of teduglutide after its repeated systemic administration. Considering the unmet medical need in infants with SBS and intestinal failure, the consistency between the observed safety profile in adults and children with that of infants, the robust safety signal detection and Risk Management system in place at Takeda, and the ongoing Post Authorization Safety Study Registry, the MAH believes that despite the small number of infants enrolled in the clinical trials, the benefit-risk profile for the treatment of infant patients 4 months to <1 year of corrected gestational age with SBS remains favourable and that it can effectively monitor the safety profile of teduglutide post-approval.

### 2.5.2. Conclusions on clinical safety

The MAH presented safety data from all 4 clinical studies of teduglutide in which infants were enrolled for the evaluation of safety of teduglutide in infant subjects 4 to 12 months corrected gestational age with Short Bowel Syndrome (SBS) who are dependent on parenteral support (PS).

The safety data observed in infant patients treated with teduglutide was consistent with that observed in the overall adult and paediatric patients with SBS treated with teduglutide, although data from infants below 12 months are sparse.

The change of the due date for the clinical final study report for the International Short Bowel Syndrome Registry Study TED-R13-002 was considered acceptable. Due rarity of the condition (as well as the duration of exposure needed to detect a signal), the proposal was considered acceptable in order to meet the proposed sample size and therefore approved. The registry has enrolled infants below 1 year of age.

Interim data from the ongoing PASS does not support re-opening the PASS recruitment to enrol infants of any age, and it would extensively delay the completion of the study beyond the current agreed timelines. Further safety data from infants below 1 year of age will be provide post authorisation.

### 2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## *2.6. Risk management plan*

The MAH submitted an updated RMP version 9.2 with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 9.2 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 9.2 with the following content:

## *Safety concerns*

| Summary of safety concerns | |
|---|---|
| Important identified risks | • Biliary AEs<br>• Pancreatic AEs<br>• Cardiovascular AEs associated with fluid overload<br>• GI stenosis and obstruction<br>• GI stoma complications<br>• Intestinal polyps<br>• Benign neoplasia of the GI tract including the hepatobiliary system<br>• Tumour promoting ability<br>• Anxiety |
| Important potential risks | • AEs associated with increased absorption of oral concomitant medications<br>• Local skin reactions<br>• Potential for off-label use in patients with Crohn's disease<br>• Medication errors<br>• Compromised nutritional status |
| Missing information | • Lack of experience for administration of teduglutide in subjects with severe, clinically unstable concomitant diseases e.g. cardiovascular, respiratory, renal, infectious, endocrine, hepatic or CNS or in patients with malignancies within the last 5 years<br>• Lack of experience in pregnant or lactating women<br>• Long-term safety in the paediatric population<br>• Limited long-term safety data over 1 year of exposure<br>• Lack of data in subjects with pre-existing severe hepatic impairment |

## *Pharmacovigilance plan*

| Study status | Summary of objectives | Safety concerns addressed | Milestones | Due dates |
|---|---|---|---|---|
| **Category 1** – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation | | | | |
| TED-R13-002<br><br>Ongoing | Primary: to evaluate the long-term safety profile for patients (adults and children) with SBS who are treated with | - Biliary AEs<br>- Pancreatic AEs<br>- Cardiovascular AEs associated with fluid overload<br>- GI stenosis and obstruction<br>- Intestinal polyps | Interim reports | Four interim reports will be provided within six months after the data lock points (i.e. Q4 2016, Q4 2018, |

| | | | | |
|---|---|---|---|---|
| | teduglutide in a routine clinical setting<br><br>Secondary: to evaluate long-term clinical outcome in subjects with SBS<br><br>The primary safety outcome is the occurrence of colorectal cancer in SBS subjects with a remnant colon taking teduglutide | - Benign neoplasia of the GI tract including the hepatobiliary system<br>- Tumour promoting ability<br>- AEs associated with increased absorption of oral concomitant medications<br>- Lack of experience for administration of teduglutide in subjects with severe, clinically unstable concomitant diseases (e.g. cardiovascular, respiratory, renal, infectious, endocrine, hepatic or CNS)<br>- Lack of experience in pregnant or lactating women<br>- Lack of experience in children aged less than 1 year<br>- Long-term safety in the paediatric population<br>-Limited long-term safety data over 1 year of exposure<br>- Lack of data in subjects with pre-existing severe hepatic impairment | Final reports | Q4 2020 and Q4 2022)<br><br>Q2 2032 |
| **Category 2** – Imposed mandatory additional pharmacovigilance activities which are specific obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances | | | | |
| Not applicable. | | | | |
| **Category 3** – Required additional pharmacovigilance activities | | | | |
| Not applicable | | | | |

## *Risk minimisation measures*

| **Safety concern** | **Routine risk minimisation activities** |
|---|---|
| **Biliary adverse events** | **Routine risk communication:**<br><br>SmPC Section 4.2 "Posology and method of administration" recommends treatment to be initiated under the supervision of a medical professional with experience in the treatment of SBS.<br><br>SmPC Section 4.8 "Undesirable effects" lists cholecystitis and cholecystitis acute as common undesirable effects.<br><br>PL section 4 "Possible side effects" lists gallbladder related events as common side effect requiring immediate medical attention. |

| Safety concern | Routine risk minimisation activities |
|---|---|
| | **Routine risk minimisation activities recommending specific clinical measures to address the risk:**<br><br>SmPC Section 4.4 "Special warnings and precautions for use" provides precautionary language.<br><br>**Other routine risk minimisation measures beyond the Product Information:**<br><br>Prescription only medicine.<br><br>Use restricted to physicians in the treatment of SBS. |
| **Pancreatic adverse events** | **Routine risk communication:**<br><br>SmPC Section 4.2 "Posology and method of administration" recommends treatment to be initiated under the supervision of a medical professional with experience in the treatment of SBS.<br><br>SmPC Section 4.8 "Undesirable effects" lists pancreatitis as common undesirable effects.<br><br>PL section 4 "Possible side effects" lists the below as common side effects:<br><br>- pancreatitis requiring immediate medical attention<br><br>- narrowing or blockage of pancreatic duct as a common side effect.<br><br>**Routine risk minimisation activities recommending specific clinical measures to address the risk:**<br><br>SmPC Section 4.4 "Special warnings and precautions for use" of the SmPC provides precautionary language.<br><br>**Other routine risk minimisation measures beyond the Product Information:**<br><br>Prescription only medicine.<br><br>Use restricted to physicians in the treatment of SBS. |
| **Cardiovascular Adverse Events associated with fluid overload** | **Routine risk communication:**<br><br>SmPC Section 4.2 "Posology and method of administration recommends treatment to be initiated under the supervision of a medical professional with experience in the treatment of SBS.<br><br>SmPC Section 4.8 "Undesirable effects" lists congestive heart failure, oedema peripheral as common undesirable effects.<br><br>PL section 4 "Possible side effects" lists congestive heart failure as common side effect requiring immediate medical attention. |

| Safety concern | Routine risk minimisation activities |
|---|---|
| | **Routine risk minimisation activities recommending specific clinical measures to address the risk:**<br><br>SmPC Section 4.4 "Special warnings and precautions for use" of the SmPC provides recommendation on monitoring patient with cardiovascular diseases with regards to fluid overload and on the management of fluids during treatment with Revestive.<br><br>PL section 2 provides precautionary language.<br><br>**Other routine risk minimisation measures beyond the Product Information:**<br><br>Prescription only medicine.<br><br>Use restricted to physicians in the treatment of SBS. |
| **GI stenosis and obstruction** | **Routine risk communication:**<br><br>SmPC Section 4.2 "Posology and method of administration" recommends treatment to be initiated under the supervision of a medical professional with experience in the treatment of SBS.<br><br>SmPC Section 4.8 Undesirable effects lists intestinal obstruction is a common undesirable effect.<br><br>PL section 4 "Possible side effects" lists intestinal obstruction as common side effect requiring immediate medical attention.<br><br>**Routine risk minimisation activities recommending specific clinical measures to address the risk:**<br><br>SmPC Section 4.4 Special warnings and precautions for use provides precautionary language on intestinal obstruction and recommends close surveillance of short bowel function.<br><br>**Other routine risk minimisation measures beyond the Product Information:**<br><br>Prescription only medicine.<br><br>Use restricted to physicians in the treatment of SBS. |
| **GI stoma complications** | **Routine risk communication:**<br><br>SmPC Section 4.2 "Posology and method of administration" recommends treatment to be initiated under the supervision of a medical professional with experience in the treatment of SBS.<br><br>SmPC Section 4.8 Undesirable effects lists GI stoma complication is an undesirable effect. GI stoma complication (swelling of the stoma and associated complications) is considered to be rather a sign of efficacy than an adverse reaction.<br><br>PL section 4 "Possible side effects" lists swelling of stoma as very |

| Safety concern | Routine risk minimisation activities |
|---|---|
| | common side effect.<br><br>**Routine risk minimisation activities recommending specific clinical measures to address the risk:**<br><br>None.<br><br>**Other routine risk minimisation measures beyond the Product Information:**<br><br>Prescription only medicine.<br><br>Use restricted to physicians in the treatment of SBS. |
| **Intestinal polyps** | **Routine risk communication:**<br><br>SmPC Section 4.2 "Posology and method of administration" recommends treatment to be initiated under the supervision of a medical professional with experience in the treatment of SBS.<br><br>SmPC Section 4.8 Undesirable effects lists polyps (at varying GI site colorectal, duodenal, or gastric).<br><br>PL section 4 "Possible side effects" lists intestinal polyps (at various sites) as side effect with varying frequencies.<br><br>**Routine risk minimisation activities recommending specific clinical measures to address the risk:**<br><br>Revestive is contraindicated in patients with a history of malignancies in the GI tract including the hepatobiliary system and pancreas within the last 5 years (SmPC Section 4.3 Contraindication).<br><br>SmPC Section 4.4 "Special warnings and precautions for use" of the SmPC provides<br><br>- Instructions for polyp surveillance prior to and during treatment, in adults as well as in children and adolescents.<br><br>- Instructions to discontinue Revestive in case of malignancy.<br><br>- Precautionary language concerning GI neoplasia including hepatobiliary tract.<br><br>PL section 2 mentions instructions for polyp surveillance prior to and during treatment<br><br>**Other routine risk minimisation measures beyond the Product Information:**<br><br>Prescription only medicine.<br><br>Use restricted to physicians in the treatment of SBS. |
| **Benign neoplasia of the GI tract including the** | **Routine risk communication:** |

| Safety concern | Routine risk minimisation activities |
|---|---|
| **hepatobiliary system** | SmPC Section 4.2 "Posology and method of administration" recommends treatment to be initiated under the supervision of a medical professional with experience in the treatment of SBS.<br><br>**Routine risk minimisation activities recommending specific clinical measures to address the risk:**<br><br>SmPC Section 4.3 "Contraindication" of the SmPC includes:<br><br>- Contraindicated in Patients with a history of malignancies in the GI tract including the hepatobiliary system and pancreas within the last 5 years.<br><br>SmPC Section 4.4 "Special warnings and precautions for use" includes:<br><br>- Precautionary language concerning gastrointestinal neoplasia including hepatobiliary tract;<br><br>- Instructions for monitoring of small bowel, gallbladder and bile ducts, and pancreas.<br><br>- Instructions for polyp surveillance prior to and during treatment, in adults as well as in children and adolescents.<br><br>- Instructions to discontinue Revestive in case of malignancy.<br><br>SmPC Section 5.1 "Pharmacodynamic properties" describes the mechanism of action believed to be associated with the risk for the promotion of small intestinal and/or colonic neoplasia.<br><br>PL section 2 includes:<br><br>- GI and hepatobiliary cancer within the last 5 years or its suspicion as a contraindication.<br><br>- Instructions for polyp surveillance prior to and during treatment, in adults as well as in children and adolescents.<br><br>- Instructions to discontinue Revestive in case of malignancy.<br><br>- Instructions for monitoring of small bowel, gallbladder and bile ducts, and pancreas.<br><br>**Other routine risk minimisation measures beyond the Product Information:**<br><br>Prescription only medicine.<br><br>Use restricted to physicians in the treatment of SBS. |
| **Tumour promoting ability** | **Routine risk communication:**<br><br>SmPC Section 4.2 "Posology and method of administration" recommends treatment to be initiated under the supervision of a |

| Safety concern | Routine risk minimisation activities |
|---|---|
| | medical professional with experience in the treatment of SBS.<br><br>**Routine risk minimisation activities recommending specific clinical measures to address the risk:**<br><br>SmPC Section 4.3 "Contraindication" of the SmPC includes:<br><br>- Contraindicated in Patients with a history of malignancies in the GI tract including the hepatobiliary system and pancreas within the last 5 years).<br><br>SmPC Section 4.4 "Special warnings and precautions for use" includes:<br><br>- Precautionary language concerning gastrointestinal neoplasia including hepatobiliary tract;<br><br>- Instructions for monitoring of small bowel, gallbladder and bile ducts, and pancreas,<br><br>- Instructions for polyp surveillance prior to and during treatment, in adults as well as in children and adolescents.<br><br>- Instructions to discontinue Revestive in case of malignancy<br><br>SmPC Section 5.1 "Pharmacodynamic properties" describes the mechanism of action believed to be associated with the risk for the promotion of small intestinal and/or colonic neoplasia.<br><br>PL section 2 includes:<br><br>- GI and hepatobiliary cancer within the last 5 years or its suspicion as a contraindication.<br><br>- Instructions for polyp surveillance prior to and during treatment, in adults as well as in children and adolescents.<br><br>- Instructions to discontinue Revestive in case of malignancy.<br><br>- Instructions for monitoring of small bowel, gallbladder and bile ducts, and pancreas.<br><br>**Other routine risk minimisation measures beyond the Product Information:**<br><br>Prescription only medicine.<br><br>Use restricted to physicians in the treatment of SBS. |
| **Anxiety** | **Routine risk communication:**<br><br>SmPC Section 4.8 Undesirable effects lists anxiety as a common undesirable effect.<br><br>PL section 4 "Possible side effects" lists anxiety as common side effect. |

| Safety concern | Routine risk minimisation activities |
|---|---|
| | **Other routine risk minimisation measures beyond the Product Information:**<br><br>Prescription only medicine.<br><br>Use restricted to physicians in the treatment of SBS. |
| **AEs associated with increased absorption of oral concomitant medications** | **Routine risk communication:**<br><br>SmPC Section 4.4 "Special warnings and precautions for use" recommends close monitoring of patients receiving oral concomitant medicinal products.<br><br>SmPC Section 4.5 "Interaction with other medicinal products and other forms of interaction" informs prescribers on the potential for increased absorption of concomitant medicinal products.<br><br>**Routine risk minimisation activities recommending specific clinical measures to address the risk:**<br><br>PL section 2 mentions regarding the potential effect on oral concomitant medications.<br><br>**Other routine risk minimisation measures beyond the Product Information:**<br><br>Prescription only medicine.<br><br>Use restricted to physicians in the treatment of SBS. |
| **Local skin reactions** | **Routine risk communication:**<br><br>SmPC Section 4.8 "Undesirable effects" lists Injection site reactions as very common adverse drug reactions.<br><br>PL section 4 "Possible side effects" lists injection site reaction as very common side effect.<br><br>**Other routine risk minimisation measures beyond the Product Information:**<br><br>Prescription only medicine.<br><br>Use restricted to physicians in the treatment of SBS. |
| **Potential for off-label use in patients with active Crohn's disease** | **Routine risk communication:**<br><br>SmPC Section 4.1 "Therapeutic indications", Section 4.2 "Posology and method of administration".<br><br>PL section 1 mentions the indication for use of Revestive.<br><br>PL section 3 mentions the instructions to use Revestive.<br><br>**Other routine risk minimisation measures beyond the Product** |

| Safety concern | Routine risk minimisation activities |
|---|---|
| | **Information:**<br><br>Prescription only medicine.<br><br>Use restricted to physicians in the treatment of SBS. |
| **Medication errors** | **Routine risk minimisation activities recommending specific clinical measures to address the risk:**<br><br>Instructions for correct administration are provided in Sections 4.2 "Posology", Section 4.9 "Overdose" and Section 6.6 "Special precautions for disposal and other handling" of the SmPC.<br><br>PL Section 3 mentions instructions for use and Section 5 mentions instructions for storage of Revestive.<br><br>**Other routine risk minimisation measures beyond the Product Information:**<br><br>Prescription only medicine.<br><br>Use restricted to physicians in the treatment of SBS. |
| **Compromised nutritional status** | **Routine risk communication:**<br><br>SmPC Section 4.2 "Posology and method of administration" recommends treatment to be initiated under the supervision of a medical professional with experience in the treatment of SBS.<br><br>**Routine risk minimisation activities recommending specific clinical measures to address the risk:**<br><br>SmPC Section 4.2 "Posology and method of administration" provides<br><br>- Instructions to initiate treatment when it is reasonable to assume that a patient is stable following a period of intestinal adaptation.<br><br>- Instructions for optimisation and stabilisation of IV fluid and nutrition support before initiation of treatment.<br><br>PL section 2 mentions regular monitoring of body fluids and electrolytes.<br><br>**Other routine risk minimisation measures beyond the Product Information:**<br><br>Prescription only medicine.<br><br>Use restricted to physicians in the treatment of SBS. |
| **Lack of experience for administration of teduglutide in subjects with severe, clinically unstable concomitant** | **Routine risk communication:**<br><br>SmPC Section 4.4 Special warnings and precautions for use.<br><br>PL section 2. |

| Safety concern | Routine risk minimisation activities |
|---|---|
| **diseases, e.g., cardiovascular, respiratory, renal, infectious, endocrine, hepatic or CNS, or in patients with malignancies within the last 5 years** | |
| **Lack of experience in pregnant or lactating women** | **Routine risk communication:**<br><br>SmPC Section 4.6 Fertility, pregnancy and lactation.<br><br>PL Section 2. |
| **Long-term safety in the paediatric population** | **Routine risk communication:**<br><br>SmPC Section 4.2 "Posology" and Section 4.8 "Undesirable Effects".<br><br>PL Section 1 and Section 4. |
| **Limited long-term safety data over 1 year of exposure** | No risk minimisation activities are proposed at this time. Additional safety data will be available following completion of the NIS. |
| **Lack of data in subjects with pre-existing severe hepatic impairment** | **Routine risk communication:**<br><br>SmPC Section 4.2 Posology.<br><br>PL Section 2 mentions severely decreased liver function under "Warnings and Precautions". |

## *2.7. Update of the Product information*

As a result of this group of variations, section(s) 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are being updated. The Package Leaflet (PL) is updated accordingly.

Changes are made to the Opinion Annex II conditions as detailed in the recommendations section above.

Please refer to appended SmPC which includes all agreed changes to the Product Information.

### 2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

- The content of the current Package Leaflet (PL) has been fully tested and assessed for readability.
- The proposed revisions to the PL are minor: the proposed dose for patients aged 4 months to less than 1 year corrected gestational age is the same as the recommended dose in children

and adolescents aged 1 to 17 years; the side effects in this population are similar to those seen in as in children and adolescents aged 1 to 17 years and adults.

- Paediatric patients aged 4 months to less than 1 year corrected gestational age will be assisted by carers/ parents and the PL has already been tested in this population.

# 3. Benefit-Risk Balance

## *3.1. Therapeutic Context*

Teduglutide is a recombinant analogue of naturally occurring GLP-2. It is a 33 amino acid peptide that acts through the similar mechanism as GLP-2 and differs from the native peptide only in the substitution of glycine for alanine at the second position at the N-terminus.

Teduglutide binds to the same receptor as native GLP-2. In animal studies and previous human clinical trials, teduglutide has been shown to increase villus height and crypt depth in the intestinal epithelium, thereby increasing the absorptive surface area of the intestines.

The approved indication is for the treatment of patients aged 1 year and above with Short Bowel Syndrome (SBS). Patients should be stable following a period of intestinal adaptation after surgery.

The MAH now presents data to support the benefit/risk assessment of teduglutide in infant subjects 4 months to <1 year corrected gestational age with short bowel syndrome (SBS) who are dependent on parenteral support (PS).

### 3.1.1. Disease or condition

Short bowel syndrome (SBS) is a rare, serious, disabling, socially incapacitating, and potentially life-threatening condition which is the leading cause of intestinal failure. Intestinal failure from SBS results from surgical resection or congenital defects and is defined as the reduction of gut function below the minimum necessary for the absorption of macronutrients and/or water and electrolytes. Common causes of SBS in young children or infants include necrotizing enterocolitis, midgut volvulus, intestinal atresia, and gastroschisis. Short bowel syndrome is characterized by the inability to maintain protein-energy, fluid, electrolyte, or micronutrient balances when on a conventionally accepted, normal diet.

### 3.1.2. Available therapies and unmet medical need

Currently, there are no approved therapies that promote intestinal adaptation in infants with SBS. Therapy for infants is limited to nutritional and surgical measures as well as treatment of SBS complications, but no treatment to directly influence nutrient absorption and intestinal maturation (ie, intestinal adaptation) is available.

### 3.1.3. Main clinical studies

The efficacy data presented are derived from 1 controlled and 1 un-controlled core studies for a 28-week duration, and 2 extension studies for up to 9 cycles (24 weeks per cycle) of teduglutide treatment. These studies included infants 4 months to < 12 months corrected gestational age:
10 infants (2 infants aged 4 to < 6 months, 8 aged 6 to < 12 months) in the controlled study (5 in teduglutide treatment arm and 5 in standard of care arm), 2 infants in the un-controlled study (both

treated). From the core controlled study, 6 of the 10 infants completed the study, and continued in the extension study (5 treated and 1 non-treated). From the core uncontrolled study, 2 infants completed the study and continued in the second extension study (both treated). The infants in these studies were treated with teduglutide 0.05 mg/kg/day.

## *3.2. Favourable effects*

**The controlled core study**

*Complete weaning*

No subject achieved enteral autonomy, i.e., complete weaning off PS during either core or extension studies.

*Reduction in parenteral nutrition volume*

In the controlled core study, based on subject diary data, 3 (60.0%) subjects enrolled in the TED arm and 1 (20.0%) subject in the SOC arm experienced at least 20% reduction in PS volume at end of treatment (EOT) from baseline (2 subjects in the SOC arm had missing data). In the TED arm, the mean change in PS volume at EOT from baseline was -21.5±28.91 ml/kg/day (-24.8%). In the SOC arm, the mean change in PS volume at EOT from baseline was -9.5±7.50 ml/kg/day (-16.8%).

*Reduction in parenteral nutrition calories*

In the controlled core study, based on subject diary data, the mean percentage change in PS caloric intake at EOT from baseline was -27.0±29.47% for subjects in the TED arm and -13.7±21.87% in the SOC arm.

*Reduction in infusion time*

In the controlled core study, in the TED arm, the change in diary PS infusion time at EOT from baseline was -3.1±3.31 hours/day (-28.9%) and -1.9±2.01 days/week (-28.5%). In the SOC arm, the change in diary PS infusion time at EOT from baseline was -0.3±0.63 hours/day (-1.9%) and no change was observed on the days per week of PS infusion time.

**The un-controlled core study**

*Complete weaning*

No infant subjects reached complete weaning.

*Reduction in parenteral nutrition volume*

Among the 2 infants included in and completed the study, a ≥ 20% reduction in PS volume was recorded in 1 infant during the teduglutide treatment. The mean change in PS volume at EOT from baseline was - 26.2±13.61 ml/kg/day (-26.7%).

*Reduction in parenteral nutrition calories*

In infants, the mean change in PS caloric intake at EOT from baseline was -13.8±3.17 kcal/kg/day (-25.7)

*Reduction in infusion time*

There was no change in daily PS usage hours in the 2 infants during the study.

## *3.3. Uncertainties and limitations about favourable effects*

No infant subject enrolled in any of the core- or extension studies achieved enteral autonomy, i.e. complete weaning off PS during the study.

Efficacy results were based on subjects' diary data, which previously was shown to be more reliable than prescription data. Diary data may also be subject to variability but can be accepted for this extension of indication procedure.

While it is agreed based on the results from studies SHP633-301 and SHP633-302 that teduglutide as add-on to standard care treatment is beneficial in infants 4 months to <1 year of age in achieving the primary endpoint of ≥20% reduction at EOT in diary PS volume, the number of patients is still small.

SoC in SHP633-301 was to be according to clinical guidelines. Potential differences between the two treatment arms cannot be completely excluded, although measures were taken to maintain consistency with respect to nutritional support adjustment guidelines.

The evaluated dose of 0.05 mg/kg once daily in the infants aged 4 months through <1 year was taken from study TED-C13-003, that evaluated the 3 doses of teduglutide (0.0125 mg/kg, 0.025 and 0.05 mg/kg), and 0.05 mg/kg were found to be the optimal dose. Importantly, no infants were included in that study. Thus, the use of 0.05 mg/kg dose in infants 4 months to <1 year is based on the model-finding that the exposure-response relationship is stronger related to $C_{max,ss}$ than to $AUC_{tau,ss,}$ and the observation that the median $C_{max,ss}$ of teduglutide in the 4 months to <1 year was similar to those observed in the other paediatric age groups. This modelling has been supported through descriptive box-plot presentation of the observed data in the infants 4 months to <1 year, which shows similar exposure in terms of observed concentrations in the time window of ≤3 h (representing the time window for $C_{max}$) across the age-groups. This is accepted.

## *3.4. Unfavourable effects*

The safety data observed in infant patients treated with teduglutide was consistent with that observed in the overall adult and paediatric patients with SBS treated with teduglutide.

## *3.5. Uncertainties and limitations about unfavourable effects*

The MAH states that the safety evaluation of teduglutide in infant patients with SBS is consistent with the previous experience from adults and children with SBS and that no new safety issues were observed. However, only 8 infants of 718 subjects have been treated with teduglutide, hence the safety profile information for infants aged 4 – 12 months is sparse.

## *3.6. Effects Table*

**Table 1.** Effects Table for Revestive, Indication: Short Bowel Syndrome in patients from 4 months corrected gestational aged 1 year and above.

| Effect | Short description | Unit | Treatment | Control | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|---|
| **Favourable Effects** | | | | | | |
| ≥ 20% Reduction in PS volume | Reduction in weight-normalised PS volume ≥ 20% at EOT (24 weeks treatment) ITT population | N (%) | Teduglutide (n=5) | Standard of Care (n=5) | • Open-Label<br>• Subject Diary Data<br>• 5 infants in each arm for efficacy evaluation | SHP633-301 |
| | | | 3 (60) | 1 (20) | | |
| | Reduction in weight-normalised PS volume ≥ 20% at EOT (24 weeks treatment) PP population | N (%) | Teduglutide (n=4) | Standard of Care (n=3) | | |
| | | | 3 (75) | 1 (33.3) | | |
| Change from baseline in PS volume | Change from baseline in PS volume at EoT | ml/kg/day (mean SD) | Teduglutide (n=5) | Standard of Care (n=5) | | |
| | | Baseline PS volume (ml/kg/day) | 95.3 (45.93) | 70.9 (14.44) | | |
| | | Absolute change from baseline at EoT (ml/kg/day) | -21.5 (28.91) | -9.5 (7.50) | | |
| | | % change from baseline at EoT | -24.8 (34.72) | -16.8 (16.39) | | |
| **Unfavourable Effects** | | | | | | |
| | | N(%) m | Teduglutide (n=5) | Standard of Care (n=5) | | SHP633-301 |
| Any TEAE | Treatment emergent adverse events | | 5 (100) 58 | 5 (100) 29 | | |
| By severity | mild | | 2 (40) | 2 (40) | | |
| | moderate | | 2 (40) | 2 (40) | | |
| | Severe | | 1 (20) | 2 (40) | | |
| Related TEAE | | | 2 (40) 9 | 0 | | |

| Effect | Short description | Unit | Treatment | Control | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|---|
| TESAEs | Any serious adverse events | | 4 (80) 5 | 3 (60) 6 | | |
| | Related TESAE | | 0 | 0 | | |
| | TEAEs leading to treatment discontinuation | | 1 (20) 5 | 0 | | |
| | TEAEs of special interest* | | 0 | 0 | | |

## *3.7. Benefit-risk assessment and discussion*

### 3.7.1. Importance of favourable and unfavourable effects

Given the sparse data from only 7 patients on teduglutide in the target age group 4 months to <1 year a reliable PK-bridging is essential. The population-PK modelling results did not fully support the prediction of the exposure in the target age-group. It was also considered that further model updates may still not result in an adequate fit to data across all age groups. Therefore, new graphical plots of observed data were requested to support similar exposure in the treatment of paediatric infants 4 months to <1 year corrected gestational age with SBS who are dependent on PS, with a proposed dose of 0.05 mg/kg teduglutide SC administered once daily.

The box plots provided suggest a similar exposure in terms of observed concentrations in the time window of ≤3 h (representing the time window for $C_{max}$) across the age-groups even if the variation of the individual observed concentrations seems quite large, in particular for the age-group <1 year. The fact that the concentrations were being collected within a time window, rather than at a particular timepoint (such as Tmax) may explain some of the variation. To further substantiate the PK bridging the Applicant provided information about the patients with outlying plasma concentrations and no shared patient characteristics in the 4 subjects with outliers were identified. This is accepted.

In the course of the assessment it has been questioned if similar exposure can be expected to result in similar efficacy. The exposure-response model previously provided was based on actual PS volume changes from baseline (L/Week) which is not a suitable measure in children with increasing baseline PS volume needs due to growth. Because clinical study efficacy data from infants with this rare condition are naturally sparse to directly support efficacy in infants aged 4 months to 1 year, the PK bridging effort has been complemented by additional arguments that the exposure is expected to result in similar efficacy and safety between age groups and/or that the efficacy shown in the target age-group relative to the older age-groups is clinically justified. In particular it was observed that the percentage reduction in PS volumes appear to be smaller in the younger age-groups versus the older age-groups.

However, it is accepted that the following factors can explain to an acceptable degree the apparent differences between younger versus older children with respect to the percentage reduction in PS volumes:

PS volumes are adjusted conservatively in infants to minimize the risk of potential dehydration and electrolyte imbalances and medical needs. In addition, it is expected that changes in the prescribed PS while on the treatment are much lower compared to older children, given that SBS in infants are much more dependent on the nutrition provided to them and they are not able to feed on their own. Therefore, management of parental nutrition in infants with SBS is much more conservative than that for older children.

Furthermore, it is accepted that complete weaning is not expected to be the same across age groups, as individual response is driven by their small intestine length due to SBS, receptor responses and expressions, physiological requirements, and clinical pharmacology properties.

In the extension studies, based on diary data, totally 3/6 infants achieved a ≥20% reduction in PS volume at Cycle 1. They all received teduglutide treatment in the core- and extension study (TED/TED).

An improvement of ≥20% reduction at EOT in diary PS volume in infants treated with teduglutide is considered clinically relevant to optimizing enteral nutrition to maximize the adaptive process and to minimize PS requirements. Data to support safety in infants aged 4 months to 1 year are naturally sparse in this rare condition. The Safety profile of teduglutide has in previous studies been related to severe adverse events i.e. growth of pre-existing polyps of the colon and benign neoplasia of the gastrointestinal tract. None of these adverse events of special interest have been observed in the small number of infants in the clinical studies, or in the ongoing PASS TED-R13-002, so far. However, as only 8 infants of 718 subjects have been treated with teduglutide, it has been ensured that the ongoing PASS TED-R13-002, which has recently completed recruitment, has included 10 infants <1 year of age in the ever-treated cohort, of whom 9 subjects are continuing in the study for long-term follow-up, i.e. minimum 10 years. The overall safety profile observed so far in the infant population of this study is consistent with those observed in children above 1 year of age and adults. From a safety perspective it is also reassuring that lowest systemic exposure is seen in the youngest age group (infants 4 months to <1 year), following multiple doses at 0.05 mg/kg QD.

Given the low safety incidence rate and relatively rarity of eligible patients, it is considered that re-opening the recruitment of infants =>4 months to <1 year is unlikely to provide significantly more safety data in this particular age-group than what is being generated already.

It is, therefore, considered that the current Risk Management Plan and planned pharmacovigilance activities are adequate and neither re-opening of recruitment of infants =>4 months to <1 year in PASS TED-R13-002, nor initiating a new study in this age-group alone is recommended. The final study report for the Annex II Condition will be provided in Q2 2032.

## 3.7.2. Balance of benefits and risks

Only sparse data from 7 patients on teduglutide in the target age group 4 months to <1 year had been provided in this application. The population-PK modelling did not fully support the prediction of the exposure in the target age-group but graphical plots of observed data supported a similar exposure in terms of observed concentrations in the time window of ≤3 h (representing the time window for $C_{max}$) across the age-groups with the proposed dose of 0.05 mg/kg teduglutide SC administered once daily. Furthermore apparent differences between younger versus older children with respect to the percentage reduction in PS volumes can be explained by the more conservative management of

parenteral nutrition in infants with SBS. No infant subject reached complete weaning however complete weaning is not expected to be the same across age groups, as individual response is driven by their small intestine length due to SBS, receptor responses and expressions, physiological requirements, and clinical pharmacology properties. An improvement of ≥20% reduction at EOT in diary PS volume in infants treated with teduglutide is considered clinically relevant to optimizing enteral nutrition to maximize the adaptive process and to minimize PS requirements. Taken together the data on the PK bridging and the efficacy data provided are considered sufficient to conclude on clinical efficacy in this age. This is weighed against an overall safety profile in the infant population that is consistent with the one observed in children above 1 year of age and adults. Further data on infants will be provided post authorisation by means of an Annex II Condition PASS TED-R13-002 post authorisation. The change of the final study report was considered acceptable in order for the Applicant to meet the proposed sample size.

### *3.8. Conclusions*

The overall B/R of Revestive is positive.

## 4. Recommendations

### *Outcome*

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variations to the terms of the Marketing Authorisation, concerning the following changes:

| **Variations accepted** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | Type II | I, II and IIIB |
| C.I.11.z | C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation | Type IB | I, II and IIIB |

Extension of indication to include patients from 4 months corrected gestational aged 1 year and above. Consequently sections 4.1, 4.2, 4.8, 5.1 and 5.2 are updated. The Package leaflet is updated accordingly. RMP Version 9.2 has also been submitted.

Update of annex II to amend the date of completion of the post authorisation study to Q2 2032.
The MAH took the opportunity to also amend local representatives.

### *Amendments to the marketing authorisation*

In view of the data submitted with the group of variations, amendments to Annex(es) I, II and IIIB and to the Risk Management Plan are recommended.

This recommendation is subject to the following amended condition: amended submission for the

Internal Short Bowel Syndrome Registry final study report.

### *Conditions or restrictions with regard to the safe and effective use of the medicinal product*

## Risk management plan (RMP)

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

## Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measure:

| Description | Due date |
|---|---|
| International Short Bowel Syndrome Registry<br>Non-interventional study (NIS) to gather further safety data, in order to further elucidate the potential and identified risk as outlined in the RMP, based on a CHMP approved protocol.<br>Interim data for the NIS should be provided every second year.<br><br>Final study report | Four interim reports will be provided within six months after the data lock points (i.e., Q4 2016, Q4 2018, Q4 2020, and Q4 2022).<br><br>Q2 2033 |

# 5. EPAR changes

The EPAR will be updated following Commission Decision for this group of variations. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

## *Scope*

Please refer to the Recommendations section above.

## *Summary*

Please refer to Scientific Discussion ‘Revestive-H-C-002345-II-0054-G’