EMA/225706/2019
Committee for Medicinal Products for Human Use (CHMP)

CHMP Type II variation assessment report

Procedure No. EMEA/H/C/002345/II/0043

Invented name: Revestive

International non-proprietary name: teduglutide

Marketing authorisation holder (MAH): Shire Pharmaceuticals Ireland Limited

This application is in the area of: (Non-)Clinical

eCTD sequences related to the procedure: 0112, 0113, 0119, 0121

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure:	02 Apr 2018	02 Apr 2018	☐
☐	CHMP Rapporteur Assessment Report	07 May 2018	03 May 2018	☐
☐	CHMP members comments	22 May 2018	22 May 2018	☐
☐	Updated CHMP Rapporteur Assessment Report	24 May 2018	n/a	☐
☐	Request for Supplementary information	31 May 2018	31 May 2018	☐
☐	MAH Submission	26 June 2018	26 Jun 2018	☐
☐	Re -Start of procedure:	27 June 2018	27 Jun 2018	☐
☐	CHMP Rapporteur Assessment Report	11 July 2018	11 July 2018	☐
☐	CHMP members comments	16 July 2018	16 July 2018	☐
☐	Updated CHMP Rapporteur Assessment Report	19 July 2018	n/a	☐
☐	2nd Request for Supplementary information	26 July 2018	26 July 2018	☐
☐	Responses	21 Aug 2018	21 Aug 2018	☐
☐	Re -Start of procedure:	22 Aug 2018	22 Aug 2018	☐
☐	CHMP Rapporteur Assessment Report	05 Sept 2018	05 Sep 2018	☐
☐	CHMP members comments	10 Sept 2018	10 Sep 2018	☐
☐	Updated CHMP Rapporteur Assessment Report	13 Sept 2018	n/a	☐
☐	3rd Request for Supplementary information	20 Sep 2018	20 Sep 2018	☐
☐	Responses	16 Oct 2018	15 Oct 2018	☐
☐	Re -Start of procedure:	17 Oct 2018	17 Oct 2018	☐
☐	CHMP Rapporteur Assessment Report	31 Oct 2018	31 Oct 2018	☐
☐	CHMP members comments	05 Nov 2018	05 Nov 2018	☐
☐	Updated CHMP Rapporteur Assessment Report	08 Nov 2018	n/a	☐
☐	4rd Request for Supplementary information	15 Nov 2018	15 Nov 2018	☐
☐	MAH Submission	20 Nov 2018	20 Nov 2018	☐
☐	Re -Start of procedure:	21 Nov 2018	21 Nov 2018	☐
☐	CHMP Rapporteur Assessment Report	28 Nov 2018	28 Nov 2018	☐
☐	CHMP members comments	03 Dec 2018	03 Dec 2018	☐
☐	Updated CHMP Rapporteur Assessment Report	06 Dec 2018	06 Dec 2018	☐
☒	Opinion or RSI	13/12/2018	13/12/2018	☐

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

[2] Criteria for PRAC plenary discussion: proposal for update of SmPC/PL, introduction of or changes to imposed conditions or additional risk minimisation measures (except for generics aligning with the originator medicinal product), substantial changes to the pharmacovigilance plan (relating to additional pharmacovigilance activities, except for generics adapting aligning with the originator medicinal product), substantial disagreement between the Rapporteur and other PRAC members, at the request of the Rapporteur, any other PRAC member, the Chair or EMA.

Criteria for CHMP plenary discussion: substantial disagreement between the Rapporteur and other CHMP members and/or at the request of the Rapporteur or the Chair.

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Shire Pharmaceuticals Ireland Limited submitted to the European Medicines Agency on 15 March 2018 an application for a variation.

The following changes were proposed:

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

Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC based on the final CSR of study TED-C14-006 (a 24-Week Double-blind, Safety, Efficacy, and Pharmacodynamic Study Investigating Two Doses of Teduglutide in Pediatric Subjects Aged 1 Year Through 17 Years With Short Bowel Syndrome who are Dependent on Parenteral Support); this is a category 3 study in the RMP. The Package Leaflet is updated accordingly.

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

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

TED-C14-006 was a phase 3, multi-center, multi-national, randomized, double blind, safety, efficacy, and PK study in children, aged less than 18 years with intestinal failure due to short bowel syndrome (SBS). The study contained 2 arms: a teduglutide treatment arm and a standard of care (SOC) arm. Subjects chose the arm in which they enrolled, but subjects in the teduglutide treatment arm were randomised to either 0.025 or 0.05 mg/kg subcutaneous once daily in a double-blinded manner. Fifty subjects enrolled in the teduglutide treatment arm and 9 subjects enrolled in the SOC arm.

The percentage of subjects achieving a ≥20% reduction in PN/IV volume increased over the course of the 24-week treatment period in both teduglutide dose groups but not the subjects treated with SOC. Both teduglutide dose groups experienced greater reductions in PN/IV volume and calories, days per week on PN/IV and hours per day, increases in enteral nutritional volume and calories from baseline to EOT than the SOC arm. There did not seem to be substantial differences in efficacy between the 2 dosage schedules of teduglutide. Thus, the study overall demonstrated a clinical relevant efficacy of teduglutide. However, no formal statistical tests were used to document efficacy.

Teduglutide was generally well tolerated by paediatric patients with SBS. The safety profile was favourable and consistent with the prior 12-week paediatric study, the underlying disease, and previous experience with teduglutide in adult patients with SBS.

Overall, it is endorsed that the MAH includes information regarding children less than 18 years of age based on a 24-week study (TED-C14-006) in sections 4.2, 4.4, 4.8 and 5.1 of the SmPC for Revestive. While it is acknowledged that the posology 0.05 mg/kg is approved for children ≥1 year, it is noticed that the PK data in children <2 years is limited (N=4). The wording "*a treatment period of 6 months is recommended after which treatment effect should be evaluated*" has been accepted in section 4.2 provided that the teduglutide treatment should be evaluated after 12 weeks in children below the age of two years.

In conclusion, the variation is recommended for approval.

3. Recommendations

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

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

Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC based on the final CSR of study TED-C14-006 (a 24-Week Double-blind, Safety, Efficacy, and Pharmacodynamic Study Investigating Two Doses of Teduglutide in Pediatric Subjects Aged 1 Year Through 17 Years With Short Bowel Syndrome who are Dependent on Parenteral Support); this is a category 3 study in the RMP. The Package Leaflet is updated accordingly.

☒ is recommended for approval

Amendments to the marketing authorisation

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

4. EPAR changes

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

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion "EMEA/H/C/002345/II/0043"

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

5. Introduction

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

The variation is to cover the submission of a clinical study report (TED-C14-006); a 24-Week Double-blind, Safety, Efficacy, and Pharmacodynamic Study investigating two doses of teduglutide in pediatric Subjects Through 17 Years of Age with Short Bowel Syndrome who are Dependent on Parenteral Support

The MAH propose to update the following sections of the SmPC and the PL:

SmPC

Section 4. Clinical particulars

- 4.2 Posology and method of administration
- 4.4 Special warnings and precautions for use
  - Colorectal polyps/Neoplasia
  - Pediatric population
- 4.8 Undesirable effects

Section 5. Pharmacological properties

- 5.1 Pharmacodynamic properties

PL

Section 2. What you need to know before you use Revestive

- Warnings and precautions
- Children and adolescents

Section 4. Possible side effects

Use in children and adolescents

6. Clinical Pharmacology aspects

POPULATION PK MODELING TO SUPPORT DOSING RATIONALE OF TEDUGLUTIDE IN PEDIATRIC PATIENTS WITH PARENTERAL NUTRITION-DEPENDENT SHORT BOWEL SYNDROME

Teduglutide is a 33-amino acid peptide that differs from native GLP-2 in the substitution of glycine for alanine at the second position at the N-terminus. As a result, teduglutide demonstrates resistance to degradation by dipeptidyl peptidase 4 and therefore maintains a longer elimination half-life ($t_{1/2}$) of approximately 2 hours compared to the native peptide, which has a $t_{1/2}$ of approximately 7 minutes. Teduglutide has been shown in animal studies and previous human clinical trials to increase villus height and crypt depth in the intestinal epithelium, thereby increasing the absorptive surface area of the intestines.

The addressable adult patient population is between 3000 to 5000 patients, it is estimated that, at most, there are a few hundred children 1 year and older with SBS.

OBJECTIVES

To enrich the dataset with additional Phase I clinical studies (CL0600-018 and C09-001) and an additional study performed in pediatric patient with SBS (TED-C14-006) to ultimately support dosing in pediatric patients.

Assessor's comments

The MAH has provided a sufficient introduction to the teduglutide (SHP633) POP PK model in pediatric patients with SBS, and the objectives of the analysis has been described sufficiently. Furthermore, the MAH has overall described the studies from which the data included in the analysis originate, sufficiently. Of notice, CL0600-004, TED-C13-003 and TED-C14-006 were pediatric studies covered by the EMEA-000482-PIP01-08-M04.

6.1. Methods – analysis of data submitted

Population PK Analysis of Teduglutide

The population PK analyses were performed using NONMEM or Phoenix NLME.

A one-compartment disposition model with a first-order absorption rate constant (Ka) and a lagtime (ALAG), including allometric functions on PK parameters (Ka, CL/F and Vc/F) was previously developed. This model was used as a starting point to assess the PK of teduglutide based on data collected in 12 studies.

Overall, the population PK models for teduglutide consisted of the following: i) Description of the relationships between plasma concentration and time ii) A variance component characterizing between-subject variability (BSV) in model parameters iii) Residual unexplained variability was modelled using additive, proportional or additive and proportional models.

An allometric component accounting for the effect of weight on Ka, CL/F and Vc/F was included in the base PK model (estimated exponents). Model evaluation was based on standard model diagnostics and goodness-of-fit criteria (e.g. log-likelihood difference) and by looking at pertinent graphical representations of goodness-of-fit (e.g. fitted and observed concentrations versus time, weighted residuals vs. time).

If an important number of samples with concentrations below the limit of quantitation (BLQ) is observed, a truncated likelihood method that takes into account the censoring of concentrations was considered (M3 method).

Assessor's comment

The MAH has described the handling of concentrations values below BLQ. However, with reference to the EMA Guideline on reporting the results of population pharmacokinetic analyses (Doc.ref. CHMP/EWP/185990/06, June 2007), the MAH is asked to:

- Apply the type of bioanalytical methods used and the LLOQ for each analyte in each method **(OC)**.
- Discuss the possible consequences of ignoring the concentrations below BLQ/LLOQ **(OC).**

Model qualification of population PK models for teduglutide was based on the following diagnostic plots: i) Observed data versus population predicted data (DV vs. PRED) and individual predicted data (DV vs. IPRED) with a line of unity and a trend line. ii) Observed Data vs. Time after dose with trend lines of DV and PRED. iii) Conditional weighted residuals vs. predicted data (CWRES vs. PRED) with zero line and a trend line. iv) Conditional weighted residuals versus time after dose [CWRES vs. time] with zero line and a trend line. v) Quantile-quantile plot of CWRES (QQ plot).

Assessor's comment

The MAH has provided a relevant overview of the POP PK model process.

Outlier data for teduglutide (i.e., concentration values associated to absolute CWRES greater than 6) were reviewed. A sensitivity analysis was performed to determine the impact of outlier data. The results of the model fitted to the entire dataset are compared with the results obtained from the fit to the subset data, excluding potential outliers. If the model failed to successfully minimize with the outliers included, or the parameter estimates differ substantially, the results of both models are presented in the report. If the results of the model estimation with and without the outliers are largely consistent, the model fitted to the entire dataset (including the outliers) are considered the final model. All outliers excluded from the analysis, either during model building or in the final model, are identified in exclusion listings along with a rationale for their exclusion.

Assessor's comment

The MAH has described the procedure of detecting outliers adequately.

Co-variates:

Intrinsic: Age (after taking into account body weight), elderly (>65 years), adults (≥ 18 to 65 years), adolescents (12 to 17 years), pediatrics (1 to 11 years), sex, race, white, black, asian, and others. Liver function, categories of liver impairment according to Child Pugh criteria: No hepatic impairment (Normal), mild hepatic impairment, if available, moderate hepatic impairment, if available, severe hepatic impairment, if available, Marker of liver function: alanine transferase (ALT), aspartate transferase (AST) and bilirubin, renal Function, markers of renal function, estimated glomerular filtration rate (eGFR), estimated glomerular filtration rate capped to 150 mL/min/1.73 m^2 (eGFRT). Categories of renal impairment: Normal renal function (eGFR ≥90 mL/min/1.73 m^2), mild renal impairment (eGFR ≥ 60 to 89 mL/min/1.73 m^2), moderate renal impairment (eGFR ≥ 30 to 59 mL/min/1.73 m^2), severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2), end-stage renal disease (eGFR < 15 mL/min/1.73 m^2 or requiring dialysis).

Extrinsic: Disease Status: Healthy, SBS/Crohn's disease, hepatic impairment or renal impairment Extrinsic Factors. Site of SC dosing (abdomen, arm, thigh, and missing). Dose (therapeutic vs. supra-therapeutic [20 mg])

Assessor's comment

The MAH has presented the covariates selected for the model sufficiently. However in addition the pediatric age groups should be stratified as follows: <2, 2-<6, 6-<12, 12-<18 years. **(OC)**.

The effect of covariates on PK parameters of teduglutide was assessed using a forward inclusion (ΔOFV of 6.63, $p < 0.01$ for one degree of freedom) and backward exclusion (ΔOFV of 10.83, $p < 0.001$ for one degree of freedom) procedure.

Assessor's comment

The MAH has adequately presented a stepwise covariate building model procedure, herein the statistical significance criteria for covariate selection.

The performance of the final population PK model of teduglutide was evaluated using several diagnostic plots, as well as predictive check. Prediction-corrected visual predictive checks (VPC)

6.2. Results

Baseline Characteristics and Exploratory Analysis

A total of 459 subjects were included on the population PK analysis.

The population included a total of 259 (56.4%) healthy subjects and 200 (43.6%) patients with SBS or Crohn' disease. The population consisted of 287 (62.5%) male and 172 (37.5%) female subjects. The majority of subjects were of white origin (86.3%).

Assessor's comment

The MAH should provide the number/percentage of subjects with SBS and Crohn' disease, respectively. **(OC).**

- A total of 355 (77.3%) subjects received SC dosing of teduglutide in the abdomen, while 51 (11.1%) received a SC dosing in the thigh and a total of 28 (6.1%) received a SC dosing in the arm.
- The population included a total of 78 (17.0%) pediatric subjects (1 to 11 years), 7 (1.5%) adolescent subjects (12 to 17 years), and 354 (77.1%) adult subjects (≥ 18 to 65 years). The population also included 20 (4.4%) elderly (> 65 years) subjects.

Assessor's comment

The MAH should describe the number of pediatric trial participants in the age group as follows: <2 years, 2-<6, 6-<12, 12-<18 years. **(OC).**

- A total of 275 (59.9%) subjects had normal renal function. A total of 142 (30.9%), 28 (6.1%) and 8 (1.7%) subjects presented mild, moderate severe renal impairment. A total of 6 (1.3%) subjects were at ESRD.
- Median age in the overall population was 34.0 years. The median (range) age of pediatric patients with SBS enrolled in study TED-C13-003 and TED-C14-006 were 4.42 years (1.67 – 14.7) and 6.00 (1.00 – 15.0) years, respectively.

- Median body weight in the overall population was 67.2 kg. The median (range) body weight of pediatric patients with SBS enrolled in study TED-C13-003 and TED-C14-006 were 16.1 (10.1 – 48.7) kg and 19.1 (10.6 – 47.0) kg, respectively.
- Median estimated glomerular filtration rate (eGFR) in the overall population was 107 mL/min/1.73 m^2
- The median (range) eGFR of pediatric patients with SBS enrolled in study TED-C13-003 and TED-C14-006 were 175 (113 – 247) mL/min/1.73 m^2 and 166 (85.8 – 473) mL/min/1.73 m^2, respectively.

A total of 459 subjects from 12 clinical studies were evaluable for the population PK analysis. The dataset included 6733 measurable teduglutide concentrations of which 670 (9.1%) were BLQ. Values below the limit of quantitation were set to missing for the preliminary population PK analysis. Exploratory analyses were first performed to visually assess concentration-time profiles of teduglutide

Concentration-time profiles suggests that teduglutide was absorbed slowly following SC dosing and that concentrations declined in a mono-exponential manner. A one-compartment model with linear elimination and allometric components accounting for the effect of body weight on Ka, CL/F and Vc/F were used in a first step. Exponents for the effect of body weight were estimated. The population PK model was not customized for organ maturation since the youngest patient was 1 year of age and kidney function is expected to be 90% matured at this age. Various error models Population PK Analysis teduglutide (SHP633) Shire Pediatric Patients with SBS Confidential Page 26 23-Feb-2018 were considered (additive, proportional and mixed error models). A mixed error model (run02) was associated with the lowest OFV (47926.946). The base PK model adequately fitted the observed teduglutide concentrations in pediatric and adult patients and CWRES values homogeneously distributed around 0. An exploratory analysis was performed to assess sources of variability. Scatter plots and boxplots were used to display relationships between random effects of PK vs. continuous or categorical covariates. Based on the exploratory figures, the following covariates were tested on CL/F and Vc/F: ALT, age, sex, site of injection, race, dose and disease status (healthy vs. patients with SBS/Crohn's disease). In addition, eGFR (capped to 150 mL/min/1.73m^2, eGFRT) was tested on CL/F. A stepwise covariate analysis was performed to identify sources of variability in PK parameters of teduglutide. A summary of covariates resulting in the maximum reduction of the OFV and included in each step of the analysis is presented in Table 1.

Table 1 – Population PK Analysis of Teduglutide: Stepwise Covariate Analysis

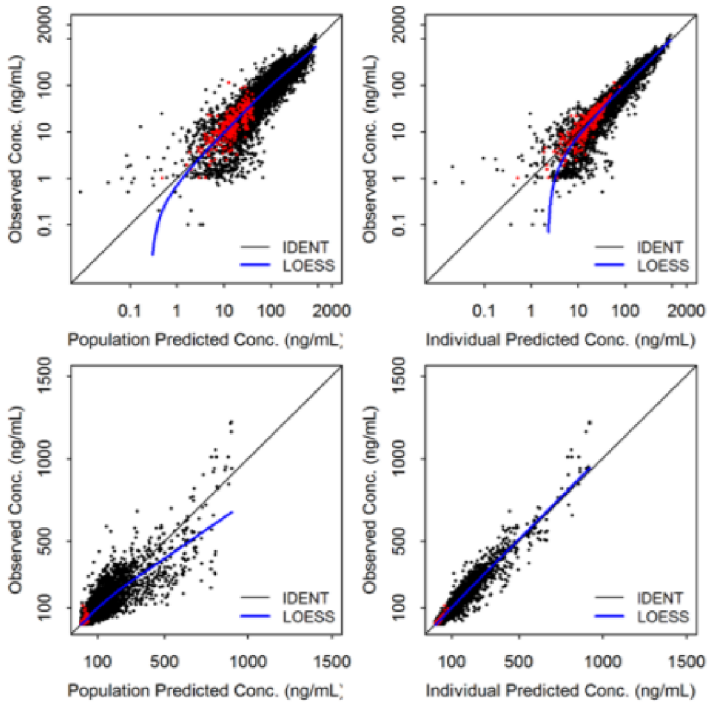
Steps	Forward Inclusion [p-value of 0.01 (ΔOFV=6.63)]	OFV	ΔOFV
Base Model	**1-compartment Model with Lag, Diagonal (CL/F, Vc/F and Ka), Mixed error model**	47926.946	
Step 1	+ Site of injection on Ka (Reference= abdomen vs. others)	47597.578	-329.368
Step 2	+ eGFRT on CL/F	47518.116	-79.462
Step 3	+ Population on CL/F (Reference=SBS/Crohn's disease vs others)	47474.275	-43.841
Step 4	+ Age on Vc/F	47451.385	-22.890
Step 5	+ ALT on CL/F	47428.908	-22.477
Step 6	+ Dose on Vc/F (Therapeutic vs. Supra-therapeutic)	47420.193	-8.715
Step 7	+ Sex on CL/F	47411.795	-8.398

ALT = alanine aminotransferase at baseline; CL/F = apparent clearance; eGFRT = estimated glomerular filtration rate capped to 150 mL/min/1.73m^2; Ka = first-order rate constant of absorption; OFV = objective function value; SBS = short bowel syndrome; Vc/F = apparent central volume of distribution,

The effect of site of injection on Ka resulted in the most important decrease in OFV as part of the 1st step of the analysis (ΔOVF= -329.368). In the 2nd iteration, the effect of eGFRT on CL/F resulted in the most important decrease in OFV (ΔOVF= -79.462). In the 3rd iteration, the effect of age on Vc/F

resulted in the most important decrease in OFV (ΔOVF= -43.841). In the 4th iteration, the effect of age on Vc/F resulted in the most important decrease in OFV (ΔOVF= -22.890). In the 5th iteration, the effect of ALT on CL/F resulted in the most important decrease in OFV (ΔOVF= -22.477). In the 6th iteration, the effect of dose (supra-therapeutic) on Vc/F resulted in the most important decrease in OFV (ΔOVF= -8.715). In the 7th iteration, the effect of sex on CL/F resulted in the most important decrease in OFV (ΔOVF= -8.398). No other covariates were included as part of the forward testing. During the backward testing, the effect of dose on Vc/F and the effect of sex on CL/F were removed.

The model resulted in adequate goodness of fit, but a bias was observed for the prediction of low concentrations of teduglutide in adults and pediatric subjects. It is to be noted that 670 (9.1%) samples were BLQ. In study TED-C13-003 and TED-C14-006, the total number of BLQ samples were 60 (33%) and 1 (0.7%), respectively. As a result, a truncated likelihood method that takes into account the censoring of BLQ data (M3 method) was implemented in the current population PK model with covariates (run130des). The goodness-of-fit derived with the final population PK model is presented in Figure 1.



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
Samples collected between the first dose and the lagtime of absorption had PRED and IPRED=0. Those samples are not presented on the log-scale plots

Figure 1 – Goodness-of-Fit Plots – Final Population PK Model Including M3 Method

Assessor's comment

The MAH should elucidate the handling of BLQ samples further, and discuss the possible consequences in relation to the final model. **(OC).**

The LOESS regression of observed concentrations of teduglutide versus both individual and population predicted values fell along the line of identity. Overall, the final population PK model was deemed to be appropriately specified, with population typical values and covariate effects, precisely estimated. VPC

were performed to qualify the model, whereby 1000 replicates of the observed subjects were simulated and stratified by study. The VPC for concentrations of teduglutide in patients with SBS/Crohn's disease in each study are presented in Figure 2.

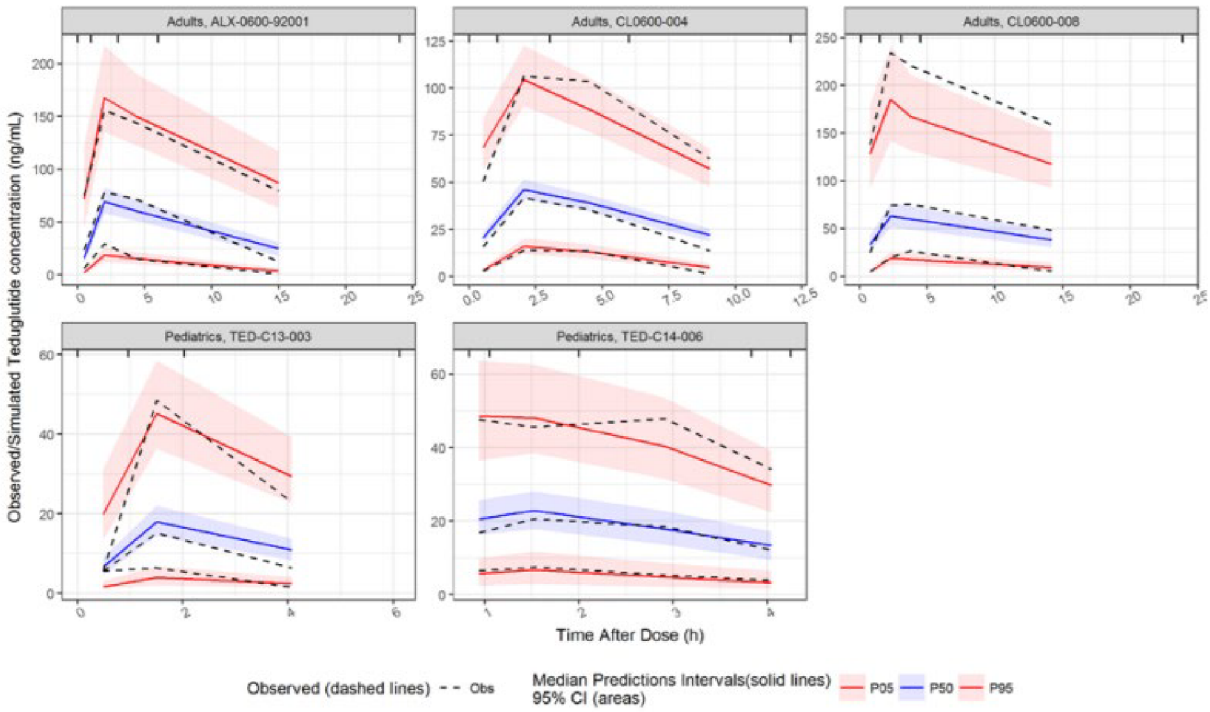


Figure 2 – Visual Predictive Check of Teduglutide Concentration (Including M3 Method) in Patients with SBS of Crohn's Disease

Observed median, 5th and 95th percentiles of teduglutide concentrations were contained within the model-predicted ranges (shaded areas) for all studies, including pediatric patients with SBS enrolled in study TED-C14-006.

Assessor's comment

The MAH has presented the pcVPCs of the final model accordingly. The model appears to capture the teduglutide concentrations well.

Population PK parameters are presented in Table 2.

Table 2 – Population PK Parameters of Teduglutide (Including M3 Method)

PK Parameters	Typical Values	BSV (%)	Shrinkage
CL/F (L/h)	13.6 x (Body Weight/70)$^{0.590}$ x (eGFRT/102)$^{0.322}$ x (ALT /24.0)$^{0.125}$ x 0.833 if not SBS/Crohn's Disease	26.3	14.0%
Vc/F (L)	33.1 x (Body Weight/70)$^{1.65}$ x (Age/34.0)$^{-0.332}$	39.2	21.4%
Ka (h^{-1})	0.318 x (Body Weight/70)$^{-0.624}$ x 0.690 for SC administration other than abdomen	26.1	35.0%
ALAG (h)	0.207	0, Fixed	NA
Error Model			
Additive Error (ng/mL)	7.16	NA	NA
Proportional Error (%)	24.4	NA	NA

ALAG = Lag time; ALT = alanine aminotransferase; BSV = between-subjects variability; CL/F = apparent clearance; eGFRT = estimated glomerular filtration rate capped to 150 mL/min/1.73m^2; Ka = first-order rate constant of absorption; PK= Pharmacokinetic; Vc/F = apparent central volume of distribution; NA= Not applicable.

$$CL/F = 13.6 \times \left(\frac{Body\ Weight}{70}\right)^{0.590} \times \left(\frac{eGFRT}{102}\right)^{0.322} \times \left(\frac{ALT}{24.0}\right)^{0.125} \times 0.833\ if\ not\ SBS\ or\ Crohn's\ Disease$$

$$Vc/F = 33.1 \times \left(\frac{Body\ Weight}{70}\right)^{1.65} \times \left(\frac{Age}{34}\right)^{-0.332}$$

$$Ka = 0.318 \times \left(\frac{Body\ Weight}{70}\right)^{-0.624} \times 0.690\ for\ SC\ administration\ other\ than\ abdomen$$

Population estimates of CL/F and Vc/F of teduglutide were 13.6 L/h and 33.1 L, respectively. The typical half-life of teduglutide is 1.69 h. The rate of absorption of teduglutide following SC dosing is 0.318 h-1. The absorption lag time was 0.207 h, corresponding to 12.4 min. Covariate effects on CL/F are discussed below.

The CL/F of teduglutide was dependent on body weight. The exponent for the effect of weight CL/F was 0.590 [(Body Weight/70)0.590]. These results suggest lower CL/F values in lighter subjects. For example, typical subjects with body weight values of 10.1 and 127 kg (corresponding to minimum and maximum values in the population) are expected to have CL/F values 68% lower and 42% higher (4.34 and 19.3 L/h, respectively) relative to a typical subject with a body weight of 70 kg, respectively.

Teduglutide mainly undergoes urinary excretion. The CL/F of teduglutide was dependent on baseline eGFR (capped to 150 mL/min/1.73m^2, eGFRT). The exponent for the effect of capped eGFR on CL/F was 0.322 [(eGFRT/102)0.322]. These results suggest lower CL/F values in subjects with lower eGFR. For example, typical subjects with eGFR values of 4.43 and 473 mL/min/1.73m^2 (corresponding to minimum and maximum values in the population) are expected to have CL/F values 64% lower and 64% higher (4.95 and 22.3 L/h, respectively) relative to a typical subject with an eGFR of 102 mL/min/1.73m^2, respectively.

- The CL/F of teduglutide was dependent on ALT levels. The exponent for the effect of ALT on CL/F was 0.125 [(ALT/24.0) 0.125]. These results suggest lower CL/F values in subjects with lower ALT levels. For example, typical subjects with ALT levels of 3 and 412 U/L (corresponding to minimum and maximum values) are expected to have CL/F values 23% lower and 43% higher (10.5 and 19.4 L/h, respectively) relative to a typical subject with an ALT level of 24.0 U/L, respectively.
- The typical CL/F in subjects without SBS or Crohn's disease was approximately 20% lower relative to those in patients with SBS or Crohn's disease. Covariate effects on Vc/F are discussed below.
- The Vc/F of teduglutide was highly dependent on body weight. The exponent for the effect of weight Vc/F was 1.65 [(Body Weight/70)1.65]. These results suggest lower Vc/F values in lighter

subjects. For example, typical subjects with body weight values of 10.1 and 127 kg (corresponding to minimum and maximum in the population) are expected to have Vc/F values 96% lower and 2.7-fold higher (1.36 and 88.4 L, respectively) relative to a typical subject with a body weight of 70 kg, respectively.

- The Vc/F of teduglutide was dependent on age. The exponent for the effect of age on Vc/F was -0.332 [(Age/34)-0.332]. These results suggest higher Vc/F values in younger subjects. For example, typical subjects of 1 and 79 years of age (corresponding to minimum and maximum values in the population) are expected to have Vc/F 3-fold higher and 24% lower (107 and 25.0 L, respectively) values relative to a typical subject 34 years of age, respectively. Covariate effects on Ka are discussed below.
- The Ka of teduglutide was dependent on body weight. The exponent for the effect of body weight on Ka was -0.624 [(Body Weight/70) -0.624]. These results suggest higher Ka values in subjects with lower body weight. For example, typical subjects with body weight values of 10.1 and 127 kg (corresponding to minimum and maximum in the population) are expected to have a Ka values 3.3-fold higher and 31% lower (1.06 and 0.219 h-1, respectively) relative to a typical subject with a body weight of 70 kg, respectively.
- The typical Ka in subjects receiving SC dosing in the arm or thigh were 31% lower relative to those who received SC dosing in the abdomen. The residual variability on predicted concentrations of teduglutide was low based on the error model. For example, the unexplained error associated with a fitted concentration of 35 ng/mL (corresponding approximately to the typical C_{max} in adults) was approximately 15.7 ng/mL [(35 x 0.244) + 7.16 ng/mL]. The residual variability represents the sum of all variability that is not explained by the model, including bioanalytical and experimental variability.

The geometric mean CL/F of teduglutide in pediatric patients (1 to 11 years of age) was approximately 44% lower than that observed in adult patients, respectively. The above change in CL/F was associated with a 49% reduction in AUC_{ss} in pediatric patients relative to adult subjects. For example, a typical 70-kg adult patient treated with a 0.05 mg/kg dose (3.5 mg) and a CL/F of 13.3 L/h is expected to have an AUCss of 263 ng.h/mL (3,500,000 ng / 13,300 mL/h). Conversely, a typical 20-kg pediatric patient treated with a 0.05 mg/kg dose (1 mg) and a CL/F of 7.45 L/h is expected to have an AUC_{ss} of 134 ng.h/mL (1,000,000 ng / 7,450 mL/h).

The geometric mean Vc/F of teduglutide in pediatric patients (1 to 11 years of age) was approximately 70% lower than that observed in adult patients, respectively. Conversely, the geometric mean Ka of teduglutide in pediatric patients (1 to 11 years of age) was approximately 38% higher than that observed in adult patients, respectively.

Descriptive statistics of exposure parameters of teduglutide by age for a 0.05 mg/kg dose are presented in Table 3.

Table 3 – Descriptive Statistics of Teduglutide Parameters Following SC Dosing of 0.05 mg/kg as a Function of Age

Age Categories	Age	Mean (SD) Median (90% CI)						
		Body Weight (kg)	$Cmax_{ss}$ (ng/mL)	AUC_{ss} (ng.h/mL)	$C_{8,ss}$ (ng/mL)	$C_{12,ss}$ (ng/mL)	Half-Life (h)	T_{maxss} (h)
Adults	≥18 years	60.1 (9.79) 59.3 [42.8, 80.1]	39.7 (13.5) 39.0 [20.3, 67.3]	252 (106) 224 [131, 509]	12.6 (8.60) 10.3 [3.52, 34.1]	4.57 (4.82) 3.18 [0.494, 15.4]	1.29 (0.623) 1.20 [0.598, 2.64]	2.49 (0.679) 2.40 [1.60, 3.68]
Adolescents	12 to 17 years	39.8 (2.75) 38.5 [38.0, 43.0]	29.7 (8.37) 31.3 [20.7, 37.2]	154 (17.6) 152 [138, 173]	5.58 (1.29) 4.88 [4.78, 7.06]	1.37 (0.950) 0.866 [0.784, 2.47]	0.953 (0.00574) 0.952 [0.948, 0.959]	2.07 (0.289) 1.90 [1.90, 2.40]
Pediatrics	8 to 11 years	25.4 (4.55) 26.2 [18.5, 34.9]	31.0 (9.37) 30.5 [21.1, 51.5]	137 (26.4) 129 [113, 199]	3.93 (1.87) 3.83 [0.652, 7.68]	0.807 (0.459) 0.810 [0.0281, 1.54]	0.798 (0.226) 0.765 [0.568, 1.32]	1.78 (0.286) 1.80 [1.20, 2.20]
	6 to 7 years	21.2 (3.35) 21.2 [17.2 25.4]	42.4 (11.8) 37.3 [35.1, 59.9]	152 (27.1) 152 [124, 182]	2.68 (2.60) 1.61 [0.959, 6.55]	0.410 (0.584) 0.151 [0.0587, 1.28]	0.723 (0.278) 0.662 [0.469, 1.10]	1.55 (0.387) 1.45 [1.20, 2.10]
	4 to 5 years	16.7 (1.70) 16.8 [13.2, 18.8]	31.5 (5.88) 30.3 [23.3, 42.2]	114 (14.7) 111 [97.0, 144]	1.78 (0.775) 1.72 [0.814, 3.38]	0.231 (0.177) 0.206 [0.0408, 0.617]	0.653 (0.118) 0.664 [0.491, 0.825]	1.47 (0.183) 1.50 [1.20, 1.80]
	2 to 3 years	13.7 (1.77) 13.8 [11.1, 16.8]	34.4 (15.5) 30.0 [21.7, 77.4]	127 (90.9) 104 [63.5, 421]	2.48 (4.30) 1.32 [0.279, 16.6]	0.412 (0.957) 0.154 [0.00674, 3.58]	0.685 (0.326) 0.598 [0.316, 1.64]	1.45 (0.279) 1.40 [1.10, 2.20]
	1 to < 2 years	[redacted] (NA)	29.3 (NA) 29.3 [29.3, 29.3]	85.1 (NA) 85.1 [85.1, 85.1]	0.546 (NA) 0.546 [0.546, 0.546]	0.0350 (NA) 0.0350 [0.0350, 0.0350]	0.503 (NA) 0.503 [0.503, 0.503]	1.20 (NA) 1.20 [1.20, 1.20]

AUC_{ss} = area under the curve at steady state; $Cmax_{ss}$ = maximum concentration at steady state; C_{8ss} =concentration at 8 h post dose under steady state; C_{12ss} = concentration at 12 h post dose under steady state; CI = confidence interval; NA = not applicable since n=1; SD = Standard deviation; Tmax = time to maximum concentration under steady state

Assessor's comment

Descriptive statistics of exposure parameters of teduglutide by age for a 0.05 mg/kg dose presented in Table 6 has been age stratified accordingly. However, the number of subjects (n) should be provided for each age group. **(OC).**

Mean C_{maxss} of teduglutide in adult and adolescent subjects were 39.7 and 29.7 ng/mL, respectively. For pediatric patients, C_{maxss} values ranged from 21.1 to 77.4 ng/mL and consistent with those in adults and adolescents (19.3 to 73.4 ng/mL). The C_{maxss} of teduglutide in the neonate patient (n=1, 1 to < 2 years of age group) was within 26% and 2% of those observed in adults and adolescents, respectively. The C_{maxss} of teduglutide in the neonate patient (1 to < 2 years of age) was consistent with those observed in other pediatric groups. Mean AUC_{ss} values were age-dependent and gradually decreased with age from a mean of 252 ng.h/mL in adults to 127 ng.h/mL in pediatric patients between 2 and 3 years of age and 85.1 ng.h/mL in the neonate patient between 1 and <2 years of age. It is to be noted that a 6-fold decrease in weight (from 60.1 kg in adults to 10.5 kg in 1 to <2 years) resulted in an approximate 3-fold decrease in AUC_{ss} (252 and 85.1 ng.h/mL in adults and 1 to <2 years old age group, respectively).

Maximum concentration-time profiles of teduglutide in pediatric patients treated with a 0.05 mg/kg dose were similar to those observed in adult patients treated with a 0.05 mg/kg dose. Since clinical data in conjunction with C_{max} were previously considered to support teduglutide dose selection (i.e., AUC was previously shown not to correlate with efficacy), the proposed 0.05 mg/kg dose in pediatric patients is expected to results in similar safety and efficacy as a 0.05 mg/kg dose in adult patients with SBS.

A gradual decrease in CL/F was observed with lower eGFR values. As per the population PK model, the CL/F of teduglutide was mainly dependent on eGFR with minimum dependency on body weight. Mean CL/F values in subjects with moderate, severe renal impairment and ESRD were approximately 8.9%, 29% and 55% lower than those in subjects with normal renal function, respectively. No difference was observed in CL/F between subjects with mild renal impairment and those with normal renal function. Based on the above results, a 50% dosage reduction is recommended in patients with moderate to severe renal impairment and ESRD. Mean Vc/F values were consistent in subjects with renal impairment (mild, moderate and severe impairment as well as ESRD) and were comparable to subjects with normal renal function. As a result, Vc/F values did not further decrease as a function of eGFR.

Descriptive statistics of PK parameters of teduglutide (0.05 mg/kg) according to site of injection (abdomen vs. other sites): Mean AUC_{ss} and C_{maxss} of teduglutide following SC administration of a 0.05 mg/kg dose in the arm or thigh were 25% and 31% lower than that observed following SC administration in the abdomen, respectively.

Overall, simulation results indicated that pediatric patients (1-17 years) are expected to display similar steady state C_{max} values of teduglutide as adults. On the other hand, simulated AUC_{ss} were highly age-dependent and gradually decreased from adults to children between 1 and 2 years of age. Clinical data in conjunction with C_{max} were considered 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.

Assessor's comment

The PK model has overall been presented in accordance with the EMA Guideline on reporting the results of population pharmacokinetic analyses (Doc.ref. CHMP/EWP/185990/06, June 2007), and are considered supportive for the suggested posology. It is acknowledged that there are few children with SBS. However, only one child in the age group 1-2 years was included in the PK model. The MAH should discuss and justify the validity of the results in relation to the posology in children < 2 years. **(OC).**

6.3. Discussion

The objective of the study (PK model) was to enrich the dataset with additional Phase I clinical studies (CL0600-018 and C09-001) and an additional study performed in pediatric patient with SBS (TED-C14-006) to ultimately support dosing in pediatric patients.

The MAH has provided a sufficient introduction to the Teduglutide (SHP633) POP PK model in pediatric patients with SBS, and the objectives of the analysis has been described sufficiently. Furthermore, the MAH has overall described the studies from which the data included in the analysis originate, sufficiently. Of notice, CL0600-004, TED-C13-003 and TED-C14-006 were pediatric studies covered by the EMEA-000482-PIP01-08-M04.

The MAH has described the handling of concentrations values below BLQ. However, with reference to the EMA Guideline on reporting the results of population pharmacokinetic analyses (Doc.ref. CHMP/EWP/185990/06, June 2007), the MAH is asked to:

- Apply the type of bioanalytical methods used and the LLOQ for each analyte in each method.
- Discuss the possible consequences of ignoring the concentrations below BLQ/LLOQ. (**OC**)

A relevant overview of the POP PK model process was provided, and the procedure of detecting outliers was described adequately. In addition, the covariates selected for the model sufficiently presented. However, the pediatric age groups should be stratified as follows: <2, 2-<6, 6-<12, 12-<18 years. **(OC)**

The stepwise covariate building model procedure has been presented adequately, herein the statistical significance criteria for covariate selection.

The MAH should elucidate the handling of BLQ samples further, and discuss the possible consequences in relation to the final model. **(OC).**

The MAH has presented the pcVPCs of the final model accordingly. The model appears to capture the teduglutide concentrations well.

In the presentation of result in general, the MAH should provide the number of pediatric trial participants in each age group as follows: <2 years, 2-<6, 6-<12, 12-<18 years. **(OC).**

Descriptive statistics of exposure parameters of teduglutide by age for a 0.05 mg/kg dose presented in Table 6 has been age stratified accordingly. However, the number of subjects (n) should be provided for each age group. **(OC).**

The MAH should provide the number/percentage of subjects with SBS and Crohn' disease, respectively. **(OC).**

The PK model has overall been presented in accordance with the EMA Guideline on reporting the results of population pharmacokinetic analyses (Doc.ref. CHMP/EWP/185990/06, June 2007), and are considered supportive for the suggested posology. It is acknowledged that there are few children with SBS. However, only one child in the age group 1-2 years was included in the PK model. The MAH is requested to discuss and justify the validity of the results in relation to the posology in children < 2 years. **(OC).**

7. Clinical Efficacy aspects

7.1. Methods – analysis of data submitted

TED-C14-006 was a study to evaluate the safety, pharmacokinetics (PK), and efficacy of teduglutide in pediatric subjects through 17 years of age with SBS and who are dependent on parenteral support. This study included 2 treatment arms: a teduglutide treatment arm and a standard of care (SOC) treatment arm. Subjects in both arms participated in a 2-week minimum screening period, a 24-week treatment period, and a 4-week follow-up period. During the screening period, subjects chose into which arm to enroll. During the 24-week treatment period, subjects in the SOC treatment arm received standard medical therapy for SBS; while those in the teduglutide treatment arm received daily subcutaneous (SC) injections of teduglutide in addition to standard medical therapy. These subjects were randomized 1:1 in a double-blinded manner into 2 parallel teduglutide dose groups: 0.025

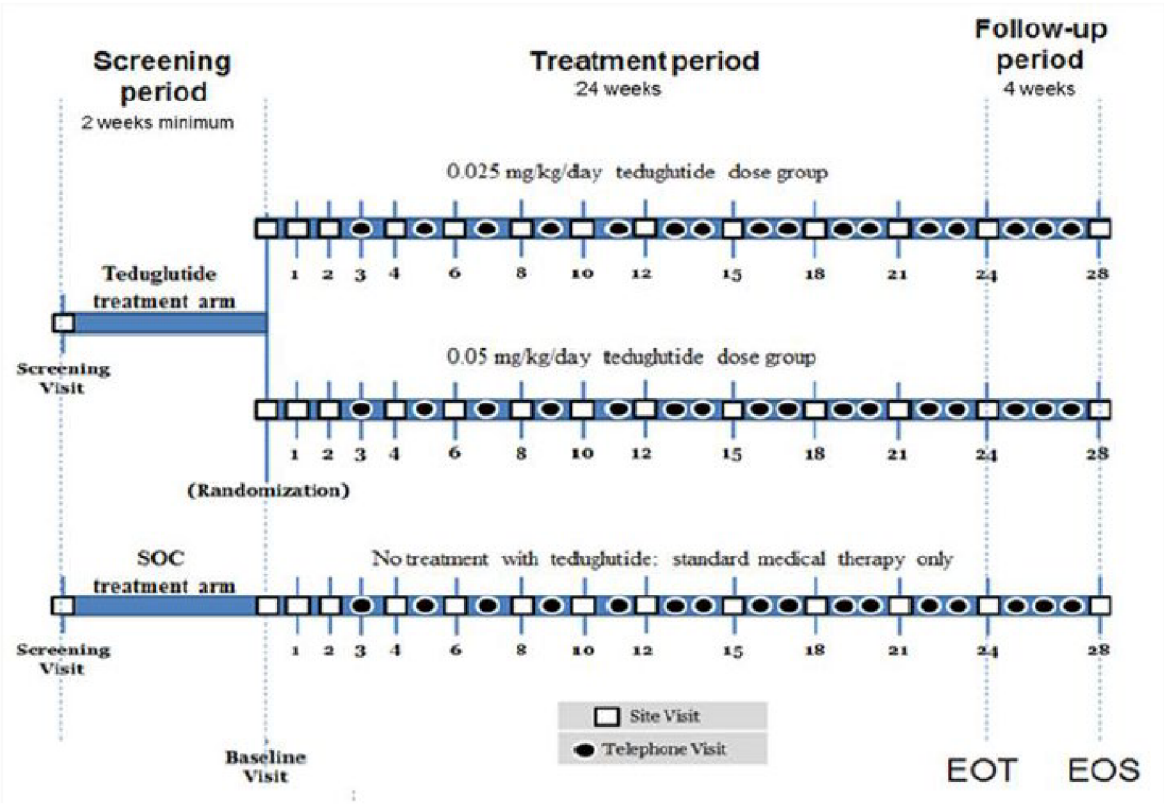
mg/kg/day and 0.05 mg/kg/day. Randomization across dose groups was stratified by age: <1 year, 1 to <12 years, 12 to <17 years, and 17 to <18 years.

Subjects in both arms followed the same visit schedule. After the screening period, subjects visited the site at baseline, weekly for the first 2 weeks (ie, Weeks 1 and 2), and then every other week through Week 12 (Weeks 4, 6, 8, 10, and 12). For the remainder of the treatment period, subjects visited the sites once every 3 weeks (ie, Weeks 15, 18, 21, and 24). For all other study weeks, subjects were contacted by telephone. At all site visits and telephone contacts, safety was monitored and nutritional support was reviewed and adjusted as needed. At the end of the treatment period (Week 24/End of Treatment [EOT]), all subjects entered a 4-week follow-up period until the end of study (Week 28/End of Study [EOS]) during which time no study drug (ie, teduglutide) was administered. A final visit occurred at Week 28, 4 weeks after EOT.

Telephone contact was made during the weeks from EOT to EOS to monitor safety and any changes in nutritional support.

Blood samples for PK analysis were collected at baseline. If a subject was unable to provide blood samples for PK at the baseline visit, then PK samples could have been collected during any other site visit while the subject was receiving treatment with teduglutide. Blood was drawn predose and 1, 2, and 4 hours postdose. In smaller children for whom blood sampling imposed unacceptable phlebotomy volume, the number of PK samples was reduced.

A schematic representation of the study design is presented in Figure 3.



EOS=end of study; EOT=end of treatment; SOC=standard of care

Figure 3 – TED-C14-006 Study Schematic

Assessor's comments

Study design, including selection of study groups, randomization and blinding, and dose selection are appropriate. The SOC treatment arm serves as an observational cohort for the 24-week treatment period. Although the relevance of an observational cohort is acknowledged, comparisons between SOC and teduglutide treatment arms may be biased. Selection criteria for inclusion into the SOC treatment arm therefore becomes important.

The MAH should discuss the selection criteria for inclusion in the SOC treatment arm in more details, and in which way they may influence (or have influenced) the interpretation of results. **(OC)**.

7.2. Results

7.2.1. Disposition of Subjects

A total of 71 subjects were screened and 59 subjects were enrolled. 50 subjects in the teduglutide treatment arm (24 subjects in the 0.025 mg/kg/day dose group and 26 subjects in the 0.05 mg/kg/day dose group) and 9 subjects in the SOC arm. All of the subjects enrolled in the teduglutide treatment arm were treated with study drug.

All 59 subjects completed treatment (Week 24) and completed the study (Week 28).

Table 4 – Subject Disposition – All subjects Screened

Category	0.025 mg/kg/day Teduglutide	0.05 mg/kg/day Teduglutide	Total Teduglutide	Standard of Care	Total
Screened					71
Enrolled Subjects	24	26	50	9	59
Treated with Study Drug	24 (100)	26 (100)	50 (100)	-	50 (84.7)
Completed Treatment (Week 24)	24 (100)	26 (100)	50 (100)	9 (100)	59 (100)
Early Treatment Discontinuation	0	0	0	0	0
Completed Study (Week 28)	24 (100)	26 (100)	50 (100)	9 (100)	59 (100)
Early Study Discontinuation	0	0	0	0	0

Note: Percentages are based on the number of subjects enrolled in each treatment group.
Note: A subject is considered enrolled in the study at the baseline visit when the choice of treatment arm (i.e., teduglutide or standard of care) has been made.
Source: Table 14.1.1.1

7.2.2. Demographics and Baseline Characteristics

Demographic and baseline characteristics of the ITT set are presented in Table 5.

The age distribution of subjects was similar in both treatment arms. Overall, the mean age was 6.3±3.76 years and the majority of subjects were 1 to <12 years of age (91.5%). No children under 1 year of age were enrolled. There were 2 subjects between 12 and 17 years of age in each teduglutide dose group. The race and ethnicity distribution was similar between the 2 teduglutide dose groups. There were a greater percentage of subjects with a race of "other" and "not provided due to local regulations" and Hispanic/Latino ethnicity in the SOC arm. Baseline growth parameters showed below average weight and height in the teduglutide treatment arm, but normal body mass index, consistent

with stunting, which is common in this patient population. The SOC arm had higher baseline weight and height z-scores, indicating better baseline nutritional status.

Table 5 – Demographics and Baseline Characteristics by Region – Intention-to-treat Set

Characteristic	0.025 mg/kg/day Teduglutide (N=24)	0.05 mg/kg/day Teduglutide (N=26)	Total Teduglutide (N=50)	Standard of Care (N=9)	Total (N=59)
Age (years), Mean (SD)	6.6 (3.61)	6.2 (3.67)	6.4 (3.61)	5.7 (4.72)	6.3 (3.76)
Age Group, n (%)					
<1 years	0	0	0	0	0
1 - <12 years	22 (91.7)	24 (92.3)	46 (92.0)	8 (88.9)	54 (91.5)
12 - <17 years	2 (8.3)	2 (7.7)	4 (8.0)	0	4 (6.8)
17 - <18 years	0	0	0	1 (11.1)	1 (1.7)
Sex, n (%)					
Male	16 (66.7)	19 (73.1)	35 (70.0)	6 (66.7)	41 (69.5)
Female	8 (33.3)	7 (26.9)	15 (30.0)	3 (33.3)	18 (30.5)
Premenarchal [1]	7 (87.5)	7 (100)	14 (93.3)	2 (66.7)	16 (88.9)
Child-bearing Potential [1]	1 (12.5)	0	1 (6.7)	1 (33.3)	2 (11.1)
Race, n (%)					
White	16 (66.7)	21 (80.8)	37 (74.0)	2 (22.2)	39 (66.1)
Black or African American	3 (12.5)	3 (11.5)	6 (12.0)	1 (11.1)	7 (11.9)
Asian	1 (4.2)	1 (3.8)	2 (4.0)	1 (11.1)	3 (5.1)
Other	1 (4.2)	0	1 (2.0)	2 (22.2)	3 (5.1)
Not allowed based on local regulations	3 (12.5)	1 (3.8)	4 (8.0)	3 (33.3)	7 (11.9)
Ethnicity, n (%)					
Hispanic or Latino	5 (20.8)	5 (19.2)	10 (20.0)	4 (44.4)	14 (23.7)
Not Hispanic or Latino	16 (66.7)	20 (76.9)	36 (72.0)	2 (22.2)	38 (64.4)
Not Reported	3 (12.5)	1 (3.8)	4 (8.0)	3 (33.3)	7 (11.9)
Weight Z-Score at Baseline, Mean (SD)	-0.85 (1.08)	-0.88 (1.11)	-0.86 (1.08)	-0.22 (0.81)	-0.77 (1.07)
Height Z-Score at Baseline, Mean (SD)	-1.28 (1.22)	-1.31 (1.18)	-1.30 (1.19)	-0.39 (1.59)	-1.16 (1.28)
BMI Z-Score at Baseline, Mean (SD)	-0.09 (1.05)	-0.03 (1.18)	-0.06 (1.11)	0.08 (0.56)	-0.04 (1.04)
Head Circumference Z-Score at Baseline, Mean (SD)	-1.79 (0.50)	-0.13 (0.49)	-0.84 (1.00)	-0.97 (-)	-0.86 (0.93)

Note: [1] Percentage of menarchal status are based on the number of females in each treatment group. Unless specified, percentage are based on the number of subjects in the analysis set in each treatment group by region.
Note: Head circumference is scheduled to be collected only for subjects <= 36 months of age at the time of measurement.
Source: Table 14.1.2.1

The SBS history of the ITT set is presented in Table 6. The primary underlying causes of SBS were similar in both treatment arms. Overall, the most common causes of SBS were gastroschisis (37.3% [22/59] subjects), midgut volvulus (32.2% [19/59] subjects), and necrotizing enterocolitis (16.9% [10/59] subjects). The mean small intestine length was similar in both treatment arms, and was 43.27±32.52 cm overall. A similar fraction of subjects in each treatment arm had an ostomy, which was present in 22.0% (13/59) subjects overall. Of those with an ostomy, 69.2% (9/13) subjects had a jejunostomy, 15.4% (2/13) subjects had an ileostomy, and 15.4% (2/9) subjects had a colostomy. A total of 94% (47/59) subjects in the teduglutide treatment arm and 66.7% (6/9) subjects in the SOC arm had at least some remaining colon. The mean percent of remaining colon was similar in both treatment arms, and was 64.5±32.8% overall. Among those with any remaining colon, the remnant colon was not in continuity in 3 subjects, all of whom were in the 0.05 mg/kg/day dose group. The percent of subjects with a distal or terminal ileum was similar in both treatment arms, and was 35.6% (21/59) subjects overall. Of those with a distal or terminal ileum, 76.2% (16/21) subjects had an intact ileocecal valve.

Table 6 – Short Bowel Syndrome History – Intention-to-treat Set

Characteristic	0.025 mg/kg/day Teduglutide (N=24)	0.05 mg/kg/day Teduglutide (N=26)	Total Teduglutide (N=50)	Standard of Care (N=9)	Total (N=59)
Primary Reason for the Diagnosis of SBS, n (%)					
Necrotizing enterocolitis	5 (20.8)	3 (11.5)	8 (16.0)	2 (22.2)	10 (16.9)
Midgut volvulus	10 (41.7)	6 (23.1)	16 (32.0)	3 (33.3)	19 (32.2)
Intestinal atresia	2 (8.3)	1 (3.8)	3 (6.0)	0	3 (5.1)
Gastroschisis	6 (25.0)	14 (53.8)	20 (40.0)	2 (22.2)	22 (37.3)
Long-segment Hirschprung disease	1 (4.2)	1 (3.8)	2 (4.0)	2 (22.2)	4 (6.8)
Other	0	1 (3.8)	1 (2.0)	0	1 (1.7)
Subjects with a stoma, n (%)	5 (20.8)	5 (19.2)	10 (20.0)	3 (33.3)	13 (22.0)
Type of Stoma[a], n (%)					
Jejunostomy	3 (60.0)	4 (80.0)	7 (70.0)	2 (66.7)	9 (69.2)
Ileostomy	0	1 (20.0)	1 (10.0)	1 (33.3)	2 (15.4)
Colostomy	2 (40.0)	0	2 (20.0)	0	2 (15.4)
Subject with any remaining colon, n (%)	22 (91.7)	25 (96.2)	47 (94.0)	6 (66.7)	53 (89.8)
Estimated percent of colon remaining, Mean (SD)	60.9 (36.10)	68.8 (30.72)	65.1 (33.13)	60.3 (33.45)	64.5 (32.84)
Colon in continuity[b], n (%)	22 (100)	22 (88.0)	44 (93.6)	6 (100)	50 (94.3)
Total estimated remaining small intestinal length (cm), n (%)	38.20 (38.76)	46.75 (27.90)	42.86 (33.15)	45.28 (31.05)	43.27 (32.52)
Distal/terminal Ileum present, n (%)	9 (37.5)	9 (34.6)	18 (36.0)	3 (33.3)	21 (35.6)
Ileocecal valve present[c], n (%)	6 (66.7)	7 (77.8)	13 (72.2)	3 (100)	16 (76.2)

Characteristic	0.025 mg/kg/day Teduglutide (N=24)	0.05 mg/kg/day Teduglutide (N=26)	Total Teduglutide (N=50)	Standard of Care (N=9)	Total (N=59)

SBS=Short bowel syndrome.
[a] Percentages are based on the number of subjects with a stoma in each treatment group.
[b] Percentages are based on the number of subjects who have remaining colon in each treatment group.
[c] Percentages are based on the number of subjects with distal/terminal ileum present in each treatment group.
Note: Percentages are based on the number of subjects in the analysis set in each treatment group unless indicated otherwise.
Source: Table 14.1.3.1

Assessor's comments

Demographic and baseline characteristics and treatment compliance were (roughly) similar in all treatment arms.

Only 9 patients were enrolled in the SOC arm, while in total 50 patients received teduglutide treatment. The MAH should discuss and justify this bias in regards of interpretation of the results. **(OC).**

When presenting demographics and results in general, the MAH should divide the paediatric subgroups as follows: <2, 2-<6, 6-<12, 12-<18. **(OC).**

7.2.3. Efficacy Results

Administration of 0.025 and 0.05 mg/kg/day of teduglutide for up to 24 weeks reduced PN/IV support in pediatric subjects with SBS. Based on subject diary data, which was considered a more representative measure than the investigator prescribed data, 54.2% of subjects in the 0.025 mg/kg group, 69.2% of subjects in the 0.05 mg/kg group, and 11.1% of subjects in the SOC arm achieved the primary endpoint of a ≥ 20% reduction in PN/IV volume.

Notably, 2 children in 0.025 mg/kg group and 3 children in the 0.05 mg/kg group achieved enteral autonomy, ie, complete weaning off of parenteral support. No children in the SOC arm achieved enteral autonomy during the study.

Clinically meaningful reductions in PN/IV volume and calories were achieved in the subjects treated with teduglutide, but not the subjects treated with SOC. From baseline to EOT there were 36% and 42% decreases in mean PN/IV volume in the 0.025 and 0.05 mg/kg/day groups, respectively, and a 10% decrease in mean PN/IV volume the SOC arm. Similarly, there were 42% and 44% decreases in mean PN/IV calories in the 0.025 and 0.05 mg/kg/day groups, respectively, and a 2% increase in mean PN/IV calories the SOC arm.

Teduglutide treatment was associated with an average reduction in PN/IV infusions of about 1 day per week. A night free from an IV pump is expected to improve the quality of sleep for both patients and caregivers. Teduglutide treatment was also associated with a reduction in the duration of the PN/IV infusions by 2.5 to 3 hours per day. This provides 2.5 to 3 new hours per day for free movement. No such changes were observed in the SOC arm.

The reductions in PN/IV volume and calories were associated with increases in EN intake, suggesting that the changes were due to improved intestinal absorptive capacity. In the teduglutide treatment arm, EN volume increased by 75% and 79% in the 0.025 and 0.05 mg/kg/day groups, respectively, and by 3% in the SOC arm. Enteral nutrition calories increased by 81% and 86% in the 0.025 and 0.05 mg/kg groups, respectively, and by 37% in the SOC arm.

As evidence of pharmacodynamic effects on the small intestinal mucosa, teduglutide was associated with increases in plasma citrulline, a biomarker of enterocyte mass. The observed increase supports the therapeutic hypothesis that an increase in intestinal surface area underlies the improvements in intestinal adaptation seen in the subjects treated with teduglutide (Crenn et al., 2000). Citrulline levels declined within 4 weeks after teduglutide discontinuation.

7.2.3.1. 20% Reduction in PN/IV Volume

The primary efficacy endpoint was weight-normalized reduction in PN/IV volume of at least 20% at EOT compared to baseline (TED-14-006, Section 11.1.1.1). In the ITT analysis based on the subject diary data, 13 (54.2%) subjects in the 0.025 mg/kg group, 18 (69.2%) subjects in the 0.05 mg/kg group, and 1 (11.1%) subjects in the SOC arm achieved the primary endpoint.

In general, the percentage of subjects achieving a ≥ 20% reduction in PN/IV volume increased over the course of the 24-week treatment period in both teduglutide dose groups but not the subjects treated with SOC.

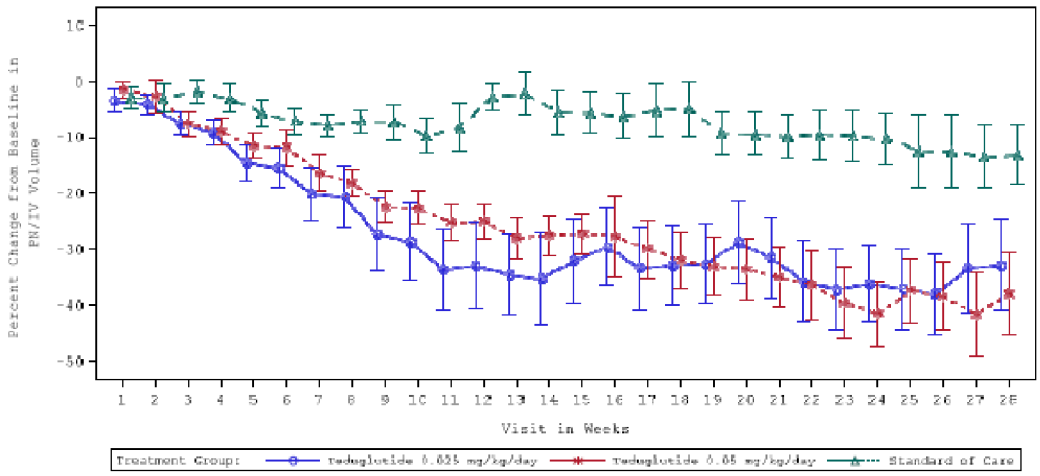
7.2.3.2. Complete Weaning

A total of 2 of 24 subjects (8.3%) in 0.025 mg/kg dose group and 3 of 26 subjects (11.5%) in the 0.05 mg/kg dose group achieved enteral autonomy, ie, complete weaning off of parenteral support by EOT. No subjects in the SOC arm achieved enteral autonomy during the study.

7.2.3.3. Reduction in PN/IV Volume Support

Clinically meaningful reductions in PN/IV volume were achieved in the subjects treated with teduglutide, whereas no such change was observed in the SOC arm (Figure 4). Mean change in PN/IV volume from baseline to EOT was -16.16±10.52 mL/kg/day from a baseline of 56.84±25.24 mL/kg/day and -23.30±17.50 mL/kg/day from a baseline of 60.09±29.19 mL/kg/day in the 0.025 and

0.05 mg/kg/day groups, corresponding to percentage change of -36.17±30.65% and -41.57±28.90%, respectively. Mean change in PN/IV volume from baseline to EOT in the SOC arm was -6.03±4.5 mL/kg/day from a baseline of 79.59±31.12 mL/kg/day, corresponding to a percentage change of -10.21±13.59%.

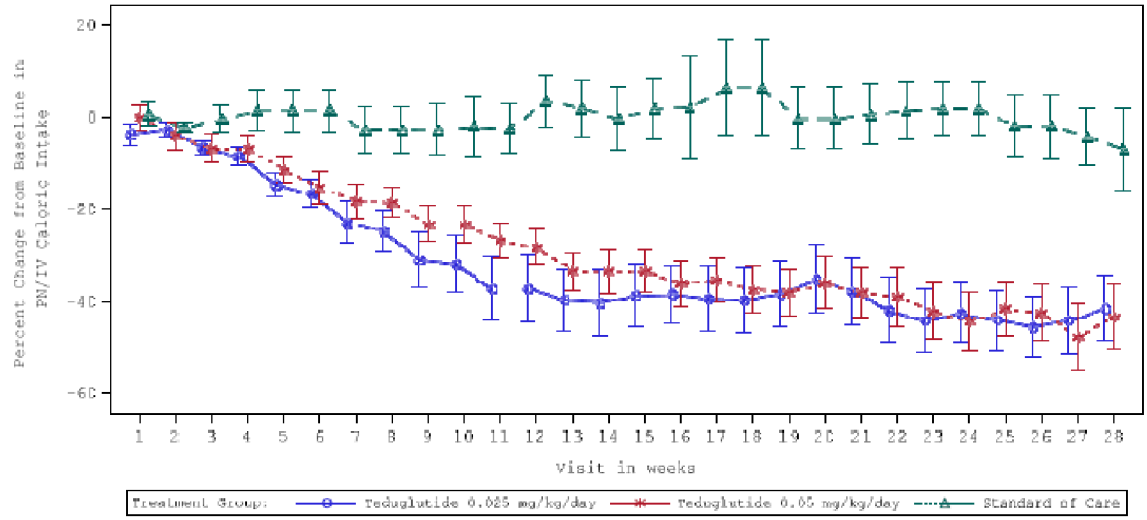


PN/IV=parenteral nutrition/intravenous fluids; SE=standard error
Note: Week 24 is the end of treatment visit; Week 28 is the end of study visit.
Note: Average daily value is calculated as [(sum of non-missing daily values in the diary / number of days with non-missing values)]/last available body weight prior to the visit.
Source: TED-C14-006, Figure 14.2.4.3

Figure 4 – Percent Change in PN/IV Volume (mL/kg/day) by Week Based on Subject Diary Data – Intention-to-treat Set

Reduction in PN Calories

Overall, the changes in PN/IV calories mirrored the changes in PN/IV volume (Figure 5). Mean change in PN/IV calories from baseline to EOT was -14.92±8.29 kcal/kg/day from a baseline of 43.34±21.10 kcal/kg/day and -18.99±14.28 kcal/kg/day from a baseline of 43.28±16.52 kcal/kg/day in the 0.025 and 0.05 mg/kg/day groups, corresponding to a percentage change of -42.48±29.15% and -44.29±31.28%, respectively. Mean change in PN/IV calories from baseline to EOT in the SOC arm was -0.46±4.95 kcal/kg/day from a baseline of 44.63±22.53 kcal/kg/day, corresponding to a percentage change of 1.88±17.58%.



PN/IV=parenteral nutrition/intravenous fluids; SE=standard error
Note: Week 24 is the end of treatment visit; Week 28 is the end of study visit.
Note: 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.
Source: TED-C14-006, Figure 14.2.5.3

Figure 5 – Percent Change in PN/IV Calories (kgal/kg/day) by Week Based on Subject Diary Data – Intention-to-treat Set

7.2.3.4. Reduction in Infusion Time

Teduglutide treatment was associated with reductions in days of parenteral support, whereas no such change was observed in the SOC arm. Mean change in PN/IV infusion days per week from baseline to EOT was -0.88±1.78 days/week from a baseline of 6.5±1.10 days/week and -1.34±2.24 days/week from a baseline of 6.6±0.79 days/week in the 0.025 and 0.05 mg/kg/day groups, corresponding to a percentage change of -16.03±31.34% and a -21.33±34.09%, respectively. There was no reduction in PN/IV infusion days per week in the SOC arm.

The mean duration of the PN/IV infusions was reduced in the teduglutide treatment arm, whereas minimal change was observed in the SOC arm. Mean change in PN/IV infusion hours per day from baseline to EOT based on subject diary data was -2.47±2.73 hours/day from a baseline of 11.7±3.03 hours/day and -3.03±3.84 hours/day from a baseline of 11.2±2.99 hours/day in the 0.025 and 0.05 mg/kg/day groups, corresponding to a percentage change of -26.04±31.56% and -26.09±36.14%, respectively. Mean change in PN/IV infusion hours per day from baseline to EOT in the SOC arm was -0.21±0.69 hours/day from a baseline of 12.6±5.50 hours/day, corresponding to a percentage change of -1.75±5.89%.

7.2.3.5. Increase in Enteral Volume and Calories

Reductions in PN/IV volume were associated with increases in EN volume. Mean change in EN volume from baseline at Week 24 based on subject diary data was 7.69±13.46 mL/kg/day from a baseline of 17.80±24.45 mL/kg/day and 10.96±16.59 mL/kg/day from a baseline of 27.64±29.47 mL/kg/day in the 0.025 and 0.05 mg/kg/day groups, corresponding to a percentage change of 76.89±117.19% and a 79.52±134.49%, respectively. Mean change in EN volume from baseline to EOT in the SOC arm was 0.74±5.91 mL/kg/day from a baseline of 14.04±18.19 mL/kg/day, corresponding to a percentage change of -2.50±33.87%.

Changes in EN calories were similar to the observed changes in EN volume. Mean change in EN calories from baseline at Week 24 based on subject diary data was 8.43±14.39 kcal/kg/day from a baseline of 19.87±25.88 kcal/kg/day and 12.98±18.93 kcal/kg/day from a baseline of 24.14±21.25 kcal/kg/day in the 0.025 and 0.05 mg/kg/day groups, corresponding to a percentage change of 82.71±136.27% and a 86.47±128.11%, respectively. Mean change in EN calories from baseline to EOT in the SOC arm was 4.22±13.75 kcal/kg/day from a baseline of 12.44±17.37 kcal/kg/day, corresponding to a percentage change of 37.10±107.53%.

Plasma Citrulline

During the 24 week treatment period, plasma citrulline increased in the teduglutide treatment arm but remained unchanged in the SOC arm. The mean increase in the 0.05 mg/kg/day dose group was larger than the mean increase in the 0.025 mg/kg/day dose group. Mean change in plasma citrulline from baseline to EOT was 7.7±8.50 µmol/L from a baseline of 17.9±12.64 µmol/L and 12.0±12.00 µmol/L from a baseline of 16.0±11.54 µmol/L in the 0.025 and 0.05 mg/kg/day groups, respectively. Mean change in plasma citrulline from baseline to EOT in the SOC arm was 0.1±7.79 µmol/L from a baseline of 12.6±8.43 µmol/L.

Assessor's comments

The study demonstrated that the percentage of subjects achieving a ≥ 20% reduction in PN/IV volume increased over the course of the 24-week treatment period in both teduglutide dose groups but not the subjects treated with SOC (primary efficacy endpoint). Also, secondary efficacy endpoints (PN/IV volume Support, PN/IV calories, infusion time, enteral volume and calories and plasma citrulline concentrations) changed beneficially in treatment groups, while no changes were observed in SOC group. The changes in efficacy variables seemed to be gradual over time and no with no obvious differences between the teduglutide groups were observed. However, only descriptive statistics are used.

The MAH should explain why statistical tests were not employed in order to better qualify differences between groups **(OC)**.

The MAH states that: *"a total of 2 of 24 subjects (8.3%) in 0.025 mg/kg dose group and 3 of 26 subjects (11.5%) in the 0.05 mg/kg dose group achieved enteral autonomy, ie, complete weaning off of parenteral support by EOT. No subjects in the SOC arm achieved enteral autonomy during the study."*

It is acknowledged that complete weaning of parenteral support is a clinical important and relevant endpoint. However, this was not a predefined endpoint (primary endpoint: a ≥ 20% reduction in PN/IV volume.), and this conclusion can therefore not be made. The wording as follows marked with italics*: Complete weaning*

Three (3) children in the 0.05 mg/kg group achieved complete weaning off parenteral support by week 24." should either be removed from the SmPC section 5.1, or alternatively it should be emphasized that this was not a predefined endpoint. **(OC).**

7.3. Discussion

TED-C14-006 was a study to evaluate the safety, pharmacokinetics (PK), and efficacy of teduglutide in paediatric subjects through 17 years of age with SBS and who are dependent on parenteral support.

Study design, including selection of study groups, randomization and blinding, and dose selection are generally appropriate. The SOC treatment arm serves as an observational cohort for the 24-week

treatment period. Although the relevance of an observational cohort is acknowledged, comparisons between SOC and teduglutide treatment arms may be biased. Selection criteria for inclusion into the SOC treatment arm therefore becomes important.

The MAH should discuss the selection criteria for inclusion in the SOC treatment arm in more depth and in which way they may influence (or have influenced) the interpretation of results **(OC)**.

Demographic and baseline characteristics and treatment compliance were (roughly) similar in all treatment arms.

Only 9 patients were enrolled in the SOC arm, while in total 50 patients received teduglutide treatment. The MAH should discuss and justify this bias in regards of interpretation of the results. **(OC).**

When presenting demographics and results in general, the MAH should divide the paediatric subgroups as follows: <2, 2-<6, 6-<12, 12-<18. **(OC).**

No children < 1 year were enrolled in the study, and only one child between 1 and 2 years has received teduglutide treatment.

The percentage of subjects achieving a ⩾20% reduction in PN/IV volume increased over the course of the 24-week treatment period in both teduglutide dose groups but not the subjects treated with SOC. Two of 24 children (8.3%) in 0.025 mg/kg dose group and 3 of 26 children (11.5%) in the 0.05 mg/kg dose group achieved enteral autonomy, within 8 to 21 weeks of treatment. No children in the SOC arm achieved enteral autonomy during the study. Both teduglutide dose groups experienced greater reductions in PN/IV volume and calories, days per week on PN/IV and hours per day, increases in enteral nutritional volume and calories from baseline to EOT than the SOC arm. There did not seem to be substantial differences in efficacy between the 2 dosage schedules of teduglutide. Efficacy variables seemed to be stable during the follow up period between Week 24 (EOT) and Week 28 (EOS), during which no teduglutide treatment was given. During the 24-week treatment period, plasma citrulline increased in the teduglutide treatment arm but remained unchanged in the SOC arm.

Thus, the study demonstrated clinical relevant efficacy of teduglutide. The efficacy endpoint variables seemed to improve gradually over time, and to be similar for the 2 dosages used (0,025 and 0,05 mg/kg). No formal statistical tests, however, were used to document efficacy.

The MAH should explain why statistical tests were not employed in order to better qualify differences between groups **(OC)**.

The MAH states that: *"a total of 2 of 24 subjects (8.3%) in 0.025 mg/kg dose group and 3 of 26 subjects (11.5%) in the 0.05 mg/kg dose group achieved enteral autonomy, ie, complete weaning off of parenteral support by EOT. No subjects in the SOC arm achieved enteral autonomy during the study."*

It is acknowledged that complete weaning off of parenteral support is a clinical important and relevant endpoint. However, this was not a predefined endpoint (primary endpoint: a ≥ 20% reduction in PN/IV volume.), and this conclusion can therefore not be made. The wording as follows marked with italics*: Complete weaning*

Three (3) children in the 0.05 mg/kg group achieved complete weaning off parenteral support by week 24." should either be removed from the SmPC section 5.1, or alternatively it should be emphasized that this was not a predefined endpoint. **(OC).**

8. Clinical Safety aspects

8.1. Methods – analysis of data submitted

8.1.1. Extent of Exposure

Exposure to teduglutide is presented for the Safety set in Table 7. The exposure to teduglutide was similar in the 0.025 mg/kg/day and 0.05 mg/kg/day groups. In the 0.025 mg/kg/day group, the mean duration of exposure to teduglutide was 169.0±2.69 days (range: 165 to 178 days). In the 0.05 mg/kg/day group, the mean duration of exposure to teduglutide was 167.8±1.33 days (range: 165 to 171 days). The majority of subjects in both groups had ≥ 24 weeks (168 days) of treatment (0.025 mg/kg/day: 19 [79.2%] subjects; 0.05 mg/kg/day: 17 [65.4%] subjects).

Table 7 – Extent of Exposure – Safety Analysis Set

Parameter	0.025 mg/kg/day Teduglutide (N=24)	0.05 mg/kg/day Teduglutide (N=26)
Extent of Exposure (days)		
Mean (SD)	169.0 (2.69)	167.8 (1.33)
Median	169.0	168.0
Min/Max	165, 178	165, 171
<4 weeks	0	0
4 - <12 weeks	0	0
12 - <24 weeks	5 (20.8)	9 (34.6)
≥ 24 weeks	19 (79.2)	17 (65.4)

Note: Extent of exposure is calculated as (last study dose date – first study dose date + 1).
Note: Subjects in the standard of care group do not receive study drug.
Source: Table 14.3.10.3

Since all the subjects in the ITT set received the assigned study treatment, the exposure of the ITT set is the same as the safety set.

The exposure to teduglutide was similar in the 0.025 mg/kg/day and 0.05 mg/kg/day groups. In the 0.025 mg/kg/day group, the mean duration of exposure to teduglutide was 169.1±2.62 days (range: 165 to 178 days). In the 0.05 mg/kg/day group, the mean duration of exposure to teduglutide was 167.8±1.35 days (range: 165 to 171 days). The majority of subjects in both groups had ≥ 24 weeks of treatment (0.025 mg/kg/day: 16 [84.2%] subjects; 0.05 mg/kg/day: 16 [64.0%] subjects).

Assessor's comments

The MAH has presented an overview of the cumulative teduglutide exposure for the 0.025 vs. 0.05 mg/kg/day group, measured in days and weeks. However, the MAH should describe the exposure in more details in regards of PK values (AUC) and then elucidate whether there is an association between exposure and the occurrence of AE´s. **(OC).**

8.2. Results

8.2.1. Adverse Events

8.2.1.1. Brief Summary of Adverse Events

Table 8 presents the overall summary of all TEAEs. Overall, there were a total of 286 TEAEs in 24 (100%) subjects in the 0.025 mg/kg group, 228 TEAEs in 25 (96.2%) subjects in the 0.05 mg/kg group, and 73 TEAEs in 9 (100%) subjects in the SOC arm. The majority of TEAEs reported by subjects during the study were mild or moderate in severity. Overall, there were a total of 12 related TEAEs in 8 (33.3%) subjects in the 0.025 mg/kg group and 10 related TEAEs in 7 (26.9%) subjects in the 0.05 mg/kg group. There were 32 TESAEs in 15 (62.5%) subjects in the 0.025 mg/kg group, 43 TESAEs in 20 (76.9%) subjects in the 0.05 mg/kg group, and 10 TESAEs in 4 (44.4%) subjects in the SOC arm. Of these, 2 related TESAEs were reported, both in the 0.025 mg/kg group. There were no TEAEs leading to treatment discontinuation or death.

Table 8 – Overall Summary of Treatment Emergent Adverse Events – Safety Analysis Set

	0.025 mg/kg/day Teduglutide (N=24)		0.05 mg/kg/day Teduglutide (N=26)		Total Teduglutide (N=50)		Standard of Care (N=9)	
Category	n(%)	E	n(%)	E	n(%)	E	n(%)	E
Any TEAE	24 (100)	286	25 (96.2)	228	49 (98.0)	514	9 (100)	73
TEAE Highest Severity[a]								
Mild	4 (16.7)		7 (26.9)		11 (22.0)		4 (44.4)	
Moderate	15 (62.5)		9 (34.6)		24 (48.0)		5 (55.6)	
Severe	5 (20.8)		9 (34.6)		14 (28.0)		0	
TEAE Relationship								
Not Related	24 (100)	274	25 (96.2)	218	49 (98.0)	492	-	-
Related	8 (33.3)	12	7 (26.9)	10	15 (30.0)	22	-	-
Any TESAE	15 (62.5)	32	20 (76.9)	43	35 (70.0)	75	4 (44.4)	10
TESAE Relationship								
Not Related	14 (58.3)	30	20 (76.9)	43	34 (68.0)	73	-	-
Related	2 (8.3)	2	0		2 (4.0)	2	-	-
TEAE Leading to Treatment Discontinuation	0		0		0		-	
TEAE Leading to Death	0		0		0		0	

E=events; TEAE=treatment emergent adverse event; TESAE=treatment emergent serious adverse event.
[a] Only highest severity per subject is counted for incidence and percentage.
Note: Percentages are based on the number of subjects in the safety analysis set 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 arms and adverse events that started or worsened on or after the baseline visit for standard of care group. 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.
Source: Table 14.3.1.1

Assessor's comments

TEAE (most mild or moderate in severity, and most not related) and TESAE were roughly similar in two teduglutide groups. No TEAEs leading to treatment discontinuation or death were observed.

No further comments.

8.2.1.2. Display of Adverse Events

Table 9 presents the summary of TEAEs by system organ class and by PT for TEAEs that occurred in ≥ 2 subjects in the total teduglutide arm or the SOC arm. The percentage of subjects with TEAEs was similar in both treatment arms. Overall, there were a total of 286 TEAEs in 24 (100%) subjects in the 0.025 mg/kg group, 228 TEAEs in 25 (96.2%) subjects in the 0.05 mg/kg group, and 73 TEAEs in 9 (100%) subjects in the SOC arm.

There was no clear difference in TEAE frequency between the 0.025 and 0.05 mg/kg groups. For the total teduglutide arm, the system organ classes with the highest percentage of subjects reporting TEAEs were Infections and infestations (88.0%), Gastrointestinal disorders (78.0%), and General disorders and administration site conditions (58.0%). The most frequent (≥ 15% of the subjects in the teduglutide arm), TEAEs were pyrexia (38.0%), vomiting (36.0%), upper respiratory tract infection (30.0%), cough (24.0%), diarrhea (22.0%), nasopharyngitis (20.0%), abdominal pain (20.0%), dehydration (18.0%), ALT increased (18.0%), and headache (16.0%).

There were 18 events in 13 (26.0%) subjects in the teduglutide arm in the system organ class of Product issues. All of these TEAEs were related to central line complications, and not due to complications of the investigational product and ancillary supplies.

For the SOC arm, the system organ classes with the highest percentage of subjects reporting TEAEs were Infections and infestations (77.8%), General disorders and administration site conditions (66.7%), and Gastrointestinal disorders (55.6%). The most frequent (≥ 15% of subjects in the SOC arm), TEAEs were vomiting (55.6%), pyrexia (44.4%), cough (33.3%), catheter site erythema (22.2%), and nasopharyngitis (22.2%).

Table 9 – Summary of Treatment emergent Adverse Events by System Organ Class and Preferred Term Occuring in ≥2 Subjects in the Total Teduglutide Arm or the Standard of Care Arm – Safety Analysis Set

	0.025 mg/kg/day Teduglutide (N=24)		0.05 mg/kg/day Teduglutide (N=26)		Total Teduglutide (N=50)		Standard of Care (N=9)	
Category	n(%)	E	n(%)	E	n(%)	E	n(%)	E
Any TEAE	**24 (100)**	**286**	**25 (96.2)**	**228**	**49 (98.0)**	**514**	**9 (100)**	**73**
Ear and labyrinth disorders	**2 (8.3)**	**3**	**1 (3.8)**	**1**	**3 (6.0)**	**4**	**1 (11.1)**	**1**
Ear pain	1 (4.2)	1	1 (3.8)	1	2 (4.0)	2	1 (11.1)	1
Eye disorders	**1 (4.2)**	**1**	**1 (3.8)**	**2**	**2 (4.0)**	**3**	**0**	**0**
Ocular hyperaemia	1 (4.2)	1	1 (3.8)	1	2 (4.0)	2	0	0
Gastrointestinal disorders	**19 (79.2)**	**62**	**20 (76.9)**	**47**	**39 (78.0)**	**109**	**5 (55.6)**	**14**
Vomiting	10 (41.7)	24	8 (30.8)	17	18 (36.0)	41	5 (55.6)	7
Diarrhoea	8 (33.3)	9	3 (11.5)	4	11 (22.0)	13	1 (11.1)	1
Abdominal pain	4 (16.7)	5	6 (23.1)	7	10 (20.0)	12	0	0
Abdominal pain upper	3 (12.5)	8	3 (11.5)	3	6 (12.0)	11	1 (11.1)	1
Nausea	3 (12.5)	3	3 (11.5)	3	6 (12.0)	6	1 (11.1)	1
Abdominal distension	0	0	2 (7.7)	2	2 (4.0)	2	0	0
Abdominal pain lower	2 (8.3)	2	0	0	2 (4.0)	2	0	0
Constipation	1 (4.2)	1	1 (3.8)	1	2 (4.0)	2	0	0

Table 9 – Summary of Treatment emergent Adverse Events by System Organ Class and Preferred Term Occuring in ≥2 Subjects in the Total Teduglutide Arm or the Standard of Care Arm – Safety Analysis Set

Category	0.025 mg/kg/day Teduglutide (N=24)		0.05 mg/kg/day Teduglutide (N=26)		Total Teduglutide (N=50)		Standard of Care (N=9)	
General disorders and administration site conditions	**14 (58.3)**	**28**	**15 (57.7)**	**30**	**29 (58.0)**	**58**	**6 (66.7)**	**11**
Pyrexia	8 (33.3)	12	11 (42.3)	17	19 (38.0)	29	4 (44.4)	7
Injection site bruising	3 (12.5)	4	1 (3.8)	1	4 (8.0)	5	0	0
Pain	2 (8.3)	2	1 (3.8)	1	3 (6.0)	3	0	0
Injection site swelling	1 (4.2)	1	1 (3.8)	1	2 (4.0)	2	0	0
Medical device site pain	0	0	2 (7.7)	2	2 (4.0)	2	1 (11.1)	1
Catheter site erythema	0	0	1 (3.8)	1	1 (2.0)	1	2 (22.2)	2
Immune system disorders	**1 (4.2)**	**1**	**2 (7.7)**	**2**	**3 (6.0)**	**3**	**0**	**0**
Seasonal allergy	1 (4.2)	1	2 (7.7)	2	3 (6.0)	3	0	0
Infections and infestations	**20 (83.3)**	**55**	**24 (92.3)**	**66**	**44 (88.0)**	**121**	**7 (77.8)**	**21**
Upper respiratory tract infection	7 (29.2)	9	8 (30.8)	10	15 (30.0)	19	4 (44.4)	5
Nasopharyngitis	4 (16.7)	4	6 (23.1)	9	10 (20.0)	13	2 (22.2)	2
Device related infection	1 (4.2)	2	5 (19.2)	5	6 (12.0)	7	0	0
Rhinitis	1 (4.2)	1	5 (19.2)	6	6 (12.0)	7	0	0
Viral infection	3 (12.5)	4	3 (11.5)	4	6 (12.0)	8	1 (11.1)	2
Influenza	2 (8.3)	2	3 (11.5)	3	5 (10.0)	5	0	0
Catheter site infection	1 (4.2)	1	3 (11.5)	3	4 (8.0)	4	0	0
Conjunctivitis	3 (12.5)	3	1 (3.8)	1	4 (8.0)	4	0	0
Ear infection	1 (4.2)	1	3 (11.5)	3	4 (8.0)	4	1 (11.1)	1
Gastroenteritis viral	3 (12.5)	3	0	0	3 (6.0)	3	0	0
Urinary tract infection	2 (8.3)	6	1 (3.8)	1	3 (6.0)	7	1 (11.1)	1
Cellulitis	2 (8.3)	3	0	0	2 (4.0)	3	0	0
Device related sepsis	1 (4.2)	1	1 (3.8)	1	2 (4.0)	2	0	0
Gastrointestinal bacterial overgrowth	2 (8.3)	6	0	0	2 (4.0)	6	0	0
Pharyngitis	0	0	2 (7.7)	2	2 (4.0)	2	0	0
Respiratory tract infection	0	0	2 (7.7)	3	2 (4.0)	3	0	0
Injury, poisoning and procedural complications	**7 (29.2)**	**7**	**3 (11.5)**	**13**	**10 (20.0)**	**20**	**1 (11.1)**	**1**
Stoma site erythema	0	0	2 (7.7)	3	2 (4.0)	3	0	0
Investigations	**14 (58.3)**	**43**	**7 (26.9)**	**8**	**21 (42.0)**	**51**	**2 (22.2)**	**2**
Alanine aminotransferase increased	7 (29.2)	7	2 (7.7)	2	9 (18.0)	9	0	0
Aspartate aminotransferase increased	5 (20.8)	5	0	0	5 (10.0)	5	0	0
Blood bicarbonate decreased	4 (16.7)	5	0	0	4 (8.0)	5	0	0
Blood triglycerides increased	2 (8.3)	2	1 (3.8)	1	3 (6.0)	3	0	0
Gamma-glutamyltransferase increased	2 (8.3)	2	0	0	2 (4.0)	2	0	0
Lymph node palpable	2 (8.3)	2	0	0	2 (4.0)	2	1 (11.1)	1

Table 9 – Summary of Treatment emergent Adverse Events by System Organ Class and Preferred Term Occuring in ≥2 Subjects in the Total Teduglutide Arm or the Standard of Care Arm – Safety Analysis Set

Category	0.025 mg/kg/day Teduglutide (N=24)		0.05 mg/kg/day Teduglutide (N=26)		Total Teduglutide (N=50)		Standard of Care (N=9)	
Metabolism and nutrition disorders	**10 (41.7)**	**25**	**5 (19.2)**	**6**	**15 (30.0)**	**31**	**0**	**0**
Dehydration	8 (33.3)	13	1 (3.8)	1	9 (18.0)	14	0	0
Acidosis	2 (8.3)	2	1 (3.8)	1	3 (6.0)	3	0	0
Metabolic acidosis	2 (8.3)	5	1 (3.8)	1	3 (6.0)	6	0	0
Hypokalaemia	1 (4.2)	3	1 (3.8)	1	2 (4.0)	4	0	0
Musculoskeletal and connective tissue disorders	**2 (8.3)**	**4**	**0**	**0**	**2 (4.0)**	**4**	**1 (11.1)**	**1**
Pain in extremity	2 (8.3)	2	0	0	2 (4.0)	2	0	0
Nervous system disorders	**4 (16.7)**	**5**	**7 (26.9)**	**9**	**11 (22.0)**	**14**	**1 (11.1)**	**5**
Headache	3 (12.5)	4	5 (19.2)	7	8 (16.0)	11	1 (11.1)	3
Product issues	**7 (29.2)**	**11**	**6 (23.1)**	**7**	**13 (26.0)**	**18**	**0**	**0**
Device breakage	3 (12.5)	5	3 (11.5)	4	6 (12.0)	9	0	0
Device occlusion	3 (12.5)	3	1 (3.8)	1	4 (8.0)	4	0	0
Device dislocation	2 (8.3)	2	1 (3.8)	1	3 (6.0)	3	0	0
Respiratory, thoracic and mediastinal disorders	**6 (25.0)**	**8**	**14 (53.8)**	**18**	**20 (40.0)**	**26**	**3 (33.3)**	**9**
Cough	2 (8.3)	2	10 (38.5)	11	12 (24.0)	13	3 (33.3)	4
Rhinorrhoea	3 (12.5)	3	0	0	3 (6.0)	3	1 (11.1)	1
Epistaxis	1 (4.2)	1	1 (3.8)	1	2 (4.0)	2	0	0
Nasal congestion	1 (4.2)	1	1 (3.8)	1	2 (4.0)	2	1 (11.1)	2
Productive cough	1 (4.2)	1	1 (3.8)	1	2 (4.0)	2	0	0
Skin and subcutaneous tissue disorders	**7 (29.2)**	**25**	**4 (15.4)**	**9**	**11 (22.0)**	**34**	**3 (33.3)**	**4**
Dermatitis diaper	2 (8.3)	20	0	0	2 (4.0)	20	0	0
Eczema	1 (4.2)	1	1 (3.8)	1	2 (4.0)	2	1 (11.1)	1
Rash	1 (4.2)	1	1 (3.8)	4	2 (4.0)	5	1 (11.1)	1

TEAE=Treatment-emergent adverse event.
Note: Percentages are based on the number of subjects in the safety analysis set 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 arms and adverse events that started or worsened on or after the baseline visit for standard of care group. 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.
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 system organ class and preferred term using MedDRA dictionary, Version 19.1.
Note: Primary system organ classes are sorted by alphabetically and preferred terms are sorted by the descending order of the frequency of Total Teduglutide treatment group.
Source: Table 14.3.1.2

Assessor's comments

The relatively high frequency and sorts of adverse events is to be expected in children with SBS dependent on parenteral nutritional support. There was no clear difference in TEAE frequency between the 0.025 and 0.05 mg/kg groups.

No further comments.

8.2.1.3. Analysis of Adverse Events

Adverse Events by Relationship

Table 10 presents the related TEAEs by system organ class and by PT for the subjects treated with teduglutide. Overall, there were a total of 12 related TEAEs in 8 (33.3%) subjects in the 0.025 mg/kg teduglutide dose group and 10 related TEAEs in 7 (26.9%) subjects in the 0.05 mg/kg teduglutide dose group. The majority of related TEAEs were single events that were experienced by a single subject. Related TEAEs that occurred in 2 (4.0%) subjects treated teduglutide included injection site bruising, abdominal pain, and vomiting. There was no clear difference in the frequency of related TEAEs between the 0.025 and 0.05 mg/kg groups.

Table 10 – Summary of Related Treatment-emergent Adverse Events by System Organ Class and Preferred Term Occurring in Subjects Treated with Teduglutide - Safety Analysis Set

Category	0.025 mg/kg/day Teduglutide (N=24) n(%)	E	0.05 mg/kg/day Teduglutide (N=26) n(%)	E	Total Teduglutide (N=50) n(%)	E
Any Related TEAE	**8 (33.3)**	**12**	**7 (26.9)**	**10**	**15 (30.0)**	**22**
Gastrointestinal disorders	**4 (16.7)**	**6**	2 (7.7)	**2**	6 (12.0)	**8**
Abdominal pain	1 (4.2)	1	1 (3.8)	1	2 (4.0)	2
Vomiting	1 (4.2)	1	1 (3.8)	1	2 (4.0)	2
Faecaloma	1 (4.2)	2	0	0	1 (2.0)	2
Flatulence	1 (4.2)	1	0	0	1 (2.0)	1
Ileus	1 (4.2)	1	0	0	1 (2.0)	1
General disorders and administration site conditions	**4 (16.7)**	**5**	**3 (11.5)**	**3**	**7 (14.0)**	**8**
Injection site bruising	2 (8.3)	3	0	0	2 (4.0)	3
Injection site mass	0	0	1 (3.8)	1	1 (2.0)	1
Injection site reaction	1 (4.2)	1	0	0	1 (2.0)	1
Injection site swelling	0	0	1 (3.8)	1	1 (2.0)	1
Oedema peripheral	1 (4.2)	1	0	0	1 (2.0)	1
Pain	0	0	1 (3.8)	1	1 (2.0)	1
Investigations	**1 (4.2)**	**1**	**2 (7.7)**	**2**	**3 (6.0)**	**3**
Alanine aminotransferase increased	0	0	1 (3.8)	1	1 (2.0)	1
Gastrointestinal stoma output increased	0	0	1 (3.8)	1	1 (2.0)	1
Platelet count decreased	1 (4.2)	1	0	0	1 (2.0)	1
Metabolism and nutrition disorders	**0**	**0**	**1 (3.8)**	**1**	**1 (2.0)**	**1**
Decreased appetite	0	0	1 (3.8)	1	1 (2.0)	1
Skin and subcutaneous tissue disorders	**0**	**0**	**1 (3.8)**	**2**	**1 (2.0)**	**2**
Alopecia	0	0	1 (3.8)	1	1 (2.0)	1
Eczema	0	0	1 (3.8)	1	1 (2.0)	1

E=events; TEAE=treatment-emergent adverse event.
Note: Percentages are based on the number of subjects in the safety analysis set in each treatment group.
Note: Treatment Emergent Adverse Events (TEAEs) are defined as adverse events that started or worsened on or after the date of first dose for treatment arms and adverse events that started or worsened on or after the baseline visit for standard of care group. 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.
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 system organ class and preferred term using MedDRA dictionary, Version 19.1.
Note: Primary system organ classes are sorted by alphabetically and preferred terms are sorted by the descending order of the frequency of Total Teduglutide treatment group.
Source: Table 14.3.1.3

Adverse Events by Severity

The majority of TEAEs reported by subjects during the study were mild or moderate in severity. There was no clear difference in the severity of TEAEs between the 0.025 and 0.05 mg/kg dose groups, but TEAEs in the SOC arm tended to be less severe. In the 0.025 mg/kg/day teduglutide dose group based on the TEAE with the highest severity, 4 (16.7%) subjects experienced a mild TEAE, 15 (62.5%) subjects experienced a moderate TEAE, and 5 (20.8%) subjects experienced a severe TEAE. In the 0.05 mg/kg/day teduglutide dose group based on the TEAE with the highest severity, 7 (26.9%) subjects experienced a mild TEAE, 9 (34.6%) subjects experienced a moderate TEAE, and 9 (34.6%) subjects experienced a severe TEAE. In the SOC arm based on the TEAE with the highest severity, 4 (44.4%) subjects experienced a mild TEAE, 5 (55.6%) subjects experienced a moderate TEAE, and no subjects experienced a severe TEAE in the SOC arm.

A summary of the severe TEAEs is provided in Table 11. The majority of severe TEAEs were single events in single subjects. Severe TEAEs occurring in 2 or more subjects were pyrexia (2 events in 2 [8.3%] 0.025 mg/kg/day subject; 3 events in 2 [7.7%] 0.05 mg/kg/day subject); influenza (1 event in 1 [4.2%] 0.025 mg/kg/day subject; 1 event in 1 [3.8%] 0.05 mg/kg/day subject); upper respiratory tract infection (1 event in 1 [4.2%] 0.025 mg/kg/day subject; 1 event in 1 [3.8%] 0.05 mg/kg/day subject); and device breakage (1 event in 1 [4.2%] 0.025 mg/kg/day subject; 1 event in 1 [3.8%] 0.05 mg/kg/day subject). All severe TEAEs were assessed as not related by the investigators.

Table 11 – Summary of Severe Treatment-emergent Adverse Events by System Organ Class and Preferred Term – Safety Analysis Set

Category	0.025 mg/kg/day Teduglutide (N=24) n(%)	E	0.05 mg/kg/day Teduglutide (N=26) n(%)	E	Total Teduglutide (N=50) n(%)	E	Standard of Care (N=9) n(%)	E
Any Severe TEAE	**5 (20.8)**		**9 (34.6)**		**14 (28.0)**		**0**	
Gastrointestinal disorders	**1 (4.2)**	**1**	**2 (7.7)**	**2**	**3 (6.0)**	**3**	**0**	**0**
Diarrhoea	0	0	1 (3.8)	1	1 (2.0)	1	0	0
Haematemesis	0	0	1 (3.8)	1	1 (2.0)	1	0	0
Vomiting	1 (4.2)	1	0	0	1 (2.0)	1	0	0
General disorders and administration site conditions	**2 (8.3)**	**2**	**2 (7.7)**	**3**	**4 (8.0)**	**5**	**0**	**0**
Pyrexia	2 (8.3)	2	2 (7.7)	3	4 (8.0)	5	0	0
Infections and infestations	**3 (12.5)**	**4**	**6 (23.1)**	**7**	**9 (18.0)**	**11**	**0**	**0**
Catheter site infection	0	0	1 (3.8)	1	1 (2.0)	1	0	0
Device related infection	0	0	1 (3.8)	1	1 (2.0)	1	0	0
Device related sepsis	1 (4.2)	1	0	0	1 (2.0)	1	0	0
Gastroenteritis viral	1 (4.2)	1	0	0	1 (2.0)	1	0	0
Influenza	1 (4.2)	1	1 (3.8)	1	2 (4.0)	2	0	0
Pneumonia	0	0	1 (3.8)	1	1 (2.0)	1	0	0
Respiratory tract infection	0	0	1 (3.8)	1	1 (2.0)	1	0	0
Upper respiratory tract infection	1 (4.2)	1	1 (3.8)	1	2 (4.0)	2	0	0
Viral infection	0	0	1 (3.8)	1	1 (2.0)	1	0	0
Metabolism and nutrition disorders	**1 (4.2)**	**1**	**0**	**0**	**1 (2.0)**	**1**	**0**	**0**
Dehydration	1 (4.2)	1	0	0	1 (2.0)	1	0	0
Product issues	**1 (4.2)**	**1**	**2 (7.7)**	**2**	**3 (6.0)**	**3**	**0**	**0**
Device breakage	1 (4.2)	1	1 (3.8)	1	2 (4.0)	2	0	0
Device occlusion	0	0	1 (3.8)	1	1 (2.0)	1	0	0

E=Total number of events in each treatment group; TEAE=Treatment-emergent adverse event.
Note: Percentages are based on the number of subjects in the safety analysis set in each treatment group.
Note: Treatment Emergent Adverse Events (TEAEs) are defined as adverse events that started or worsened on or after the date of first dose for treatment groups and adverse events that started or worsened on or after the baseline visit for standard of care group. 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.
Note: Subjects are counted no more than once for incidence. Only maximum severity per subject per system organ class (per PT) is counted for incidence and percentage.
Note: Adverse events were coded to primary system organ class and preferred term using MedDRA dictionary, Version 19.1.
Source: Table 14.3.1.4; Table 14.3.1.5

Assessor's comments

There was no clear difference in the severity of TEAEs between the 0.025 and 0.05 mg/kg dose groups, but TEAEs in the SOC arm tended to be less severe. The majority of TEAEs reported by subjects during the study were mild or moderate in severity. The majority of severe TEAEs were single events in single subjects, severe TEAEs occurring in 2 or more subjects were influenza and device breakage. All severe TEAEs were assessed as not related by the investigators, but the MAH is asked to provide PK values to further elaborate whether the occurrence of severe AEs is dosed dependent. **(OC).**

Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Deaths

There were no deaths during the study.

Other Serious Adverse Events

Table 12 presents the summary of TESAEs by system organ class and by PT for TEAEs that occurred in ≥2 subjects in the teduglutide arm or the SOC arm. The percentage of subjects with TESAEs was higher in the subjects treated with teduglutide than in subjects treated with SOC.

For the total teduglutide-treated group, the system organ class with the highest percentage of subjects reporting TESAEs was Infections and infestations (44.0%). TESAEs occurring in more than 1 subject treated with teduglutide were pyrexia (11 [22.0%] subjects), device-related infection (8.0%), device breakage (4 [8.0%] subjects), influenza (4 [8.0%] subjects), upper respiratory tract infection (4 [8.0%] subjects), dehydration (4 [8.0%] subjects), catheter site infection (3 [6.0%] subjects), viral infection (2 [4.0%] subjects), hypokalemia (2 [4.0%] subjects), and metabolic acidosis (2 [4.0%] subjects).

For the SOC arm, the system organ class with the highest percentage of subjects reporting TESAEs was Infections and infestations (33.3%). No TESAEs were experienced by more than 1 SOC subject.

Two (4.0%) subjects treated with teduglutide 0.025 mg/kg/day experienced TESAEs assessed as related by the investigator (Table 14.3.2.2). One subject experienced faecaloma that was assessed as moderate in intensity and related to teduglutide and one subject experienced an ileus that was assessed as moderate in intensity and related to teduglutide.

In addition, 1 subject in the 0.025 mg/kg/day group experienced a TESAE of cholestasis that was assessed as not related to teduglutide by the investigator.

Table 12- Summary of Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term Occurring in ≥2 Subjects in the Total Teduglutide Arm or the Standard of Care Arm – Safety Analysis Set

	0.025 mg/kg/day Teduglutide (N=24)		0.05 mg/kg/day Teduglutide (N=26)		Total Teduglutide (N=50)		Standard of Care (N=9)	
Category	n(%)	E	n(%)	E	n(%)	E	n(%)	E
Any TESAE	15 (62.5)	32	20 (76.9)	43	35 (70.0)	75	4 (44.4)	10
General disorders and administration site conditions	4 (16.7)	6	7 (26.9)	8	11 (22.0)	14	1 (11.1)	3
Pyrexia	4 (16.7)	6	7 (26.9)	8	11 (22.0)	14	1 (11.1)	3
Infections and infestations	8 (33.3)	11	14 (53.8)	22	22 (44.0)	33	3 (33.3)	7
Device related infection	1 (4.2)	2	3 (11.5)	3	4 (8.0)	5	0	0
Influenza	2 (8.3)	2	2 (7.7)	2	4 (8.0)	4	0	0
Upper respiratory tract infection	2 (8.3)	2	2 (7.7)	2	4 (8.0)	4	0	0
Catheter site infection	0	0	3 (11.5)	3	3 (6.0)	3	0	0
Viral infection	0	0	2 (7.7)	2	2 (4.0)	2	1 (11.1)	1
Metabolism and nutrition disorders	4 (16.7)	6	2 (7.7)	3	6 (12.0)	9	0	0
Dehydration	4 (16.7)	4	0	0	4 (8.0)	4	0	0
Metabolism and nutrition disorders	4 (16.7)	6	2 (7.7)	3	6 (12.0)	9	0	0
Dehydration	4 (16.7)	4	0	0	4 (8.0)	4	0	0
Hypokalaemia	1 (4.2)	1	1 (3.8)	1	2 (4.0)	2	0	0
Metabolic acidosis	1 (4.2)	1	1 (3.8)	1	2 (4.0)	2	0	0
Product issues	3 (12.5)	4	4 (15.4)	4	7 (14.0)	8	0	0
Device breakage	2 (8.3)	3	2 (7.7)	2	4 (8.0)	5	0	0

E=events; TESAE=treatment-emergent serious adverse event.
Note: Percentages are based on the number of subjects in the safety analysis set in each treatment group.
Note: Treatment Emergent Serious Adverse Events (TESAEs) are defined as serious adverse events that started or worsened on or after the date of first dose for treatment arms and serious adverse events that started or worsened on or after the baseline visit for standard of care group. Serious 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 TESAEs.
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 system organ class and preferred term using MedDRA dictionary, Version 19.1.
Note: Primary system organ classes are sorted by alphabetically and preferred terms are sorted by the descending order of the frequency of Total Teduglutide treatment group.
Source: Table 14.3.2.1

Discontinuations Resulting from Adverse Events

There were no TEAEs leading to treatment discontinuation.

Adverse Events of Special Interest

There were no events of polyps of the colon or neoplasia.

Analysis and Discussion of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

There were no deaths, discontinuations due to TEAE, or AESIs during the study.

The percentage of subjects with TESAEs was higher in the subjects treated with teduglutide than in the subjects treated with SOC. This difference may be influenced by bias in treatment allocation, given that subjects chose whether or not to receive teduglutide treatment. Subjects with less frequent complications of SBS may have been less eager to receive teduglutide. For the subjects treated with teduglutide, the system organ class with the highest percentage of subjects reporting TESAEs was Infections and infestations. Treatment-emergent SAEs occurring in more than 1 subject treated with teduglutide included pyrexia, device-related infection, device breakage, influenza, upper respiratory tract infection, dehydration, catheter site infection, viral infection, hypokalemia, and metabolic acidosis. Two TESAEs (faecaloma, ileus) experienced by subjects treated with teduglutide 0.025 mg/kg/day were assessed as related to teduglutide by the investigator. In addition, 1 subject treated with teduglutide 0.025 mg/kg/day experienced a TESAE of cholestasis that was assessed as not related to teduglutide by the investigator.

For the SOC arm, the system organ class with the highest percentage of subjects reporting TESAEs was Infections and infestations. No TESAEs were experienced by more than 1 subject in the SOC arm.

Assessor's comments

The percentage of subjects with TESAEs was higher in the subjects treated with teduglutide than in the subjects treated with SOC. In the teduglutide groups and SOC, the system organ class with the highest percentage of subjects reporting TESAEs was Infections and infestations. Two TESAEs (faecaloma, ileus, metabolic acidosis) experienced by subjects treated with teduglutide (0.025 mg/kg/day) were assessed as related to the drug by the investigator.

Usually faecalomas occur in relation to chronic constipation, and would not be expected in patients with SBS. The MAH should explain this, and the circumstances about the faecaloma cases identified in subjects treated with teduglutide, herein how faecaloma was diagnosed. **(OC).**

The MAH should further elaborate on causalities between the Teduglutide exposure and the TESAEs observed in TED-C14-006 and other studies, and discuss whether these should lead to further pre-cautions in the pediatric population. **(OC).**

8.2.1.4. Clinical Laboratory Evaluation

Evaluation of Each Laboratory Parameter

There were no clinically meaningful changes in serum chemistry measures during the study.

There were no clinically meaningful changes in hematology measures during the study.

There were no clinically meaningful changes in urinalysis measures during the study.

Individual Subject Changes

Overall, there were no clinically significant shifts in laboratory findings were seen during the study.

Individual Clinically Significant Abnormalities

Serum Chemistry

In regards to liver biochemical markers, 2 (4.0%) subjects treated with teduglutide and 1 (11.1%) subject in the SOC arm had ALT level >8x UNL, 2 (4.0%) subjects treated with teduglutide had alkaline phosphatase level >5x UNL, 1 (2.0%) subject treated with teduglutide had AST >8x UNL, 1 (2.0%) subject treated with teduglutide had total bilirubin >3x UNL and direct bilirubin >34.208 µmol/L. For measures of kidney function 14 (34.1%) subjects <10 years old treated with teduglutide had serum creatinine >132.6 µmol/L, 1 (14.3%) subject 10 to 13 years old treated with teduglutide had serum creatinine >150.28 µmol/L, and 1 (2.0%) subject treated with teduglutide had urea nitrogen >12.495 mmol/L. In regards to pancreatic enzymes, 2 (4.0%) subjects treated with teduglutide had lipase >3xULN; no subjects had markedly elevated amylase levels. An albumin <20g/L occurred in 2 (4.0%) of subjects treated with teduglutide. The following markedly abnormal laboratory values occurred in 1 (2.0%) subject each in the teduglutide treatment arm: glucose <2.22 mmol/L, phosphate >2.254 mmol/L, potassium <2.5 mmol/L, potassium >6.5 mmol/L, and triglycerides >5.65 mmol/L.

Hematology

For the subjects treated with teduglutide, the most common markedly abnormal analyte was hematocrit >60%, which was observed in 14 (28.0%) subjects.

A markedly low hemoglobin (<70 g/L) was noted for 3 (6.0%) subjects and markedly low leukocytes (<2 X 109/L) and markedly low platelet count (≤ 75 X 109/L) was noted for 1 (2.0%) subject each. There were no markedly abnormal post-baseline hematology values in the SOC arm.

Assessor's comments

The MAH should discuss and justify all biochemical deviations and propose relevant precautions e.g. regular blood tests controlling for liver parameters, kidney function, potassium, lipids, hematology etc. **(OC).**

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

Vital Signs

Overall, no clinically meaningful vital sign changes in pulse rate, systolic blood pressure, diastolic blood pressure, or temperature were noted.

Physical Examinations

All new, clinically significant findings on physical exams that represented an adverse event are recorded as AEs.

Electrocardiograms

No clinically meaningful changes in ECGs were noted. A few subjects in 0.025mg/kg/day and 0.05 mg/kg/day groups had abnormal but not clinically significant ECG findings at baseline, Week 12, Week 24 and EOS. One subject in the SOC arm had an abnormal but not clinically significant ECG finding at Week 12.

One subject had abnormal clinically significant ECG finding of left ventricular hypertrophy at screening, Week 12, and EOT. Early repolarization was also noted at screening and EOT and possible biventricular hypertrophy was noted at screening. The ECG was normal at the EOS.

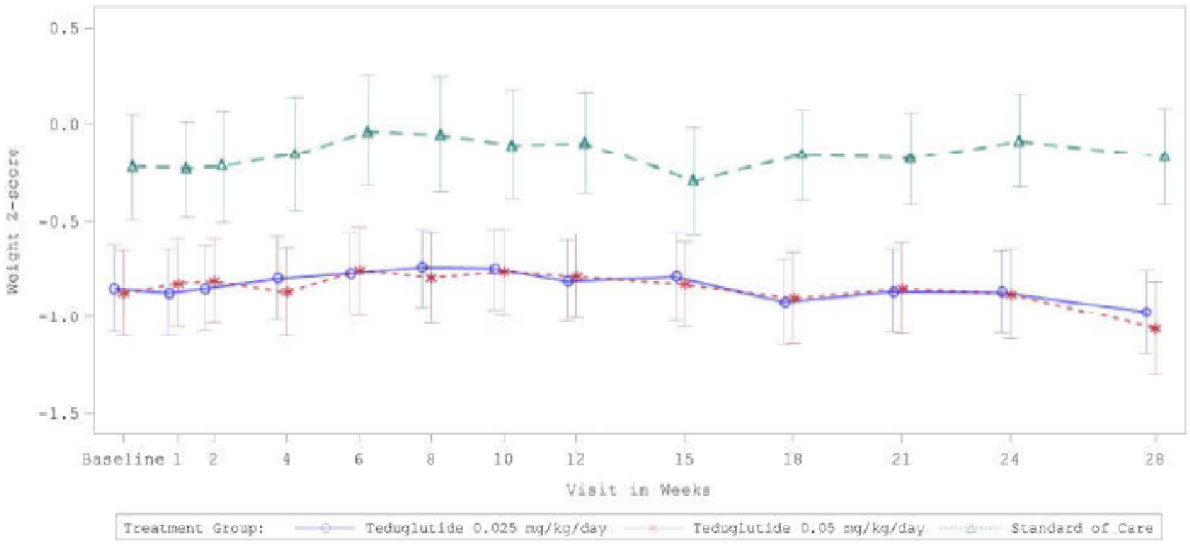
Other Observations Related to Safety

Body Weight, Height, Body Mass Index, and Head Circumference Z-scores

No clinically meaningful changes in weight, height, BMI, or head circumference Z-scores were noted, indicating that the reductions in PN/IV support in the teduglutide arm were appropriately titrated to match the subjects' nutritional needs.

Body Weight Z-score

For the 0.025 mg/kg/day teduglutide group, the mean change in body weight Z-score at EOS was -0.12±0.41 from a baseline of -0.85±1.08. For the 0.05 mg/kg/day teduglutide group, the mean change in body weight Z-score at EOS was -0.18±0.59 from a baseline of -0.88±1.11. For the SOC arm, the mean change in body weight Z-score at EOS was -0.05±0.37 from a baseline of -0.22±0.81. The mean ± SE of body weight Z-score by visit for the safety set is illustrated in Figure 6.

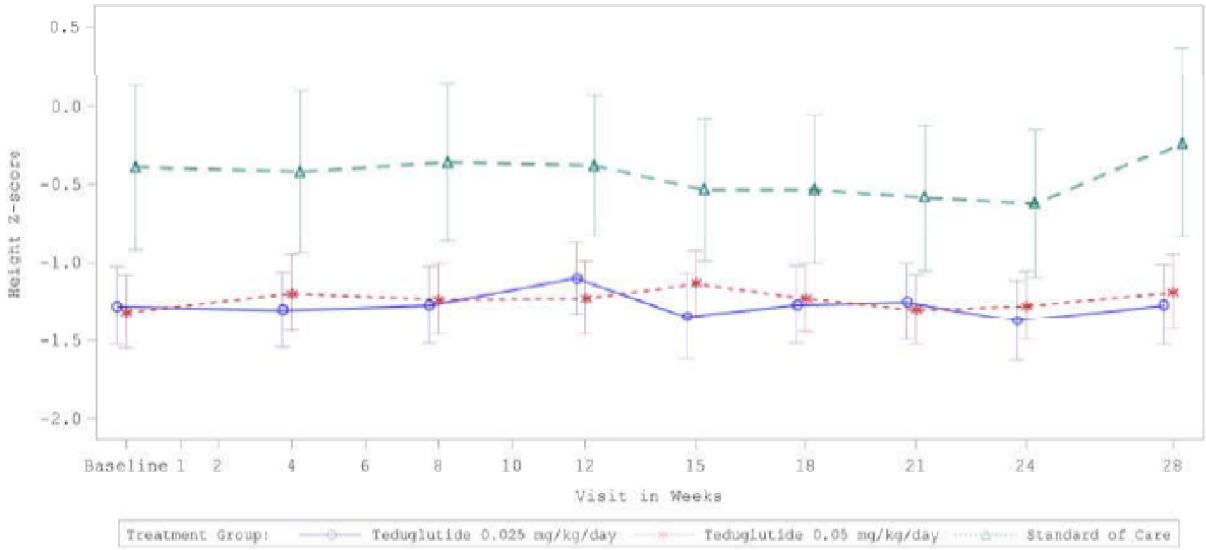


Note: Week 24 is the end of treatment visit; Week 28 is the end of study visit.
Note: Baseline is defined as the last value prior to teduglutide administration. For the standard of care treatment group, baseline is defined as the last available value on or prior to the baseline visit.
Note: Z-score is calculated as (observed value - median value of the reference population) / standard deviation value of reference population. Centers for Disease Control and Prevention (age >= 2 years old) and World Health Organization (age < 2 years old) Z-score calculation charts are used for calculation.
Source: Figure 14.3.6.3

Figure 6 – Mean Body Weight Z-score byVisit – Safety Set

Body Height Z-score

For the 0.025 mg/kg/day teduglutide group, the mean change in body height Z-score at EOS was 0.00±0.29 from a baseline of -1.28±1.22. For the 0.05 mg/kg/day teduglutide group, the mean change in body height Z-score at EOS was 0.05±0.45 from a baseline of -1.31±1.18. For the SOC arm, the mean change in body height Z-score at EOS was 0.16±0.66 from a baseline of -0.39±1.59. The mean ± SE of body weight Z-score by visit for the safety set is illustrated in Figure 7.

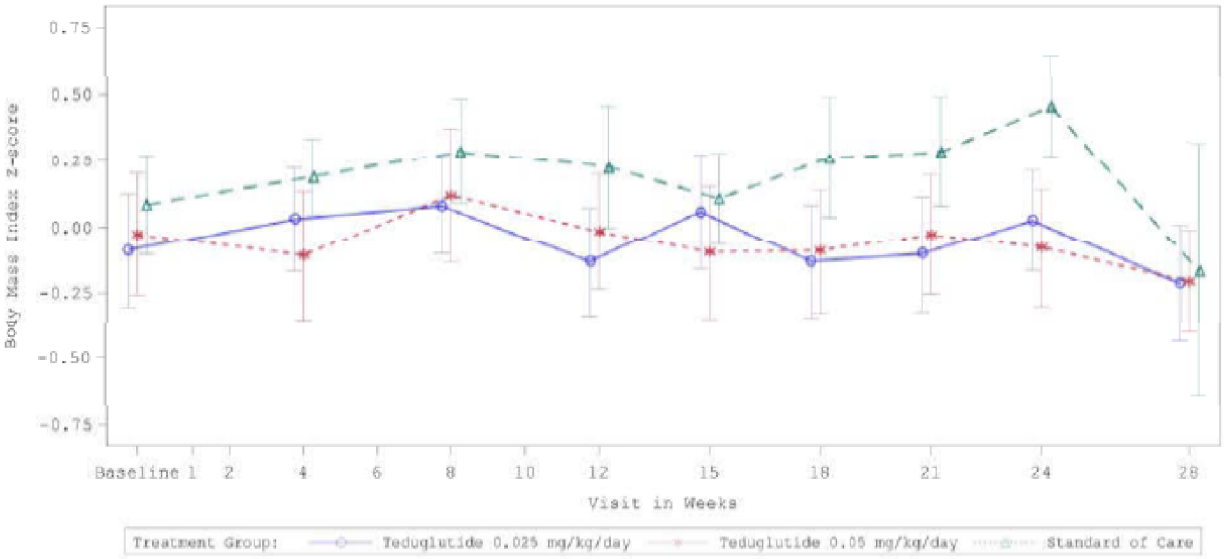


Note: Week 24 is the end of treatment visit; Week 28 is the end of study visit.
Note: Baseline is defined as the last value prior to teduglutide administration. For the standard of care treatment group, baseline is defined as the last available value on or prior to the baseline visit.
Note: Z-score is calculated as (observed value - median value of the reference population) / standard deviation value of reference population. Centers for Disease Control and Prevention (age >= 2 years old) and World Health Organization (age < 2 years old) Z-score calculation charts are used for calculation.
Source: Figure 14.3.6.3, Page 2

Figure 7 – Mean Body Height Z-score by Visit –Safety Set

Body Mass Index Z-score

For the 0.025 mg/kg/day teduglutide group, the mean change in BMI Z-score at EOS was -0.13±0.57 from a baseline of -0.09±1.05. For the 0.05 mg/kg/day teduglutide group, the mean change in BMI Z-score at EOS was -0.22±0.70 from a baseline of -0.03±1.18. For the SOC arm, the mean change in BMI Z-score at EOS was -0.25±1.42 from a baseline of 0.08±0.56. The mean ± SE of body weight Z-score by visit for the safety set is illustrated in Figure 8.

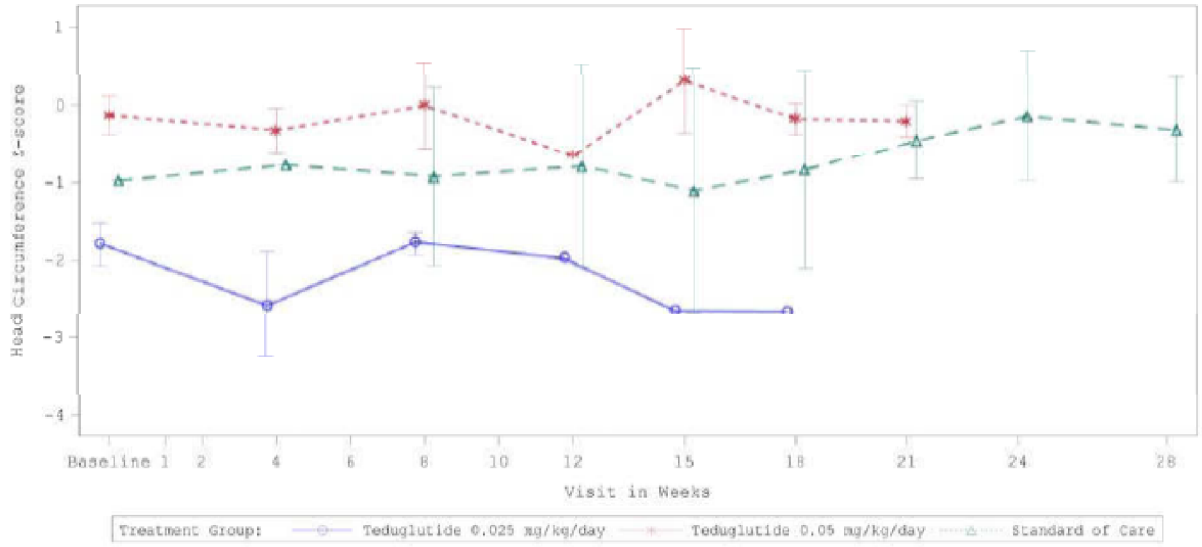


Note: Week 24 is the end of treatment visit; Week 28 is the end of study visit.
Note: Baseline is defined as the last value prior to teduglutide administration. For the standard of care treatment group, baseline is defined as the last available value on or prior to the baseline visit.
Note: BMI is calculated as body weight in kg divided by height in meters squared when both body weight and height are collected.
Note: Z-score is calculated as (observed value - median value of the reference population) / standard deviation value of reference population. Centers for Disease Control and Prevention (age >= 2 years old) and World Health Organization (age < 2 years old) Z-score calculation charts are used for calculation.
Source: Figure 14.3.6.3, Page 3

Figure 8 – Mean Body Mass Index Z-score by Visit – Safety Set

Head Circumference Z-score

Head circumference was collected only for subjects ≤ 36 months of age at the time of measurement; therefore there was limited data collected for head circumference Z-score. The mean ± SE of head circumference Z-score by visit for the safety set is illustrated in Figure 9.



Note: Week 24 is the end of treatment visit; Week 28 is the end of study visit.
Note: Baseline is defined as the last 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.
Note: Z-score is calculated as (observed value - median value of the reference population) / standard deviation value of reference population. Centers for Disease Control and Prevention (age >= 2 years old) and World Health Organization (age < 2 years old) Z-score calculation charts are used for calculation.
Note: Head circumference is scheduled to be collected only for subjects <= 36 months of age at the time of measurement.
Source: Figure 14.3.6.3, Page 4

Figure 9 – Mean Head Circumference Z-score by Visit – Safety Set

Fecal Output

On average, teduglutide-treated subjects did not have clinically meaningful changes in stool output or stool consistency during teduglutide treatment. However, individual subjects in the teduglutide treatment arm had clinically meaningful improvements in stool consistency, and such changes were not observed in the SOC arm.

In the teduglutide treatment arm, the mean change in average number of stools per day at Week 24 was 0.1±2.71 stools/day from a baseline of 3.5±2.11 stools/day. In the SOC arm, the mean change in average number of stools per day at Week 24 was -2.0±0.71 stools/day from a baseline of 5.1±1.88 stools/day.

Stool consistency was assessed using the Bristol Stool Form Score. In the teduglutide treatment arm, the mean change in Bristol Stool Form Score at Week 24 was -1.0±1.50 from a baseline of 6.6±0.58. There were too few subjects to assess change in the SOC arm.

Stool diaper weight (including mixed output) was measured in subjects who were not toilet trained and in diapers. There were 17 such subjects in the teduglutide treatment arm and 2 such subjects in the SOC arm. For non-toilet-trained subjects in the teduglutide treatment arm, the mean change in average stool diaper weight at Week 24 was -6.6±20.46 g/kg/day from a baseline of 31.0±30.74 g/kg/day. There were too few subjects to assess change in the SOC arm.

There were 9 subjects in the teduglutide arm and 3 subjects in the SOC arm who had a stoma in the study. For the subjects with a stoma in the teduglutide treatment arm, the mean change in total ostomy output at Week 24 was -7.8±34.09 mL/kg/day from a baseline of 38.5±38.11 mL/kg/day. There were too few subjects to assess change in the SOC arm.

Urine Output

No clinically meaningful changes in mean urine output occurred in either teduglutide group or the SOC arm. For the teduglutide treatment arm, the mean change in urine output at Week 24 was -2.63±16.93 ml/kg/day from a baseline of 24.40±16.81 ml/kg/day. For the SOC arm, the mean change in urine output at Week 24 was -5.17±8.93 ml/kg/day from a baseline of 27.27±17.33 ml/kg/day.

Gastrointestinal-specific Testing

Table 13 provides a summary of GI-specific testing by visit for the subjects in the teduglutide arm. A small number of subjects had clinically significant findings in post-baseline GI-specific tests (Table 14). Five subjects in the teduglutide treatment arm had post-baseline fecal occult blood tests that were deemed clinically significant. Two subjects in the teduglutide treatment arm had post-baseline endoscopic findings that were deemed clinically significant. No polyps or neoplastic lesions were identified on colonoscopy.

Table 13 – Summary of Clinically Significant Gastrointestinal-specific Testing by Visit – Safety Analysis Set

Parameter/ Visit	0.025 mg/kg/day Teduglutide (N=24) n(%)	0.05 mg/kg/day Teduglutide (N=26) n(%)	Total Teduglutide (N=50) n(%)
Abdominal Ultrasound			
Screening	4 (17.4)	0	4 (8.2)
Colonoscopy/Sigmoidoscopy			
Screening	1 (16.7)	1 (11.1)	2 (13.3)
Week 12	1 (50.0)	0	1 (25.0)
Week 24	0	1 (33.3)	1 (25.0)
Fecal Occult Blood Test			
Screening	0	2 (7.7)	2 (4.0)
Week 12	1 (4.8)	1 (4.8)	2 (4.8)
Week 24	0	1 (4.2)	1 (2.3)
Upper GI Series, Small Bowel Follow Thru			
Screening	1 (4.2)	1 (3.8)	2 (4.0)

GI=gastrointestinal
Note: Gastrointestinal-specific tests are for teduglutide treatment group subjects only.
Source: Table 14.3.9.1

Table 14 – Clinically Significant Post-Baseline Gastrointestinal-specific Testing

Subject	Teduglutide Group	Sex/ Age/ Race	Visit	Test	Abnormality or Reason for Positive Result
[redacted]	0.025 mg/kg/day teduglutide	Male/ [redacted]	Week 12	Fecal Occult Blood Test	Distal esophagus w/patchy exudate, cecum normal but 4 orifices probably represented a side to side jejunocolonic anastomaosis. No mention of bleeding on scope report. He grew Candidia per pathology.
[redacted]	0.025 mg/kg/day teduglutide	Male/ [redacted]	Week 12	Colonoscopy	Rectal ulceration, probably due to internal prolapse tendency - explains fecal occult. Otherwise upper GI & colonoscopy normal.
[redacted]	0.05 mg/kg/day teduglutide	Male/ [redacted]	Week 12	Abdominal Ultrasound	Bilateral grade II hydronephrosis
			Week 12	Fecal Occult Blood Test	Per PI, the subject had an anal fissure which caused the positive hemoccult.
[redacted]	0.05 mg/kg/day teduglutide	Female/ [redacted]	Week 26	Fecal Occult Blood Test	Unknown reason - patient unable to give fecal sample at Week 24 visit. Therefore obtained sample at Week 28 visit which was conducted with SHP633-304. Will perform colonoscopy under SHP633-304.
[redacted]	0.05 mg/kg/day teduglutide	Female/ [redacted]	Week 24	Fecal Occult Blood Test	There were histological abnormalities found in the colonoscopy. No bleeding noted on report. Pathology report noted eosinophilic colitis.
[redacted]	0.05 mg/kg/day teduglutide	Female/ [redacted]	Week 24	Colonoscopy	Colonic jejunal anastomosis with diffuse ulceration, no active bleeding, friable, dilated and erythematous, ulceration noted by prior staple lines.
[redacted]	0.05 mg/kg/day teduglutide	Male/ [redacted]	Week 12	Fecal Occult Blood Test	Cause is unknown.

Source: Appendix 16.2.8, Listing 16.2.8.8

Antibodies

The bioanalytical results for antibodies are reported in A8287M-SHP633.

A summary of antibodies to teduglutide by visit is provided in Table 15. At Week 24, 3 (12.5%) subjects treated with 0.025 mg/kg/day and 5 (19.2%) subjects treated with 0.05 mg/kg/day had antibodies to teduglutide. Of these, 1 (4.2%) subject treated with 0.025 mg/kg/day and 2 (7.7%) subjects treated with 0.05 mg/kg/day had neutralizing antibodies present. At the EOS, 4 (16.7%) subjects treated with 0.025 mg/kg/day and 5 (19.2%) subjects treated with 0.05 mg/kg/day had antibodies to teduglutide. Of these, 1 (4.2%) subject treated with 0.025 mg/kg/day had neutralizing antibodies.

One subject who was treated with 0.025 mg/kg/day had neutralizing antibodies at both Week 24 and EOS. One subject who was treated with 0.05 mg/kg/day had neutralizing antibodies at Week 24 and was negative for antibodies to teduglutide at EOS. One subject who was treated with 0.05 mg/kg/day had neutralizing antibodies at Week 24; at EOS this subject had antibodies to teduglutide but did not have neutralizing antibodies.

Among the 3 subjects, only one subject was a responder with at least 20% reduction in weight-normalized PN/IV volume at EOT, based on both prescription and diary data. Neither of the other 2 subjects was a responder based on either diary or prescription. None of these subjects experienced an injection site reaction.

Table 15 – Summary of Antibodies to Teduglutide – Safety Analysis Set

Visit Category	0.025 mg/kg/day Teduglutide (N=24)	05 mg/kg/day Teduglutide (N=26)	Total Teduglutide (N=50)
Baseline			
n	24	26	50
Negative n (%)	23 (95.8)	26 (100)	49 (98.0)
Positive n (%)	1 (4.2)	0	1 (2.0)
No Neutralizing Antibodies Present	0	0	0
Neutralizing Antibodies Present	0	0	0
Week 24			
n	24	26	50
Negative n (%)	21 (87.5)	21 (80.8)	42 (84.0)
Positive n (%)	3 (12.5)	5 (19.2)	8 (16.0)
No Neutralizing Antibodies Present	2 (8.3)	3 (11.5)	5 (10.0)
Neutralizing Antibodies Present	1 (4.2)	2 (7.7)	3 (6.0)
End of Study			
n	24	25	49
Negative n (%)	20 (83.3)	20 (76.9)	40 (80.0)
Positive n (%)	4 (16.7)	5 (19.2)	9 (18.0)
No Neutralizing Antibodies Present	3 (12.5)	5 (19.2)	8 (16.0)
Neutralizing Antibodies Present	1 (4.2)	0	1 (2.0)

Note: Baseline is defined as the last available value prior to teduglutide administration.
Note: Subject [redacted] tested positive for antibodies to teduglutide at baseline but negative for neutralizing antibodies at baseline.
Note: End of Study results do include one subject [redacted] who tested negative for anti-teduglutide antibodies at an Unscheduled visit near the End of Study visit
Source: Table 14.3.5.1

Assessor's comments

No clinically meaningful changes in weight, height, BMI, or head circumference Z-scores were noted. No clinically meaningful changes in stool output, stool consistency, or urine output were observed. Five subjects in the teduglutide treatment arm had post-baseline positive fecal occult blood. No polyps or neoplastic lesions were identified in 2 patients on colonoscopy. Neutralizing antibodies were present in few patients at 24 weeks (n=3) and end of study (n=1).

No further comments.

8.2.1.6. Abuse, Misuse, Overdose, and Medication Error

One subject received an approximate 6-fold overdose dose of study drug at the baseline visit.

One subject received approximately 0.03 ml/kg of teduglutide instead of the assigned volume of 0.005 ml/kg due to miscommunication among the investigator site staff. This dosing error was recognized immediately and the subject was monitored closely for the following week.

No AEs were associated with the overdose. Treatment with teduglutide was not interrupted and the dose group allocation of this subject was not prematurely unblinded. The subject had been allocated to the 0.05 mg/kg dose group, meaning that the subject had received approximately 0.30 mg/kg at the baseline visit without any apparent adverse effects.

One subject received 1 incorrect investigational product kit. As a result, this subject, who had been assigned to the 0.05 mg/kg dose group, received 0.025 mg/kg/day of teduglutide over a 7 day period (Weeks 4 and 6 of the treatment period). The subject was not reported to have change in clinical status during this period.

Minor rounding errors occurred in dosing of two subjects. One subject received 0.10 ml for the first 24 days of treatment instead of the 0.09 ml dose indicated by the dose calculation worksheet, which rounds the dose down to the nearest 0.01 ml increment. The subject had been allocated to the 0.025 mg/kg dose group. One subject received 0.055 ml instead of 0.05 ml for the first 17 days of the dosing period. This subject had been allocated to the 0.05 mg/kg dose group. No AEs were associated with these rounding errors . When these rounding errors were discovered, treatment with teduglutide was not interrupted and the dose group allocation of these subjects was not prematurely unblinded.

There were no instances of abuse or misuse reported.

8.3. Discussion

The MAH has presented an overview of the cumulative teduglutide exposure for the 0.025 vs. 0.05 mg/kg/day group, measured in days and weeks. However, the MAH should describe the exposure in more details in regards of PK values (AUC) and then elucidate whether there is an association between exposure and the occurrence of AE´s. **(OC).**

In generel teduglutide was well tolerated by pediatric subjects with SBS. The safety profile was favorable and consistent with the prior 12-week pediatric study, the underlying disease, and previous experience with teduglutide in adult subjects with SBS, but the MAH is asked to provide PK values to further elaborate whether the occurrence of severe AEs is dosed dependent. **(OC).**

The percentage of subjects with TESAEs was higher in the subjects treated with teduglutide than in the subjects treated with SOC. In the teduglutide groups and SOC, the system organ class with the highest percentage of subjects reporting TESAEs was Infections and infestations. Two TESAEs (faecaloma, ileus) experienced by subjects treated with teduglutide (0.025 mg/kg/day) were assessed as related to the drug by the investigator. Usually faecalomas occur in relation to chronic constipation, and would not be expected in patients with SBS. The MAH should explain this, and the circumstances about the faecaloma cases identified in subjects treated with teduglutide, herein how the diagnosis was made. **(OC).** In addition, the Applicant should further elaborate on causalities between the teduglutide exposure and the TESAEs observed in TED-C14-006 and other studies, and discuss whether these should lead to further pre-cautions in the pediatric population**. (OC).**

The MAH should also discuss and justify all biochemical deviations and propose relevant precautions e.g. regular blood tests controlling for liver parameters, kidney function, potassium, lipids, hematology etc. **(OC).**

9. Changes to the Product Information

Section 4.2

The MAH proposes a revision of the wordings in the posology section, as follows with tracked changes:

"A treatment period of 6 months is recommended after which treatment effect should be evaluated. There are no data available in pediatric patients after 6 months."

Assessor's comments

The MAH has presented new data with reference to the TED-C14-006 study, which includes a 24 week treatment period. Thus, the SmPC now reflect the availability of 6 month data, and the new wording is therefore endorsed.

Section 4.4

The MAH has prosposed to change the wordings in section 4.4, as follows with tracked changes:

"Prior to initiating treatment with Revestive, faecal occult blood testing should be done for all children and adolescents. Colonoscopy/sigmoidoscopy is required if there is evidence of unexplained blood in the stool. Subsequent faecal occult blood testing should be done annually in children while they are receiving Revestive.

Colonoscopy/sigmoidoscopy is recommended for all children and adolescents after one year of treatment, every 5 years thereafter while on continuous treatment with Revestive, and if they have new or unexplained gastrointestinal bleeding."

Assessor's comments

The MAH wants to simplify the coloscopi scedule for pediatric patients, which was justified with reference to Thakker et al. 2008, who reported the immediate complications rate of pediatric colonoscopy to be 1.1 %. Furthermore, with reference to Thakker et al. 2012, who found that polyps were not more likely to be encountered in children aged 11 to 17 years than in younger age groups.

It is acknowledged that risk of developing malignancy is most likely reduced in children as compared to adults. Even though the datasets provided by TED-C14-006 and TED-C13-003 did not provide any polyps or neoplastic lesions before, during or after treatment with teduglutide, the prevalence of colorectal polyps in a pediatric population undergoing colonoscopy has been reported to be approximately 6.1% in the age group 0-20 years (Thakker 2012). Thus, whether there exist an association between the existence of polyps in pediatric patients before treatment initiation and increased malignancy cannot be elucidated from the dataset. Before final approval of the wordings in the SmPC, the MAH should discuss this issue. (**OC**)

Section 4.8

The MAH proposes to change the wordings, as follows with tracked changes: *"In two completed clinical trials, there were 87 pediatric subjects (aged 1 to 17 years) enrolled and exposed to teduglutide for a duration of up to 6 months. No subject discontinued the studies due to an adverse event. Overall, the safety profile of teduglutide (including type and frequency of adverse reactions, and immunogenicity) in children and adolescents (ages 1-17 years) was similar to that in adults.pediatric"*

Assessor's comments

The MAH should report the number of participants in each age group, and discuss and justify the validity of data in each of the age groups as follows:

<1 years, 1-<2, 2-<6 years, 6-<12 and 12<17 years, and 17-<18 years.

Section 5.1

Assessor's comments

Deletion of the paragraphs: "*Reduction of parenteral nutrition calories,*" "*Increase in enteral nutrition volume*", and "*Increase in enteral calories*" in section 5.1 has not been justified in the clinical overview. The MAH should justify. **(OC).**

The MAH proposes to add the sentences as follows: "*Complete weaning*

Three (3) children in the 0.05 mg/kg group achieved complete weaning off parenteral support by week 24."

Assessor's comments

The sentences should be deleted or alternatively, it should be emphasised that complete weaning was not predefined primary endpoint. **(OC).**

The MAH proposes to delete the text as follows with tracked changes:" *In general, the side effects in children and adolescents are similar to those seen in adults.*

Assessor's comments

In TED-C13-003 the events proposed deleted were found more frequently reported in pediatric subjects compared to adults, while this was not the case in TED-C14-006. Deletion of the side effects observed in TED-C13-003 has not been justified sufficiently. The MAH should therefore discuss and justify the deleted terms further. Herein, the MAH should answer whether the study populations in TED-C14-006 and TED-C13-003 are comparable, and whether the safety data from the two studies can be pooled. **(OC).**

10. Request for supplementary information

10.1. Other concerns

Clinical aspects

1. The MAH has described the handling of concentrations values below BLQ. However, with reference to the EMA Guideline on reporting the results of population pharmacokinetic analyses (Doc.ref. CHMP/EWP/185990/06, June 2007), the MAH is asked to apply the type of bioanalytical methods used and the LLOQ for each analyte in each method.
2. The MAH has presented the covariates selected for the model sufficiently. However, in addition the pediatric age groups should be stratified as follows: <2, 2-<6, 6-<12, 12-<18 years.
3. The MAH should elucidate the handling of BLQ samples further, and discuss the possible consequences in relation to the final model.
4. Descriptive statistics of exposure parameters of teduglutide by age for a 0.05 mg/kg dose presented in Table 6 has been age stratified accordingly. However, the number of subjects (n) should be provided for each age group.
5. The MAH should provide the number/percentage of subjects with SBS and Crohn' disease, respectively.

6. Only one child in the age group 1-2 years was included in the PK model. The MAH should discuss and justify the validity of the results in relation to the posology in children < 2 years

7. The MAH should explain why statistical tests were not employed to better qualify differences between groups.

8. The MAH should discuss the selection criteria for inclusion in the SOC treatment arm in more details, and in which way they may have influenced the interpretation of results. Herein, that only 9 patients were enrolled in the SOC arm vs. 50 patients in the teduglutide arm, and selection bias.

9. When presenting demographics and results in general, the MAH should divide the pediatric subgroups as follows: <1, 1-<2, 2-<6, 6-<12, 12-<17, and 17-<18. The number of subjects (n) should be presented for each age group.

10. The MAH states that: "*a total of 2 of 24 subjects (8.3%) in 0.025 mg/kg dose group and 3 of 26 subjects (11.5%) in the 0.05 mg/kg dose group achieved enteral autonomy, ie, complete weaning off of parenteral support by EOT. No subjects in the SOC arm achieved enteral autonomy during the study*."

    It is acknowledged that complete weaning off of parenteral support is a clinical important and relevant endpoint. However, this was not a predefined endpoint (primary endpoint: a ≥ 20% reduction in PN/IV volume.), and this conclusion can therefore not be made. The wording as follows marked with italic*s: Complete weaning*

    Three (3) children in the 0.05 mg/kg group achieved complete weaning off parenteral support by week 24." should either be removed from the SmPC section 5.1, or alternatively it should be emphasized that this was not a predefined endpoint.

11. The MAH has presented an overview of the cumulative teduglutide exposure for the 0.025 vs. 0.05 mg/kg/day group, measured in days and weeks. However, the MAH should describe the exposure in more details in regards of PK values (AUC) and then elucidate whether there is an association between exposure/dose and the occurrence of AE´s

12. The MAH should elaborate on causalities between the teduglutide exposure and the TESAEs (eg. ilieus, faecaloma and metabolic acidosis) observed in TED-C14-006 and other studies, and discuss whether these should lead to further pre-cautions in the pediatric population

13. Usually faecalomas occur in relation to chronic constipation, and would not be expected in patients with SBS. The MAH should explain this, and the circumstances about the faecaloma cases identified in subjects treated with teduglutide, herein how faecaloma was diagnosed.

14. The MAH should discuss and justify all biochemical deviations and propose relevant precautions e.g. regular blood tests controlling for liver parameters, kidney function, potassium, lipids, hematology etc.

15. The MAH is requested to answer the questions in the appended Product Information.

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

11.1. Other concerns

Clinical aspects

Question 1

The MAH has described the handling of concentrations values below BLQ. However, with reference to the EMA Guideline on reporting the results of population pharmacokinetic analyses (Doc.ref. CHMP/EWP/185990/06, June 2007), the MAH is asked to apply the type of bioanalytical methods used and the LLOQ for each analyte in each method.

MAH's response

A truncated likelihood method that takes into account the censoring of BLQ data (i.e., M3 method) was implemented in the final population PK analysis according to the lower limit of quantitation (LLOQ) of each study (Beal. 2001). The information regarding the bioanalytical methods used to determine teduglutide concentration in each study and their respective LLOQ is summarized in Table 1.

Table 1. Bioanalytical Methods in Clinical Trials and Related Lower Limit of Quantitation

Study number	Study Title	LLOQ (ng/mL)	Assay Note
ALX-0600-1621/13	A Phase I, Single-Blind, Placebo-controlled Study in Healthy Male Patients to Investigate the Safety, Tolerability and Pharmacokinetics of Ascending Single Subcutaneous Doses	3.13 ng/ml	ELISA
CL0600-006	A Phase I, Randomized, Two-way Crossover Bioavailability Study of 0.12 mg/kg ALX 0600 in Normal Healthy Patients	1.00 ng/mL	LCMS
CL0600-015	A Phase I, Randomized, Open-Label, 3-Way Crossover Bioavailability Study of 10 mg Teduglutide in Healthy Adults	1.00 ng/mL	LCMS
CL0600-017	A Phase I, Randomized, Open-Label Clinical Study to Evaluate the Effect of Moderate Hepatic Impairment on Teduglutide Pharmacokinetics	1.00 ng/mL	LCMS
CL0600-018	Pharmacokinetics of 10 mg Teduglutide in Subjects with Renal Impairment Compared to Healthy Subjects with Normal Renal Function.	1.00 ng/mL	LC-MS-MS
CL0600-022	A Phase I, Double-Blind, Randomized, Placebo-Controlled,	1.00 ng/mL	LC-MS-MS

Study number	Study Title	LLOQ (ng/mL)	Assay Note
	Multi-Dose Tolerability and Pharmacokinetic Study of Teduglutide in Healthy Adults		
C09-001	A Randomized, 4-Period, Placebo and Active-Controlled, Single-Dose, Changeover Trial to Evaluate the Effects of Teduglutide on Cardiac Repolarization and Conduction in Healthy Male and Female Volunteers	1.00 ng/mL	LCMS
CL0600-008	A Placebo-controlled Pilot Study of the Safety and Efficacy of ALX 0600 in Patients with Moderately Active Crohn's Disease	1.00 ng/mL	LCMS
ALX-0600-92001	Open-Label, Multicenter, Dose-Ranging, Pilot Study to Examine the Safety, Tolerability and Effect of a 21 Day, Ascending, Multidose Subcutaneous Treatment with ALX-0600 in Patients with Short Bowel Syndrome	0.500 ng/mL	ELISA
CL0600-004	A Phase 3, Placebo-controlled Study of the Efficacy, Tolerability and Safety of Teduglutide in Patients with Parenteral Nutrition-Dependent Short Bowel Syndrome	1.00 ng/mL	LCMS
TED-C13-003	A 12-Week Pharmacokinetic, Safety, and Pharmacodynamic Study of Teduglutide in Pediatric Subjects Aged 1 through 17 Years, with Short Bowel Syndrome who are Dependent on Parenteral Support	1.00 ng/mL	LCMS
TED-C14-006	A 24-week Double-blind, Safety, Efficacy, and Pharmacodynamic Study Investigating Two Doses of Teduglutide in Pediatric Subjects Through 17 Years of Age with Short **BOWEL** Syndrome who are Dependent on Parenteral Support	1.00 ng/mL	LCMS

Overall, the study-specific LLOQ information was implemented as part of the final **POPULATION** PK analysis of teduglutide with the use of the M3 method.

Reference:

Beal SL. Ways to fit a PK model with some data below the quantification limit. J Pharmacokinet Pharmacodyn. 2001 Oct; 28(5): 481-504.

Assessment of the MAH's response

The MAH has adequately presented the type of bioanalytical methods used and the respective LLOQ for each analyte in Table 1. The Question is therefore considered solved.

Conclusion

Issue resolved.

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

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

Question 2

The MAH has presented the covariates selected for the model sufficiently. However, in addition the pediatric age groups should be stratified as follows: <2, 2-<6, 6-<12, 12-<18 years.

MAH's response

Descriptive statistics of teduglutide parameters following SC dosing of 0.05 mg/kg according the above-mentioned age categories are presented in Table 2.

Table 2. Descriptive Statistics of Teduglutide Parameters Following SC Dosing of 0.05 mg/kg as a Function of Age

Age Categories	Age	Mean (SD) Median (90% CI)					
		Body Weight (kg)	$Cmax_{ss}$ (ng/mL)	AUC_{ss} (ng.h/mL)	$C_{8,ss}$ (ng/mL)	Half-Life (h)	T_{maxss} (h)
Adults	≥18 years (n = 44)	60.1 (9.79) 59.3 [42.8, 80.1]	39.7 (13.5) 39.0 [20.3, 67.3]	252 (106) 224 [131, 509]	12.6 (8.60) 10.3 [3.52, 34.1]	1.29 (0.623) 1.20 [0.598, 2.64]	2.49 (0.679) 2.40 [1.60, 3.68]
Adolescents*	12 to < 18 years (n =3)	39.8 (2.75) 38.5 [38.0, 43.0]	29.7 (8.37) 31.3 [20.7, 37.2]	154 (17.6) 152 [138, 173]	5.58 (1.29) 4.88 [4.78, 7.06]	0.953 (0.00574) 0.952 [0.948, 0.959]	2.07 (0.289) 1.90 [1.90, 2.40]
Pediatrics*	6 to <12 years (n =13)	24.1 (4.55) 23.9 [17.2, 34.9]	34.5 (11.1) 33.3 [21.1, 59.9]	142 (26.5) 136 [113, 199]	3.54 (2.09) 3.60 [0.652, 7.68]	0.775 (0.234) 0.754 [0.469, 1.32]	1.71 (0.323) 1.80 [1.20, 2.20]
	2 to < 6 years (n = 23)	15.0 (2.26) 15.0 [11.1, 18.7]	33.1 (12.1) 30.0 [21.8, 71.2]	122 (68.1) 109 [66.9, 366]	2.18 (3.24) 1.47 [0.322, 14.0]	0.671 (0.252) 0.625 [0.340, 1.49]	1.46 (0.237) 1.40 [1.12, 2.12]
	< 2 years (n =1)	[redacted] (NA) [redacted]	29.3 (NA) 29.3 [29.3, 29.3]	85.1 (NA) 85.1 [85.1, 85.1]	0.546 (NA) 0.546 [0.546, 0.546]	0.503 (NA) 0.503 [0.503, 0.503]	1.20 (NA) 1.20 [1.20, 1.20]

AUC_{ss} = area under the curve at steady state; Cmaxss = maximum concentration at steady state; C8ss =concentration at 8 h post dose under steady state; CI = confidence interval; NA = not applicable since n=1; SD = standard deviation; Tmaxss = time to maximum concentration under steady state.
* Pediatric patients from both Study TED-C13-003 and TED-C14-006

Mean $Cmax_{ss}$ values in the 2 to < 6 and 6 to <12 years group were consistent (33.1 and 34.5 ng/mL, respectively).

Mean AUC_{ss} values were age-dependent and gradually decreased with age from a mean of 252 ng.h/mL in adults to 122 ng.h/mL in pediatric patients 2 to < 6 years of age and 85.1 ng.h/mL in the patient <2 years of age.

Assessment of the MAH's response

The MAH has stratified the age groups as requested, which is endorsed. The Table illustrates that some age groups contains very few subjects. The MAH should justify that only three adolescents, 12- <18 years of age have been included in TED-C13-003 and TED-C14-006. The limited data in these two age groups makes it difficult to interpret data adequately for the respective age groups. The question is therefore not considered fully resolved. **(OC).**

Conclusion

Issue not resolved.

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

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

Question 3

The MAH should elucidate the handling of BLQ samples further, and discuss the possible consequences in relation to the final model.

MAH's response

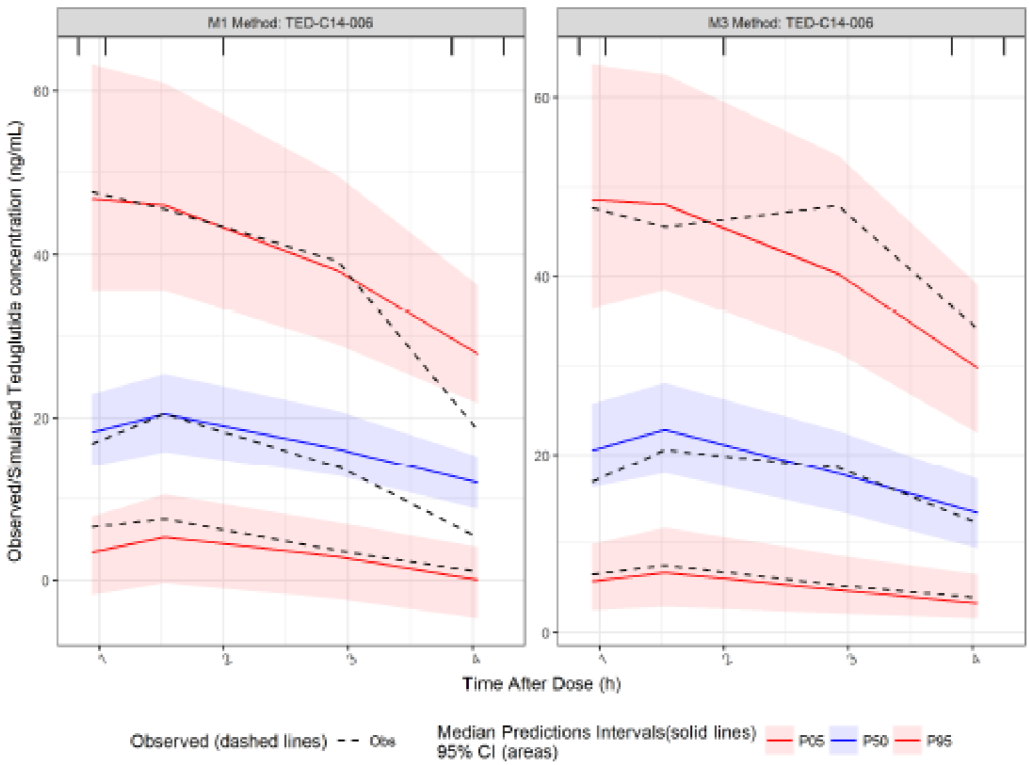
As discussed in the population PK report, a total of 670 (9.1%) postdose samples were BLQ.

In study TED-C13-003 and TED-C14-006, the total number of BLQ samples were 60 (33%) and 1 (0.7%), respectively.

During model evaluation, the M1 method resulted in biased VPC particularly in study TEDC14-006 and TED-C13-003. The predictive performance of the model was significantly improved after implementing the M3 method. The M3 method was selected based on the VPC.

For information purposes, VPCs in study TED-C14-006 and TED-C13-003 using the M1 and M3 method were provided for comparisons purposes below.

VPC for TED-C14-006 – M1 vs. M3 Method

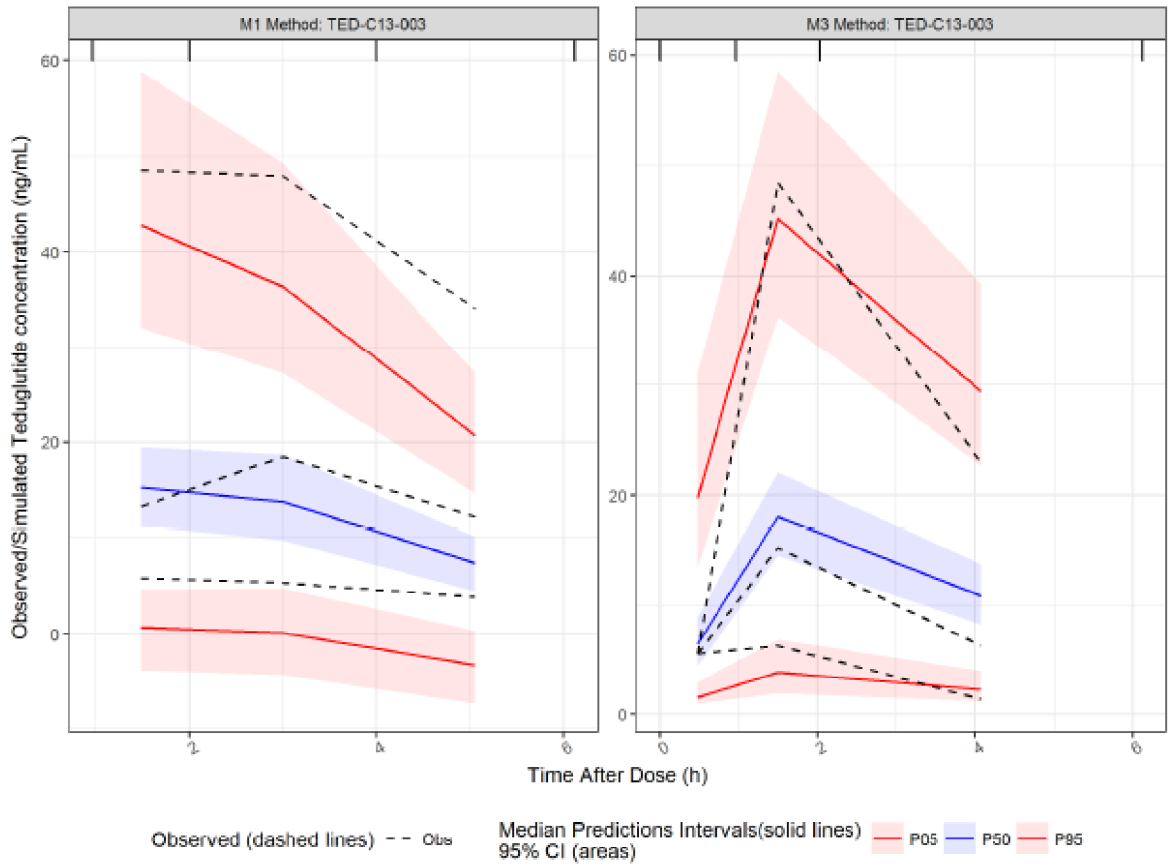


Based on the M1 method (left panel), the population PK model did not adequately capture the 50th and 95th prediction intervals during the elimination phase of teduglutide in study TEDC14-006. The M1 method would have led to biased estimates of the terminal elimination half-life of teduglutide.

On the other hand, the implementation of the M3 method (right panel), as explained in the final population PK report (Page 27), significantly improved the predictive performance of the model since the observed concentrations (dashed lines) were fully contained with the 5th, 50th and 95th prediction intervals in study TED-C14-006. The terminal elimination half-life of teduglutide derived with the M3 method was deemed to be more robustly estimated.

Overall, the superior predictive performance of the population PK model using method M3 relative to method M1 was the rationale for using the method M3 in the final report.

VPC for TED-C13-003 – M1 vs. M3 Method



Based on the M1 method (left panel), the population PK model did not adequately capture the 50th and 95th prediction intervals during the elimination phase of teduglutide in study TEDC13-003.

On the other hand, the implementation of the M3 method (right panel), as explained in the final population PK report (Page 27), significantly improved the predictive performance of the model since the observed concentrations (dashed lines) were fully contained with the 5th, 50th and 95th prediction intervals in study TED-C13-003 (with the exception of a slight bias for the 50th prediction interval during the elimination phase). Overall, the superior predictive performance of the population PK model using method M3 relative to method M1 was the rationale for using the method M3 in the final report.

Overall, the superior predictive performance of the population PK model using method M3 relative to method M1 was the rationale for using the method M3 in the final report.

VPCs using the M3 and M1 method were similar in adult patients and healthy volunteer.

Assessment of the MAH's response

The MAH has justified the selection of the M3 method based on the VPC. The Question is considered resolved.

Conclusion

Issue resolved.

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

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

Question 4

Descriptive statistics of exposure parameters of teduglutide by age for a 0.05 mg/kg dose presented in Table 6 has been age stratified accordingly. However, the number of subjects (n) should be provided for each age group.

MAH's response

The number of subjects included in each age categories have been added in Table 3.

Table 3. Descriptive Statistics of Teduglutide Parameters Following SC Dosing of 0.05 mg/kg as a Function of Age

Age Categories	Age	Mean (SD) Median (90% CI)						
		Body Weight (kg)	$Cmax_{ss}$ (ng/mL)	AUC_{ss} (ng.h/mL)	$C_{8,ss}$ (ng/mL)	$C_{12,ss}$ (ng/mL)	Half-Life (h)	T_{maxss} (h)
Adults	≥18 years (n = 44)	60.1 (9.79) 59.3 [42.8, 80.1]	39.7 (13.5) 39.0 [20.3, 67.3]	252 (106) 224 [131, 509]	12.6 (8.60) 10.3 [3.52, 34.1]	4.57 (4.82) 3.18 [0.494, 15.4]	1.29 (0.623) 1.20 [0.598, 2.64]	2.49 (0.679) 2.40 [1.60, 3.68]
Adolescents	12 to 17 years (n =3)	39.8 (2.75) 38.5 [38.0, 43.0]	29.7 (8.37) 31.3 [20.7, 37.2]	154 (17.6) 152 [138, 173]	5.58 (1.29) 4.88 [4.78, 7.06]	1.37 (0.950) 0.866 [0.784, 2.47]	0.953 (0.00574) 0.952 [0.948, 0.959]	2.07 (0.289) 1.90 [1.90, 2.40]
Pediatrics	8 to 11 years (n =9)	25.4 (4.55) 26.2 [18.5, 34.9]	31.0 (9.37) 30.5 [21.1, 51.5]	137 (26.4) 129 [113, 199]	3.93 (1.87) 3.83 [0.652, 7.68]	0.807 (0.459) 0.810 [0.0281, 1.54]	0.798 (0.226) 0.765 [0.568, 1.32]	1.78 (0.286) 1.80 [1.20, 2.20]
	6 to 7 years (n =4)	21.2 (3.35) 21.2 [17.2 25.4]	42.4 (11.8) 37.3 [35.1, 59.9]	152 (27.1) 152 [124, 182]	2.68 (2.60) 1.61 [0.959, 6.55]	0.410 (0.584) 0.151 [0.0587, 1.28]	0.723 (0.278) 0.662 [0.469, 1.10]	1.55 (0.387) 1.45 [1.20, 2.10]
	4 to 5 years (n =10)	16.7 (1.70) 16.8 [13.2, 18.8]	31.5 (5.88) 30.3 [23.3, 42.2]	114 (14.7) 111 [97.0, 144]	1.78 (0.775) 1.72 [0.814, 3.38]	0.231 (0.177) 0.206 [0.0408, 0.617]	0.653 (0.118) 0.664 [0.491, 0.825]	1.47 (0.183) 1.50 [1.20, 1.80]
	2 to 3 years (n =13)	13.7 (1.77) 13.8 [11.1, 16.8]	34.4 (15.5) 30.0 [21.7, 77.4]	127 (90.9) 104 [63.5, 421]	2.48 (4.30) 1.32 [0.279, 16.6]	0.412 (0.957) 0.154 [0.00674, 3.58]	0.685 (0.326) 0.598 [0.316, 1.64]	1.45 (0.279) 1.40 [1.10, 2.20]

Age Categories	Age	Mean (SD) Median (90% CI)						
		Body Weight (kg)	$Cmax_{ss}$ (ng/mL)	AUC_{ss} (ng.h/mL)	$C_{8,ss}$ (ng/mL)	$C_{12,ss}$ (ng/mL)	Half-Life (h)	T_{maxss} (h)
	1 to < 2 years (n =1)	[redacted] (NA) [redacted]	29.3 (NA) 29.3 [29.3, 29.3]	85.1 (NA) 85.1 [85.1, 85.1]	0.546 (NA) 0.546 [0.546, 0.546]	0.0350 (NA) 0.0350 [0.0350, 0.0350]	0.503 (NA) 0.503 [0.503, 0.503]	1.20 (NA) 1.20 [1.20, 1.20]

AUC_{ss} = area under the curve at steady state; $Cmax_{ss}$ = maximum concentration at steady state; C_{8ss} =concentration at 8 h post dose under steady state; C_{12ss} = concentration at 12 h post dose under steady state; CI = confidence interval; NA = not applicable since n=1; SD = Standard deviation; $Tmax_{ss}$ = time to maximum concentration under steady state;

A similar table was presented for pediatric subjects (<2, 2-<6, 6-<12, 12-<18 years, refer to Q2).

Assessment of the MAH's response

The MAH has provided the number of pediatrics subjects in each age group as requested. However, it is found problematic that PK data only exists from one subject in the age group under two years. The MAH is requested provide information about the the lack of PK data in pediatric patients < 2 years. **(MO).**

Conclusion

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

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

Question 5

The MAH should provide the number/percentage of subjects with SBS and Crohn's disease, respectively.

MAH's response

A total of 459 subjects were included on the population PK analysis. The population included a total of 259 (56.4%) healthy subjects, 170 patients with SBS (37.0%) and 30 patients with Crohn's Disease (6.5%) as presented in Table 4.

Table 4. Descriptive Statistics of Disease Status in the PK Population

Characteristics		Studies	Total (n = 459)
Disease Status	Healthy	ALX-0600-1621/13; CL0600-006; CL0600-015; CL0600-017; CL0600-018; CL0600-022; C09-001	259 (56.4%)
	SBS	ALX-0600-92001; CL0600-004; TED-C13-003; TED-C14-006	170 (37.0%)
	Crohn's Disease	CL0600-008	30 (6.5%)

SBS = short bowel syndrome

Assessment of the MAH's response

The MAH has provided the frequencies of children having SBS and Crohn´s disease as requested. The Question is considered solved.

Conclusion

Issue resolved.

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

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

Question 6

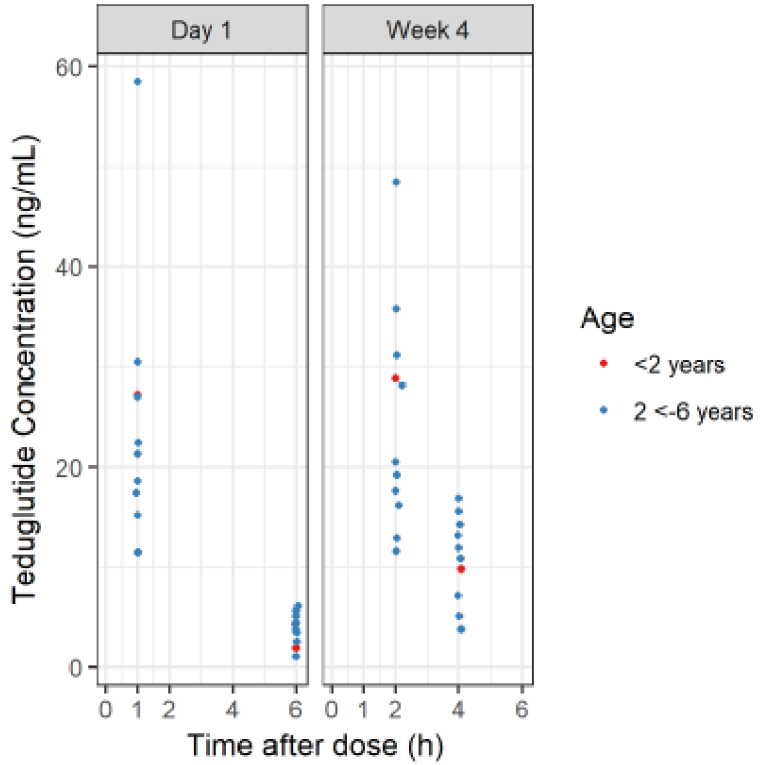
Only one child in the age group 1-2 years was included in the PK model. The MAH should discuss and justify the validity of the results in relation to the posology in children < 2 years.

MAH's response

This child was enrolled in trial TED-C13-003 and was treated with teduglutide 0.05 mg/kg/day for 12 weeks. Samples for PK analysis was collected pre-dose, at 1 and 6 hours post-dose at start of treatment and at pre-dose, 2 and 4 hours post-dose at Week 4.

Teduglutide concentration in this child are presented below (red circles) and compared with observed plasma teduglutide concentration in other children less than 6 years old of age enrolled in study TED-C13-003 and treated with teduglutide 0.05 mg/kg/day in Figure 1.

Figure 1. Teduglutide concentration in Children (< 6 years) Following Teduglutide Administration (0.05 mg/kg/day) on Day 1 and Week 4



More than sparse samples were collected in study TED-C13-003, the observed concentrations of teduglutide in the child < 2 years was consistent and within the range of those observed in older children (n=11; aged 2-5.6 years) treated with the 0.05 mg/kg dosing regimen.

Assessment of the MAH's response

The MAH has provided an overview over teduglutide plasma concentrations for the only child < 2 years of age. Plasma concentrations appears to be consistent with the range of those observed in older children (2-6 years). However, data, which consists of totally 4 plasma concentration measurements, of which the latest measurement was conducted after 4 weeks, is found too limited to support teduglutide treatment in paediatric patients < 2 years after 12 weeks as already approved. The total number of four plasma concentration measurements in paediatric patients < 2 years is new information, which has not been provided in the Application previously. The Question has therefore been upgraded to a Major Concern. In SmPC section 4.2, the MAH should provide the following information: "Data does not support teduglutide treatment in children < 2 years of age beyond 12 weeks".

Conclusion

Issue not resolved.

Question not resolved.

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

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

Question 7

The MAH should explain why statistical tests were not employed to better qualify differences between groups.

MAH's response

The design and sample size of the TED-C14-006 study was agreed with the FDA, including the ability of subjects to choose whether to receive study drug, and the lack of a placebo treatment arm. The sample size was based on the estimated feasibility of enrollment in the pediatric population with SBS rather than power calculation. The target enrollment was a minimum of 20 subjects in the teduglutide treatment arm (10 in each dose group), and 8 subjects in the SOC treatment arm. No statistical hypothesis testing of efficacy was prespecified in the protocol. Descriptive analysis was planned for the primary efficacy endpoint and secondary endpoints instead.

Even though the total actual sample size (N=59) exceeded what was planned, there was no pre-defined approach for multiplicity adjustment. The relatively small sample size in the SOC arm limits the value of statistical comparisons between the SOC arm and the teduglutide treatment arm. Therefore, only summary statistics were used to describe efficacy.

Assessment of the MAH's response

The MAH states that the relatively small sample size in the SOC arm limits the value of statistical comparisons, and therefore only summary statistics were used to describe efficacy. Thus the efficacy results are not statistically emphasized. This could be acceptable, but the MAH should justify extrapolation of adult efficacy results **(OC).**

Conclusion

Issue not resolved.

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

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

Question 8

The MAH should discuss the selection criteria for inclusion in the SOC treatment arm in more details, and in which way they may have influenced the interpretation of results. Herein, that only 9 patients were enrolled in the SOC arm vs. 50 patients in the teduglutide arm, and selection bias.

MAH's response

The study eligibility criteria for the SOC treatment arm and the teduglutide treatment arm were identical. Subjects and their parents were presented with the option in participating in either arm. The visit schedule, labs, and the nutritional support adjustment algorithm were identical for both study arms.

We suspect that more subjects and parents chose to enroll in the teduglutide treatment arm because their child had a chance to benefit from this new treatment. Teduglutide had been approved by the EMA for treatment of children with short bowel syndrome within 1 month of the first subject enrolling in the TED-C14-006 study. There are no other approved therapies that promote intestinal adaptation in

children with short bowel syndrome in Europe. In the US and Canada, there are no approved therapies to promote intestinal adaptation in children with short bowel syndrome.

Subjects and parents who chose to enroll in the SOC arm likely had different motivations.

They may have been motivated to preserve the opportunity to receive teduglutide treatment in the extension study after additional safety and efficacy data were obtained, or they may have been motivated to take a more structured and scientific approach to the medical management of their child's disease.

These differences in motivation may be the result of different patient journeys. For example, it is possible that patients who chose the teduglutide treatment arm may have had more frequent or severe SBS complications such as central line infections or liver disease prior to entering the study or their lifestyle may have been more negatively impacted by the daily provision parenteral support and intravenous fluids.

Subjects who have had frequent and severe complications of their disease are likely to continue to have frequent and severe complications in the future. This may be why severe adverse events were more common in the teduglutide treatment arm. An additional unavoidable consequence of the open-label study design is that subjects are generally less likely to report adverse events when they know they are not receiving the study drug. This may have resulted in under-reporting of adverse events in the SOC treatment arm. Despite these potential biases, the total number of TEAEs reported per subject was similar in the teduglutide treatment arm (about 10 per subject) and the standard of care treatment arm (about 8 per subject).

Assessment of the MAH's response

The MAH states that differences exist between the treatment- and SOC groups. The differences and their impact of the results have primary been discussed in relation to the higher number of TEAESs reported in the teduglutide treatment arm. The MAH should also discuss selection bias in regards of efficacy results, herein whether the group that chose treatment could have more sources, and therefore be more healthy in general than the patients, who chose the SOC arm. **(OC).**

Conclusion

Issue not resolved.

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

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

Question 9
When presenting demographics and results in general, the MAH should divide the pediatric subgroups as follows: <1, 1-<2, 2-<6, 6-<12, 12-<17, and 17-<18. The number of subjects (n) should be presented for each age group.

MAH's response

Demographics, baseline characteristics, short bowel syndrome history, exposure, and adverse events are presented by the requested age subgroups in a pooled analysis of the studies TEDC13-003 and TED-C14-006 in the attached tables. There were no clear differences in safety by age subgroup, although sample sizes for some of these subgroups were quite small.

Assessment of the MAH's response

The MAH has provided a table in which the subjects are divided into pediatric subgroups and the number of each subject in each age group, as requested. The Question is considered resolved.

Conclusion

Issue resolved.

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

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

Question 10

The MAH states that: "a total of 2 of 24 subjects (8.3%) in 0.025 mg/kg dose group and 3 of 26 subjects (11.5%) in the 0.05 mg/kg dose group achieved enteral autonomy, ie, complete weaning off of parenteral support by EOT. No subjects in the SOC arm achieved enteral autonomy during the study."

It is acknowledged that complete weaning off of parenteral support is a clinical important and relevant endpoint. However, this was not a predefined endpoint (primary endpoint: a ≥ 20% reduction in PN/IV volume.), and this conclusion can therefore not be made. The wording as follows marked with italics: Complete weaning Three (3) children in the 0.05 mg/kg group achieved complete weaning off parenteral support by week 24." should either be removed from the SmPC section 5.1, or alternatively it should be emphasized that this was not a predefined endpoint.

MAH's response

The primary efficacy endpoint in the TED-C14-006 protocol was a reduction in PN/IV volume of at least 20% at Week 24 (or EOT) compared to baseline. Additional predefined efficacy endpoints specified in the protocol include "100% reduction in PN/IV volume (complete weaning of PN/IV support) at Week 24 (or EOT) compared to baseline." This endpoint represents complete weaning off of parenteral support.

The number of subjects in the TED-C13-003 study who achieved enteral autonomy is already described in the SmPC section 5.1. The results from efficacy endpoints in TED-C13-003 such as decreases parenteral support volume and calories, increases in enteral nutrition volume and calories, and reductions in infusion days/week and hours/day are also included in SmPC section 5.1. All of these changes are relevant to understanding the efficacy of Revestive and its role in the treatment of short bowel syndrome in children.

In the proposed updates to SmPC section 5.1, we summarize only the results from analyses of pre-defined efficacy endpoints in the TED-C14-006 study.

Assessment of the MAH's response

The MAH states that 100 % reduction in PN/IV volume (complete weaning of PN/IV support) at week 24 was a predefined efficacy endpoint, which is endorsed. None the less, in the SmPC section 5.1, the MAH should emphasize that complete weaning was not a primary endpoint and that the groups investigated were inhomogeneous. The Question is not considered resolved. **(OC).**

Conclusion

Issue not resolved.

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

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

Question 11

The MAH has presented an overview of the cumulative teduglutide exposure for the 0.025 vs. 0.05 mg/kg/day group, measured in days and weeks. However, the MAH should describe the exposure in more details in regards of PK values (AUC) and then elucidate whether there is an association between exposure/dose and the occurrence of AE's

MAH's response

The association between exposure/dose and the occurrence of AE's was performed in pediatric SBS patients (Study TED-C13-003 and TED-C14-006, N= 85). The following treatment related AE's were considered for this analysis:

Vomiting

Abdominal pain

Frequency counts were derived in order to assess the association between exposure/dose and the occurrence of AE's. Multiple occurrences of the same AE and severity in an individual patient was counted only once, using the first occurrence. For each AE, day of occurrence and severity was merged with posterior Bayes steady state exposure parameters of teduglutide derived with the population PK model steady state PK exposures (e.g., AUC_{ss} and $Cmax_{ss}$).

A summary of frequency counts for vomiting in Study TED-C13-003 and TED-C14-006 are presented in Table 5.

Table 5 Summary of Teduglutide Related Events (Vomiting and Abdominal Pain) in Pediatric Patients (Study TED-C13-003 & TED– C14-006, N=85)

Vomiting	N (%)		
	0.0125 mg/kg/day (n=9)	0.025 mg/kg/day (n=36)	0.05 mg/kg/day (n=40)
No events	9 (100.0%)	35 (97.2%)	37 (92.5%)
At least one event	0 (0.0%)	1 (2.8%)	3 (7.5%)
No events	9 (100.0%)	34 (94.4%)	37 (92.5%)
At least one event	0 (0.0%)	2 (5.6%)	3 (7.5%)

A total 4 pediatric patients experienced vomiting episode. All vomiting adverse events were mild. A total 5 pediatric patients reported at least one abdominal pain events (4 mild and 1 moderate).

Descriptive statistics of teduglutide exposure by dose levels in pediatric patients who experienced teduglutide related vomiting or abdominal pain adverse events are presented in Table 6 and Table 7, respectively.

Table 6 Summary Teduglutide PK exposure in Pediatric Patients (Study TED-C13-003 & TED– C14-006, N=85) - Vomiting

Parameters	Statistics	0.0125 mg/kg/day	0.025 mg/kg/day		0.05 mg/kg/day	
		NO AE (n=9)	NO AE (n=35)	AE (n=1)	NO AE (n=37)	AE (n=3)
$Cmax_{ss}$ (ng/mL)	Mean (SD)	8.49 (1.06)	16.4 (2.95)	14.0 (NA)	32.6 (11.2)	40.5 (10.3)
	Median [Min, Max]	8.62 [6.16, 10.0]	15.7 [12.1, 23.3]	14.0 [NA]	30.5 [20.7, 77.4]	39.1 [31.0, 51.5]
AUC_{ss} (ng.h/mL)	Mean (SD)	28.9 (7.94)	64.7 (12.7)	47.2 (NA)	130 (57.1)	127 (22.3)
	Median [Min, Max]	25.4 [21.8, 41.9]	64.0 [44.8, 94.1]	47.2 [NA]	120 [63.5, 421]	136 [102, 144]

AE = adverse event; Max = maximum; Min = minimum; NA = not available since n=1; SD =standard deviation

Table 7 Summary Teduglutide PK exposure in Pediatric Patients (Study TED-C13-003 & TED– C14-006, N=85) – Abdominal Pain

Parameters	Statistics	0.0125 mg/kg/day	0.025 mg/kg/day		0.05 mg/kg/day	
		NO AE (n=9)	NO AE (n=34)	AE (n=2)	NO AE (n=37)	AE (n=3)
$Cmax_{ss}$ (ng/mL)	Mean (SD)	8.49 (1.06)	16.4 (3.00)	15.2 (NA)	33.0 (11.6)	36.7 (4.67)
	Median [Min, Max]	8.62 [6.16, 10.0]	15.7 [12.1, 23.3]	15.2 [14.8, 15.6]	30.5 [20.7, 77.4]	39.1 [31.3, 39.6]
AUC_{ss} (ng.h/mL)	Mean (SD)	28.9 (7.94)	64.2 (13.3)	65.2 (NA)	129 (57.2)	144 (8.07)
	Median [Min, Max]	25.4 [21.8, 41.9]	63.8 [44.8, 94.1]	65.2 [64.7, 65.7]	116 [63.5, 421]	144 [136, 152]

AE = adverse event; Max = maximum; Min = minimum; NA = not available since n=1; SD =standard deviation

Overall, patients with or without vomiting or abdominal pain AEs presented similar exposure to teduglutide. Patients who did not experience a vomiting AE presented $Cmax_{ss}$ and AUC_{ss} within 20% of those who experienced a vomiting AE. Patients who did not experience an abdominal pain AE presented $Cmax_{ss}$ and AUC_{ss} within 15% of those who experienced a vomiting AE.

Assessment of the MAH's response

The MAH presents Tables (5-8) illustrating the teduglutide exposure/dose and the occurrence of AE's, which is endorsed. However, multiple occurrences of the same AE and severity in an individual patient was counted only once, using the first occurrence. The MAH should count all occurrences and then conduct logistic regression to see if there is a significant association between exposure and AEs. The Question is not considered resolved. **(OC).**

Conclusion

Issue not resolved.

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

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

Question 12

The MAH should elaborate on causalities between the teduglutide exposure and the TESAEs (eg. ileus, faecaloma and metabolic acidosis) observed in TED-C14-006 and other studies, and discuss whether these should lead to further pre-cautions in the pediatric population

MAH's response

In the TED-C14-006 study there was one event of ileus. This event was serious, moderate in severity, related to teduglutide, started on study day 133, and resolved on study day 135. The study drug was interrupted during this time and was then restarted. The MAH has deemed this event to be unrelated to teduglutide for the following reasons:

1. This subject had prior similar events before starting teduglutide. As described in the SAE narratives of the CSR, this subject had previously failed screening due to an event of ileus during the prior screening period, but was subsequently rescreened.

2. There was a time to onset latency of approximately 4 months following the start of the study medication.

3. There was no recurrence of the event after teduglutide treatment was resumed.

In the TED-C14-006 study there was one event of faecaloma. This event was duplicated in the clinical database, once as serious, related to teduglutide, beginning on study day 143 and resolving on study day 149, and moderate in severity. The duplicate recording of the event was mild in severity but identical in all other aspects. The study drug was interrupted during the event and was subsequently restarted. The subject presented with abdominal distension and difficulty with spontaneous defecation. An abdominal ultrasound showed fecal stasis in the left colon and rectum, with marked dilation of the loops in the central abdominal quadrants confirmed by abdominal x-ray. Labs showed normal fluid and electrolyte balance and kidney and liver function. During hospitalization, the child passed abundant stools spontaneously. No disimpaction was performed and no laxatives were administered.

Throughout the TED-C14-006 study, stool frequency and typical Bristol stool form were collected during the 2 days prior to every clinic visit. One subject had bowel movements recorded on both days prior to every clinic visit, and the Bristol stool consistency was typically 6 (mushy). This pattern is inconsistent with chronic constipation which would be expected to precede the development of a faecaloma. Fecalomas are an extreme form of fecal impaction, are very hard and often calcified. They

require medical intervention, usually with a combination of enemas, laxatives, manual disimpaction, and occasionally endoscopic or surgical intervention. The spontaneous passage of stool by this patient and the lack of clear radiographic features of a fecaloma suggest that this may not be the most accurate term to describe the event.

The MAH has deemed this event to be unrelated to teduglutide for the following reasons:

Documented bowel habits in this subject are not consistent with chronic constipation. This subject had 1-2 bowel movements daily for the 2 days prior to every clinic visit. The Bristol stool form was 6 (mushy) at every study visit through study day 107 (week 15). The Bristol stool form was 1 and 2 (hard) on study day 125 and 126 (week 18), but on study days 146 and 147 (week 21), which occurred during the SAE, the typical Bristol stool form was recorded as 6.

There was a time to onset latency of almost 5 months.

There was no recurrence of any stool with a Bristol form less than 6 after teduglutide was restarted.

A review of integrated safety data from the completed pediatric studies TED-C14-006 and TED-C13-003 evaluated the frequencies events of constipation, faecaloma, and ileus. The overall frequency of constipation was similar between the teduglutide and SOC treated subjects.

	Teduglutide		Standard of Care	
System Organ Class Preferred Term	Patients (N=87) n (%)	Events n	Patients (N=14) n (%)	Events n
Constipation	4(4.6)	4	1(7.1)	2
Faecaloma	1(1.1)	2	0(0.0)	0
Ileus	1(1.1)	1	0(0.0)	0
Studies: TED-C13-003 and TED-C14-006				

The same analysis was performed for the placebo-controlled adult studies of SBS (CL0600-004 and CL0600-020). No events of faecaloma or ileus were identified. The frequency of constipation was similar in the teduglutide-treated and placebo-treated subjects.

	Teduglutide		Placebo	
System Organ Class Preferred Term	Patients (N=109) n (%)	Events n	Patients (N=59) n (%)	Events n
Constipation	3(2.8)	3	2(3.4)	3
Studies: CL0600-004 and CL0600-020				

A review of integrated safety data from the completed pediatric studies TED-C14-006 and TED-C13-003 evaluated the frequencies events of acidosis, metabolic acidosis, lactic acidosis, and blood bicarbonate decreased. The frequency of blood bicarbonate decreased was similar in the teduglutide

and SOC treated subjects. The acidosis and metabolic acidosis occurred at a low frequency in teduglutide treated subjects, but not in SOC treated subjects.

The small size of the SOC treated population limits the sensitivity for detecting events at a similar frequency.

	Teduglutide		Standard of Care	
System Organ Class Preferred Term	Patients (N=87) n (%)	Events n	Patients (N=14) n (%)	Events n
Blood bicarbonate decreased	10(11.5)	12	2(14.3)	2
Acidosis	3(3.4)	3	0(0.0)	0
Metabolic acidosis	3(3.4)	6	0(0.0)	0
Studies: TED-C13-003 and TED-C14-006				

The same analysis was performed for the placebo-controlled adult studies of SBS (CL0600-004 and CL0600-020). No events of blood bicarbonate decreased were reported in these studies. One event of metabolic acidosis was described in a subject who received placebo.

	Teduglutide		Placebo	
System Organ Class Preferred Term	Patients (N=109) n (%)	Events n	Patients (N=59) n (%)	Events n
Metabolic acidosis	0(0.0)	0	1(1.7)	1

Acid-base derangements are a known complication of short bowel syndrome. Acidosis in SBS can occur as a result of imbalance in chloride and acetate in the parenteral support, bicarbonate losses in the stool due to malabsorptive diarrhea, and d-lactic acidosis due to small intestinal bacterial overgrowth. These causes are all proximally related to intestinal malabsorption, which improves with teduglutide treatment.

Based on the data analysis presented above, further precautions in the pediatric population are not required.

Assessment of the MAH's response

The MAH has discussed the causalities between the teduglutide exposure and TESAEs as requested. Herein, two events of faecaloma. After further evaluation the MAH suggests that faecaloma may not to be the most accurate term to describe the event. The MAH should should therefore correct the term. The Question is not considered resolved. **(OC).**

Conclusion

Issue not resolved.

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

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

Question 13

Usually faecalomas occur in relation to chronic constipation, and would not be expected in patients with SBS. The MAH should explain this, and the circumstances about the faecaloma cases identified in subjects treated with teduglutide, herein how faecaloma was diagnosed.

MAH's response

The MAH agrees that faecaloma is not expected to occur in patients with SBS. A literature search (of BIOSIS Previews®, Embase®, International Pharmaceutical Abstracts, and MEDLINE® databases) for the published literature specific to SBS and faecaloma identified no publications describing faecaloma associated with underlying SBS.

For clinical context related to the event, please see the response to question 12.

Assessment of the MAH's response

The MAH has performed a literature search, and concludes that faecaloma is not expected to occur in patients with SBS. The circumstances and the diagnosis has been adequately described in the response to Question 12. Please also refer to the assessment of MAH's response to Question 12. Question 13 is considered resolved

Conclusion

Issue resolved

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

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

Question 14

The MAH should discuss and justify all biochemical deviations and propose relevant precautions e.g. regular blood tests controlling for liver parameters, kidney function, potassium, lipids, hematology etc.

MAH's response

Analysis of safety labs in TED-C14-006 included changes from baseline in chemistry, hematology, and urinalysis parameters by study visit, shift tables for these parameters by study visit, and listings of subjects who had markedly abnormal chemistry and hematology parameters, which were provided in tables 14.3.4.1 through 14.3.4.10. Medical review of these updated tables by a practicing board-certified pediatric gastroenterologist with experience in short bowel syndrome identified no clinically meaningful changes from baseline or shifts from baseline in any laboratory parameter.

Hepatotoxic effects of teduglutide have not been observed. Children with short bowel syndrome are prone to intestinal failure associated liver disease which may manifest as elevations in AST, ALT,

alkaline phosphatase, and total and direct bilirubin, but values for these parameters do not correlate well with the severity of the liver disease. The mechanisms of intestinal failure associated liver disease are multifactorial, including malabsorption of bile acids, disruption of hepatic bile acid and cholesterol homeostasis by phytosterols from soybased lipids, and loss of intestinal-derived hormones that regulate hepatic bile acid and cholesterol production. The primary interventions to minimize liver injury are minimization of phytosterol exposure in soy-based lipids, prevention of catheter-associated bloodstream infections, and maximizing intestinal adaptation. In TED-C14-006, transient increases in AST, ALT, and direct bilirubin were observed in individual subjects, but overall, the mean values of liver parameters did not exhibit clinically meaningful changes in association with teduglutide treatment. In the standard treatment of stable pediatric patients with SBS, liver tests are typically monitored every 1 to 3 months. In children treated with teduglutide, no additional monitoring of liver tests is needed beyond standard clinical practice.

Children with short bowel syndrome are vulnerable to electrolyte abnormalities, dehydration, and fluid overload, detected in laboratory values as either elevated or depressed values of serum sodium, potassium, chloride, and bicarbonate, and increases in blood urea nitrogen and creatinine. In standard clinical practice, children with SBS who have stable parenteral support requirements typically have chemistry testing performed on a weekly to monthly basis. Due to the vulnerability of SBS patients to fluid and electrolyte shifts, standard clinical practice includes biochemical evaluation after adjustment to parenteral support. Transient changes in the electrolytes were observed in individual subjects during TED-C14-006, and investigators responded appropriately by making adjustments to nutritional support. Overall, the mean values of biochemistry parameters did not exhibit clinically meaningful changes in association with teduglutide treatment. Consistent with standard clinical practice, chemistry panels should be obtained after adjustments to parenteral support, whether or not this occurs in association with teduglutide treatment.

Children with short bowel syndrome are prone to iron deficiency anemia due to iron malabsorption and frequent phlebotomy. Baseline mean hemoglobin and hematocrit values for patients in TED-C14-006 were at the low end of normal. The mean values of hematology parameters did not exhibit clinically meaningful changes in association with teduglutide treatment. In the standard treatment of stable pediatric patients with SBS, hematology parameters are typically monitored every 1 to 3 months. In children treated with teduglutide, no additional monitoring of hematology parameters is needed beyond that of standard clinical practice.

Children with short bowel syndrome typically have malabsorption of bile acids and cholesterol and a compensatory increase in cholesterol synthesis, but this does not typically result in abnormal cholesterol levels in the blood. Serum triglycerides rise during intravenous lipid infusions, so knowledge sampling time relative to the lipid infusion time is required to interpret the results of lipid measurements. Post-infusion hypertriglyceridemia can occur when the liver's capacity to process the lipid infusions is exceeded, but this is uncommon.

Lipid-sparing strategies have been used to minimize hepatotoxicity of soy-based lipids, but intravenous supplementation of some amount of soy-based lipids may be required to avoid essential fatty acid deficiency, which can affect brain development. An avoidable complication of excessively rapid infusion of intravenous lipids is fat overload syndrome, which is characterized by headache, fever, jaundice, hepatosplenomegaly, respiratory distress, and spontaneous hemorrhage. No such events were observed in clinical trials of teduglutide. In the standard treatment of stable pediatric patients with SBS, lipid parameters are typically monitored every 1 to 3 months. In children treated with teduglutide, no additional monitoring of hematology parameters is needed beyond standard clinical practice.

Assessment of the MAH's response

The MAH has adequately described biochemical deviations and proposed relevant precautions. This is endorsed, and the Question is considered resolved.

Conclusion

Issue resolved.

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

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

Question 15

The MAH is requested to answer the questions in the appended Product Information.

MAH's response

Please see attached PI response document.

Assessment of the MAH's response

The MAH is requested to answer the questions to the response in the appended Product Information.

Conclusion

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

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

12. 2nd request for supplementary information

12.1. Major objections

1. The MAH has provided an overview over teduglutide plasma concentrations for the only child < 2 years of age. Plasma concentrations appears to be consistent with the range of those observed in older children (2-6 years). However, data, which consists of totally 4 plasma concentration measurements, of which the latest measurement was conducted after 4 weeks, is found too limited to support teduglutide treatment in paediatric patients < 2 years after 12 weeks as already approved. The total number of four plasma concentration measurements in paediatric patients < 2 years is new information, which has not been provided in the Application previously. The Question has therefore been upgraded to a Major Concern. In SmPC section 4.2, the MAH should provide the following information: "*Data do not support teduglutide treatment in children < 2 years of age after 12 weeks*".

12.2. Other concerns

2. The MAH has stratified the age groups as requested. Some age groups contains very few subjects. The MAH should justify that only three adolescents, 12- <18 years of age have been included in TED-C13-003 and TED-C14-006. The limited data in this age group makes it difficult to interpret data adequately.
3. The MAH states that the relatively small sample size in the SOC arm limits the value of statistical comparisons, and therefore only summary statistics were used to describe efficacy. Thus the efficacy results are not statistically emphasized. This could be acceptable, but in that case the MAH should justify extrapolation of adult efficacy results.
4. The MAH states that differences exist between the treatment- and SOC groups. The differences and their impact of the results have primary been discussed in relation to the higher number of TEAESs reported in the teduglutide treatment arm. The MAH should also discuss selection bias in regards of efficacy results, herein whether the group that chose treatment could possess more sources, and therefore be more healthy in general than the patients, who chose the SOC arm.
5. The MAH states that 100 % reduction in PN/IV volume (complete weaning of PN/IV support) at week 24 was a predefined efficacy endpoint, which is endorsed. None the less, in the SmPC the MAH should emphasize that complete weaning was not a primary endpoint and that the groups investigated were inhomogeneous.
6. The MAH presents Tables (5-8) illustrating the teduglutide exposure/dose and the occurrence of AE's, which is endorsed. However, multiple occurrences of the same AE and severity in an individual patient was counted only once, using the first occurrence. The MAH should count all occurrences and then conduct logistic regression to see if there is a significant association between exposure and AEs.
7. The MAH has discussed the causalities between the teduglutide exposure and TESAEs as requested. Herein, two events of faecaloma. After further evaluation the MAH suggests that faecaloma may not to be the most accurate term to describe the event. The MAH should should therefore correct the term which should also be reflected in the SmPC section 4.8.

13. Assessment of the responses to the 2nd request for supplementary information

13.1. Major objections

Clinical aspects

Question 1

The MAH has provided an overview over teduglutide plasma concentrations for the only child < 2 years of age. Plasma concentrations appears to be consistent with the range of those observed in older children (2-6 years). However, data, which consists of totally 4 plasma concentration measurements, of which the latest measurement was conducted after 4 weeks, is found too limited to support teduglutide treatment in paediatric patients < 2 years after 12 weeks as already approved. The total number of four plasma concentration measurements in paediatric patients < 2 years is new information, which has not been provided in the Application previously. The Question has therefore upgraded to a Major Concern. In SmPC section 4.2, the MAH should provide the following information: "*Data do not support teduglutide treatment in children < 2 years of age after 12 weeks*".

MAH's response

The population PK model was developed based on a total of 459 subjects who had PK non-BLQ concentrations, including a total of 170 subjects (37.0%) with SBS and 30 subjects (6.5%) with Crohn's disease. The SBS population consisted of 78 (45.9%) pediatric (1 to 11 years), 7 (4.12%) adolescent (12 to 17 years), 79 (46.5%) adult (18 to 65 years) and 6 (3.53%) elderly (> 65 years) subjects.

A total of 4 subjects between 1 and <2 years of age provided concentrations of teduglutide for PK assessment. Demographic data and PK parameters of teduglutide in pediatric subjects between 1 and <2 years are presented in Table 1.

Table 1 Demographics and PK Parameters of Teduglutide Pediatric Subjects with SBS (1 to < 2 years)

ID	Study	Sex	Dose (mg/kg)	Weight (kg)	CL/F (L/h)	Vc/F (L)	CL/F (L/h/kg)	Vc/F (L/kg)
[redacted]	TED-C13-003	Male	0.0125	[redacted]	5.06	3.82	0.491	0.371
	TED-C13-003	Female	0.025		5.39	3.64	0.481	0.325
	TED-C14-006	Male	0.025		5.17	5.03	0.488	0.475
	TED-C13-003	Male	0.05		5.87	4.26	0.559	0.406
			Mean (CV%)	**10.7 (3.6%)**	**5.37 (6.7%)**	**4.19 (14.8%)**	**0.505 (7.2%)**	**0.394 (16.0%)**

CL/F = apparent clearance; CV= coefficient of variation; SBS= short bowel syndrome; Vc/F = apparent central volume of distribution.

The CL/F and Vc/F (with and without adjustment for body weight) of teduglutide were similar in pediatric subjects 1 to < 2 years of age. In addition, the coefficient of variability (CV%) of CL/F and Vc/F of teduglutide was very low in pediatric subjects 1 to < 2 years (6.7% and 14.8%, respectively).

It should be noteworthy that based on the clinical package observed to date, PK properties of teduglutide are time-independent. Therefore, no change is expected in teduglutide exposure between measurement times in the samples collected either during 12 weeks or 24 weeks of treatment; and concentrations collected 4 times for one subject in Study TED-C14-006 can be merged with the others in Study TED-C13-003.

A total of 25 subjects between 2 and 3 years provided PK samples and used in the population PK analysis. PK parameters in pediatric 1 to <2 years of age (n=4) were compared to those in pediatric subjects between 2 and 3 years of age (n=25) in Table 2.

Table 2 Descriptive Statistics of PK Parameters in Pediatric Subjects with SBS – Comparison Between Subjects <2 Years and 2 to 3 Years

Age Groups	Mean (CV%) Median [Min, Max]				
	Weight (kg)	CL/F (L/h)	Vc/F (L)	CL/F (L/h/kg)	Vc/F (L/kg)
1 to <2 years old (n=4)	10.7 (3.6%) 10.6 [10.3, 11.2]	5.37 (6.7%) 5.28 [5.06, 5.87]	4.19 (14.8%) 4.04 [3.64, 5.03]	0.505 (7.2%) 0.489 [0.481, 0.559]	0.394 (16.0%) 0.388 [0.325, 0.475
2-3 years old (n=25)	12.9 (14.4%) 12.7 [10.1, 16.8]	6.23 (28.5%) 5.92 [1.64, 9.99]	5.01 (26.2%) 4.55 [3.22, 7.99]	0.483 (24.5%) 0.489 [0.119, 0.786]	0.385 (17.3%) 0.383 [0.281, 0.551]

CL/F = apparent clearance; CV = coefficient of variation; Max = maximum; Min = minimum; N = number of patients; SBS= short bowel syndrome; Vc/F = apparent central volume of distribution.

The mean weight-adjusted CL/F and Vc/F parameters in subjects 1 to <2 years of age (n=4) were within 5% of those observed in subjects 2 to 3 years of age (n=25).

Overall the above results suggest that the PK of teduglutide in pediatric subjects between 1 to <2 years was robustly assessed and representable for the concentrations extended to 24 weeks of treatment.

Assessment of the MAH's response

The MAH states that the POP PK model was based on plasma concentrations from 4 pediatric subjects aged 1-<2 years of age, and that "*the coefficient of variability (CV%) of CL/F and Vc/F of teduglutide was very low in pediatric subjects 1 to < 2 years (6.7% and 14.8%, respectively)*", which is acknowledged. Of notice, the Applicant has not provided information about the total number of plasma concentrations included in the POP PK model from pediatric subjects aged 1-< 2 years. Furthermore, in Table 2 and 3 (simulations of S.C. dose 0.05 mg/kg), previously presented in the response to question 2 and 4 only one child 1-< 2 years was included, and in Figure 6 in the response to question 6, only four plasma concentrations were presented representing the one child included. Thus data is considered too sparse to support teduglutide treatment in children < 2 years of age after 12 weeks".

The question is not considered resolved (MO).

Conclusion

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

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

13.2. Other concerns

Clinical aspects

Question 2
The MAH has stratified the age groups as requested. Some age groups contains very few subjects. The MAH should justify that only three adolescents, 12- <18 years of age have been included in TED-C13-003 and TED-C14-006. The limited data in this age group makes it difficult to interpret data adequately.

Summary of the MAH's response
The MAH respectfully notes that approval of the pediatric indication was based on the results of the TED-C13-003 study, in which three subjects 12-18 years of age were treated with teduglutide, one each at doses of 0.0125, 0.025, and 0.05 mg/kg. The target enrollment in the TED-C14-006 study was 28 subjects: 10 in each teduglutide dose group and 8 in the standard of care arm. The small number of adolescents compared to children 1-12 years of age reflects the epidemiology of this disease (J Pediatr Gastroenterol Nutr. 2003 Aug;37(2):136-41). In an effort to recruit as many adolescent subjects as possible, the enrollment in the TED-C14-006 study was extended, and more than double the total target enrollment was achieved. The additional data provided in the TED-C14-006 study includes 5 additional subjects 12-18 years of age, two of whom received 0.025 mg/kg, 2 of whom received 0.05 mg/kg, and one of whom received standard of care.

To improve our ability to detect safety signals specific to adolescents, an integrated analysis of safety data from the TED-C13-003 and TED-C14-006 studies was performed. The incidence of TEAEs and TESAEs, markedly abnormal laboratory assessments, and antiteduglutide antibodies was analyzed by dose group and age group.

In the integrated analysis, 80 subjects 1-<12 years of age were treated with teduglutide, 35 of whom had received 0.025 mg/kg and 38 of whom had received 0.05 mg/kg. 7 subjects 12- <18 years of age were treated with teduglutide, 3 of whom had received 0.025 mg/kg and 3 of whom had received 0.05 mg/kg. The frequency of overall treatment-emergent adverse events (TEAEs), severe TEAEs, and serious TEAEs was similar between the 1-<12 year age group and the 12-<18 year age group. No new safety signals were identified in the adolescent subjects.

The efficacy data in adolescent subjects also support a favorable benefit-risk assessment in this population. 100% of the adolescents treated with teduglutide in TED-C14-006 achieved the primary endpoint of at least 20% reduction in parenteral support volume at the end of treatment.

Although the sample sizes of pediatric sub-populations are inevitably a challenge in this rare disease, the new data from TED-C14-006 further support a favorable benefit assessment in adolescents.

The PK of teduglutide was assessed in a total of 170 subjects with SBS, which included 78 (45.9%) pediatric (1 to 11 years), 7 (4.12%) adolescent (12 to 17 years), 79 (46.5%) adult (18 to 65 years) and 6 (3.53%) elderly (> 65 years) subjects.

It is to be noted that a total of 7 adolescents were enrolled in study TED-C13-003 (n=3) and TED-C14-006 (n=4). In these studies, one subject received 0.0125 mg/kg, three subjects received 0.025 mg/kg and three received 0.05 mg/kg.

Age and body weight in each age group are presented in Table 3.

Table 3 Descriptive Statistics of Age and Body Weight in Each Age Group in Patients with SBS

Descriptive Statistics	Pediatrics (1 to <12 years) (n=78)	Adolescents (12 to <17 years) (n=7)	Adults (18 -65 years) (n=79)	Elderly (> 65 years) (n=7)
Age (years)				
Mean (CV%)	5.19 (50.6)	14.5 (3.12)	47.0 (26.7)	71.6 (6.19)
Median [Min, Max]	5.00 [1.00, 11.0]	14.4 [14.0, 15.0]	50.0 [19.0, 65.0]	72.0 [66.0, 79.0]
Body Weight (kg)				
Mean (CV%)	18.5 (36.5)	42.9 (9.53)	59.5 (17.0)	64.1 (14.6)
Median [Min, Max]	16.7 [10.1, 36.4]	43.0 [38.0, 48.7]	58.5 [40.1, 82.6]	63.6 [55.4, 80.8]

CV= coefficient of variation; Max= maximum; Min= minimum; n= number of patients

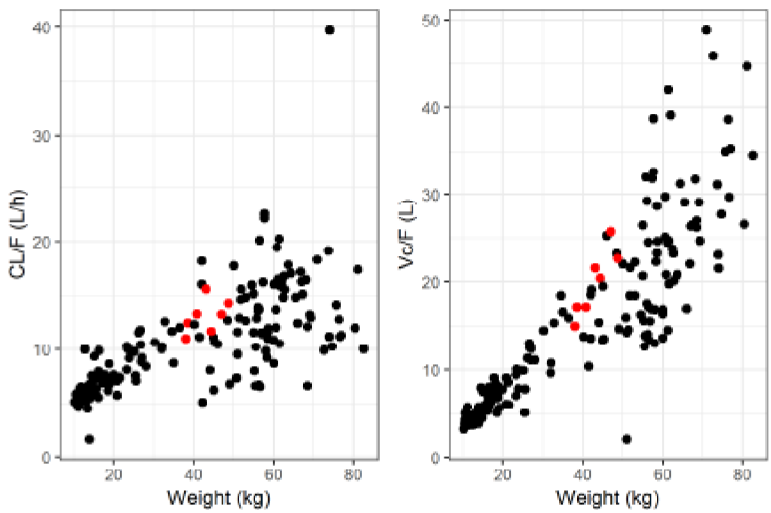
The range of body weight in adolescents (n=7) was 38.0 to 48.7 kg. Body weight in adult subjects overlapped with those observed in adolescents (i.e., a total of 11 adult subjects presented body weight values less than 48.7 kg).

Overall, a large range of body weight was available to robustly assess the relationship between body weight and PK parameters (CL/F and Vc/F) of teduglutide.

Based on the overlapping body weight in adolescent and adult subjects, the next part of the analysis focused on body weight as 1) a continuous parameter across age groups, and 2) the primary parameter explaining differences in PK parameters across age groups.

The relationship between PK parameters of teduglutide and body weight are presented in Figure 1.

Figure 1 PK Parameters of Teduglutide as Function of Body Weight



Note: Red circles represent PK parameters in adolescents (12 to <17 years) and the black circles represent PK parameters in pediatric (1 to <12 years), adult (18 -65 years) and elderly (> 65 years) subjects.

An important relationship was observed between the CL/F and body weight as per the allometric component of the population PK model (i.e., exponent of 0.590). In addition, a very steep relationship was observed between the Vc/F in weight as per the allometric component of the population PK model (i.e., exponent of 1.65).

The CL/F and Vc/F in adolescent subjects (red circles) were in good agreement with those observed in other age groups (black circles) since body weight (not age) is the primary parameter explaining

differences in PK parameters across age groups. Therefore, adolescent subjects (N=7) and adult subjects (N=11) with body weight less than 48.7 kg were both contributing to understanding in the relationship between body weight and PK properties including CL/F and Vc/F.

Overall, the above results suggest that the rich data collected in pediatric (n=78) and adult (n=79) subjects with SBS provided a robust understanding of the relationship between body weight and PK parameters (CL/F and Vc/F) and ultimately provided a robust characterization of PK parameters in adolescents (via interpolation) despite the relative low number of subjects available in this age group (n=7).

Finally, the population PK model was qualified using the adolescent subjects as an external dataset in order to assess the predictive power of the model. The robustness of PK parameters of teduglutide in adolescents was evaluated using according to the following steps.

1. A population PK analysis was performed based on a dataset excluding adolescents in a first step (n=452). A dataset including the adolescent PK information was used as an external dataset for model validation (n=7).
2. The above population PK model (n=452) was used to predict PK parameters according to subject-specific body weight and other relevant covariates (i.e., eGFR, ALT, age, sit of SC injection) in adolescent subjects.
3. PK parameters in adolescents (n=7) predicted with the above population PK model (n=452) were compared to those originally observed as part of the population PK analysis (which included concentration-time profiles of teduglutide in adolescents, n=459).

The PK parameters obtained with the exploratory model (n=452) were compared to the final model in Table 4.

Table 4 PK Analysis of Teduglutide – Population PK Analysis with or without Adolescent Subjects

PK Parameters	Original Model (Reference) n= 459	Exploratory Model without Adolescents (Test) n= 452	Relative Difference (%) [(T-R) / R]
CL/F (L/h)	13.6	13.5	-0.735
(Body Weight/70)$^{\theta}$	0.590	0.589	-0.169
(eGFRT/102)$^{\theta}$	0.322	0.321	-0.311
(ALT /24.0)$^{\theta}$	0.125	0.124	-0.800
if not SBS or Crohn's Disease	0.833	0.834	0.120
Vc/F (L)	33.1	33.0	-0.302
(Body Weight/70)$^{\theta}$	1.65	1.65	0.00
(Age/34.0)$^{\theta}$	-0.322	-0.330	-0.602
Ka (h^{-1})	0.318	0.318	0.0
(Body Weight/70)$^{\theta}$	-0.624	-0.622	-0.321
SC administration other than abdomen	0.690	0.691	0.145
ALAG (h)	0.207	0.208	0.483
Error Model			
Additive Error (ng/mL)	7.16	7.25	1.26
Proportional Error (%)	24.4	24.3	-0.410

ALAG = lag time of absorption; ALT = alanine aminotransferase; BSV = between-subjects variability; CL/F = apparent clearance; eGFRT = estimated glomerular filtration rate capped to 150 mL/min/1.73m^2; Ka = first-order rate constant of absorption; n= number of subjects; NA= not applicable; PK= pharmacokinetic; R= Reference; T= Test; Vc/F = apparent central volume of distribution; θ= covariate effect.

The exclusion of 7 adolescent subjects from the PK population did not have impact on the estimation of the population PK parameters for teduglutide. Moreover, the exclusion of 7 adolescent subjects did not have an impact on the allometric model on CL/F and Vc/F due to the data collected in pediatric (n=78) and adult (n=79) subjects with SBS.

The exploratory population PK model (n=452) was then used to interpolate PK parameters in 3 adolescents administered with the target dose of 0.05 mg/kg (refer to Table 5 in Pop PK report). Monte-Carlo simulations (500 replicates) were performed to generate PK exposure levels based on their subject-specific covariates and dosing history. Predicted PK parameters in adolescents are presented in Table 5.

Table 5 Exposure Parameters in Adolescents with SBS Administered with 0.05 mg/kg– Sensitivity Analysis

Subject ID	$Cmax_{ss}$ (ng/mL)		AUC_{ss} (ng.h/mL)	
	Original Model[a]	External Validation[b] Median [90% PI]	Original Model[a]	External Validation[b] Median [90% PI]
[redacted]	31.3	32.0 [21.4, 50.0]	152	157 [102, 240]
	20.7	24.1 [16.3, 38.2]	138	156 [101, 239]
	37.2	32.0 [21.4, 50.0]	173	150 [97.3, 230]

AUC_{ss} = area under the curve at steady state; $Cmax_{ss}$ = maximum concentration at steady state; PI = prediction interval; SBS= short bowel syndrome.
[a] Individual exposure in adolescent subjects originally derived with population PK model including pediatric, adolescent and adult subjects (n=459)
[b] Simulated exposure in adolescent subjects derived with population PK model excluding adolescent subjects (n=452)

PK parameters of teduglutide predicted with the exploratory model (i.e., external validation) were very close to those derived with the individual parameters of the original analysis. The above results suggest that the rich data collected in pediatric and adult subjects provided a robust understanding of the relationship between body weight and PK parameters (CL/F and Vc/F) and ultimately provided a robust description of PK parameters in adolescents (via interpolation) despite the relative low number of subjects available in this age group (n=7).

Assessment of the MAH's response

The Applicant presents an integrated analysis in which totally n=7 Pediatric subjects (one subject received 0.0125 mg/kg, three subjects received 0.025 mg/kg and three received 0.05 mg/kg) were enrolled as well as data from adults (n=11), who had overlapping body weights (values less than 48.7 kg). Furthermore, the Applicant has demonstrated robustness of the POP PK model describing adolescents PK data.

Conclusion

The Question is considered resolved.

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

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

Question 3

The MAH states that the relatively small sample size in the SOC arm limits the value of statistical comparisons, and therefore only summary statistics were used to describe efficacy. Thus the efficacy results are not statistically emphasized. This could be acceptable, but in that case the MAH should justify extrapolation of adult efficacy results.

MAH's response

The relative change in PS volume observed in the 0.05 mg/kg dose group in the TED-C14-006 study at week 24 (-41.6%), was somewhat greater than that observed in the 0.05 mg/kg dose group in the CL0600-020 pivotal adult phase III study at week 24 (-32%). In contrast, the relative change in PS volume observed in the SOC arm of the TED-C14-006 study at week 24 (-10.2%) was lower than that observed in the placebo group of the CL0600-020 study at week 24 (-21%). These data indicate that the relative changes in PS in children treated with 0.05 mg/kg teduglutide is comparable to that observed in adults. While it is possible that the patient self-selection into the SOC arm and the open-label nature of the SOC arm could lead to overestimation of the effect of teduglutide observed in TED-C14-006, as discussed in the Response to Question 4, this is unlikely to change the overall conclusions.

Because the enrollment achieved in the TED-C14-006 study was more than double the original target, a post-hoc statistical analysis was performed. The final population size allowed for a post hoc comparison analysis of the primary efficacy endpoint using the Fisher exact test (P values comparing each teduglutide cohort with the SOC group and with each other) and Newcombe-Wilson method with continuity correction (95% CIs of the differences), and of the percentage change in PS volume from baseline to EOT using the

Wilcoxon rank sum test (P values comparing each teduglutide cohort with the SOC group and with each other).

The primary endpoint, a ≥ 20% reduction in PS volume at Week 24, was achieved by 13 patients (54.2%) who received 0.025 mg/kg teduglutide, 18 patients (69.2%) who received 0.05 mg/kg teduglutide, and 1 patient (11.1%) who received SOC. The post hoc comparative analysis of the differences between each of the treatment arms was 43.1% (95% CI, 5.5% to 63.2%; P=0.03) for the 0.025-mg/kg and SOC groups, 58.1% (95% CI, 20.5% to 75.1%; P=0.004) for the 0.05-mg/kg and SOC groups, and 15.1% (95% CI, −11.2% to 38.9%; P=0.21) for the 0.025-mg/kg and 0.05-mg/kg groups. The relative changes in PS volume correspond to mean ± SD percentage changes from baseline of −36.2%±30.65%, − 41.6%±28.90%, and −10.2%±13.59% for the 0.025-mg/kg teduglutide, 0.05-mg/kg teduglutide, and SOC cohorts, respectively. The post hoc P values analysis for the differences in reduction of PS volume between each of the treatment arms were P=0.004 for the 0.025-mg/kg and SOC groups, P=0.0002 for the 0.05-mg/kg and SOC groups, and P=0.204 for the 0.025-mg/kg and 0.05-mg/kg groups.

Assessment of the MAH's response

The Applicant has justified that the relative changes in PS in children treated with 0.05 mg/kg teduglutide is comparable to that observed in adults.

Conclusion

The Question is considered resolved.

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

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

Question 4

The MAH states that differences exist between the treatment- and SOC groups. The differences and their impact of the results have primary been discussed in relation to the higher number of TEAESs reported in the teduglutide treatment arm. The MAH should also discuss selection bias in regards of efficacy results, herein whether the group that chose treatment could possess more sources, and therefore be more healthy in general than the patients, who chose the SOC arm.

MAH's response

It is unlikely that differences in baseline characteristics between the teduglutide treatment arm and SOC arm biased the efficacy results in favor of teduglutide. In fact, the anatomical characteristics and baseline PS requirements were more likely to have biased the efficacy results in favor of SOC.

Based on a recent post-hoc analysis of the adult clinical trial data (Gastroenterology 2018 Mar;154(4):874-885), patients expected to have the most dramatic benefit from teduglutide within a 24-week treatment period are those with high baseline PS volumes and those who lack a colon in continuity with the small bowel. Our hypothesis is that such subjects are likely the most deficient in native GLP-2, since the intestinal segments producing GLP-2 have been removed or are no longer exposed to lumenal nutrients.

In TED-C14-006, the overall short bowel syndrome history of subjects treated with teduglutide was similar to that of subjects in the SOC arm. In both groups, the most common causes of SBS included gastroschisis, volvulus, and necrotizing enterocolitis. However, Hirschprung's disease was more common in the SOC treatment arm (22%), compared to the teduglutide treatment arm (4%). Consistent with the higher prevalence of Hirschprung's disease in the SOC treatment arm, the fraction of subjects with a colon was lower in the SOC arm compared to the teduglutide-treated arm (67% and 94%, respectively). The mean remaining small bowel length was similar in both groups (45 cm in the SOC treatment arm and 43 cm in the teduglutide treatment arm). The mean baseline parenteral support volumes in the SOC arm were higher than the teduglutide treatment arm (80 ml/kg/day and 59 ml/kg/day, respectively).

Assessment of the MAH's response

The Applicant has argued that it is unlikely that differences in baseline anatomical characteristics and –PS between the tedugutide treatment arm and SOC arm are biased in favour of the SOC arm, which is acknowledged.

However, the Applicant did not answer whether there might exist a social gradient between the two groups, that could include a selection bias. The Applicant should elaborate on this issue before the question can be considered fully resolved.

Conclusion

The Question is not resolved. (OC).

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

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

Question 5

The MAH states that 100 % reduction in PN/IV volume (complete weaning of PN/IV support) at week 24 was a predefined efficacy endpoint, which is endorsed. None the less, in the SmPC the MAH should emphasize that complete weaning was not a primary endpoint and that the groups investigated were inhomogeneous.

MAH's response

The sponsor acknowledges the assessor's request. Due to the small sample sizes and the open label design of the studies, there are slight differences in the patients enrolled in the SOC arm versus the teduglutide arm, however, the sponsor respectfully disagrees that the groups investigated could be considered inhomogeneous, based on the baseline disease characteristics such as SBS history/etiology, percent remaining colon, etc. In order to address the assessor's request to denote weaning as not a primary endpoint, the sponsor proposes the following revisions to the text:

Complete weaning

Three (3) ~~children~~ paediatric subjects in the 0.05 mg/kg group achieved the additional endpoint of enteral autonomy ~~complete weaning off parenteral support~~ by week 24.

Assessment of the MAH's response

The Applicant has proposed the following revision:

Complete weaning

Three (3) ~~children~~ paediatric subjects in the 0.05 mg/kg group achieved the additional endpoint of enteral autonomy ~~complete weaning off parenteral support~~ by week 24.

The revised wording is acceptable.

Conclusion

The Question is considered resolved.

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

Question 6

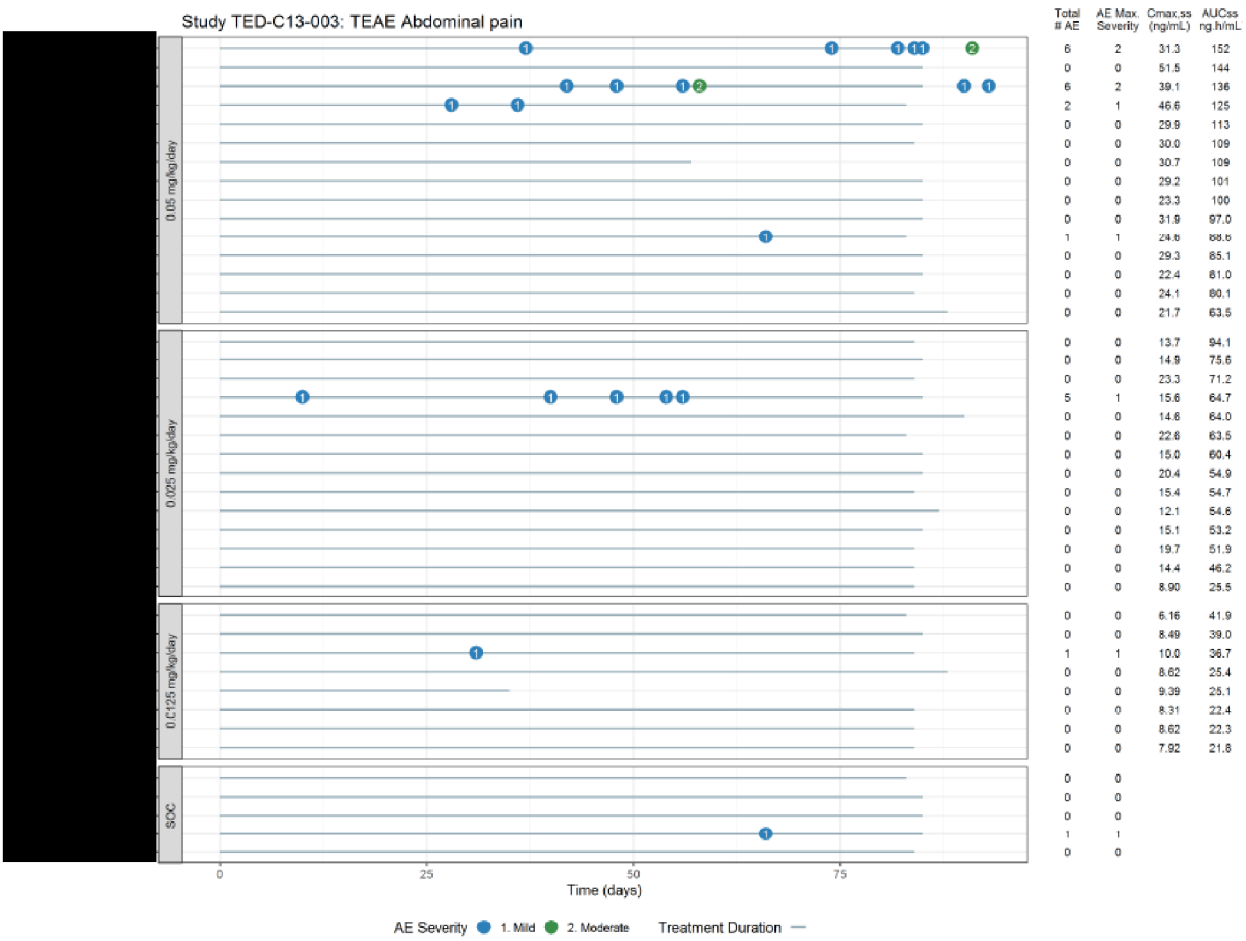
The MAH presents Tables (5-8) illustrating the teduglutide exposure/dose and the occurrence of AE's, which is endorsed. However, multiple occurrences of the same AE and severity in an individual patient was counted only once, using the first occurrence. The MAH should count all occurrences and then conduct logistic regression to see if there is a significant association between exposure and AEs.

MAH's response

The occurrence and severity of abdominal pain and vomiting treatment emergent adverse events (TEAE) over time as well as steady state PK parameters of teduglutide are presented in Figure 2 to Figure 5.

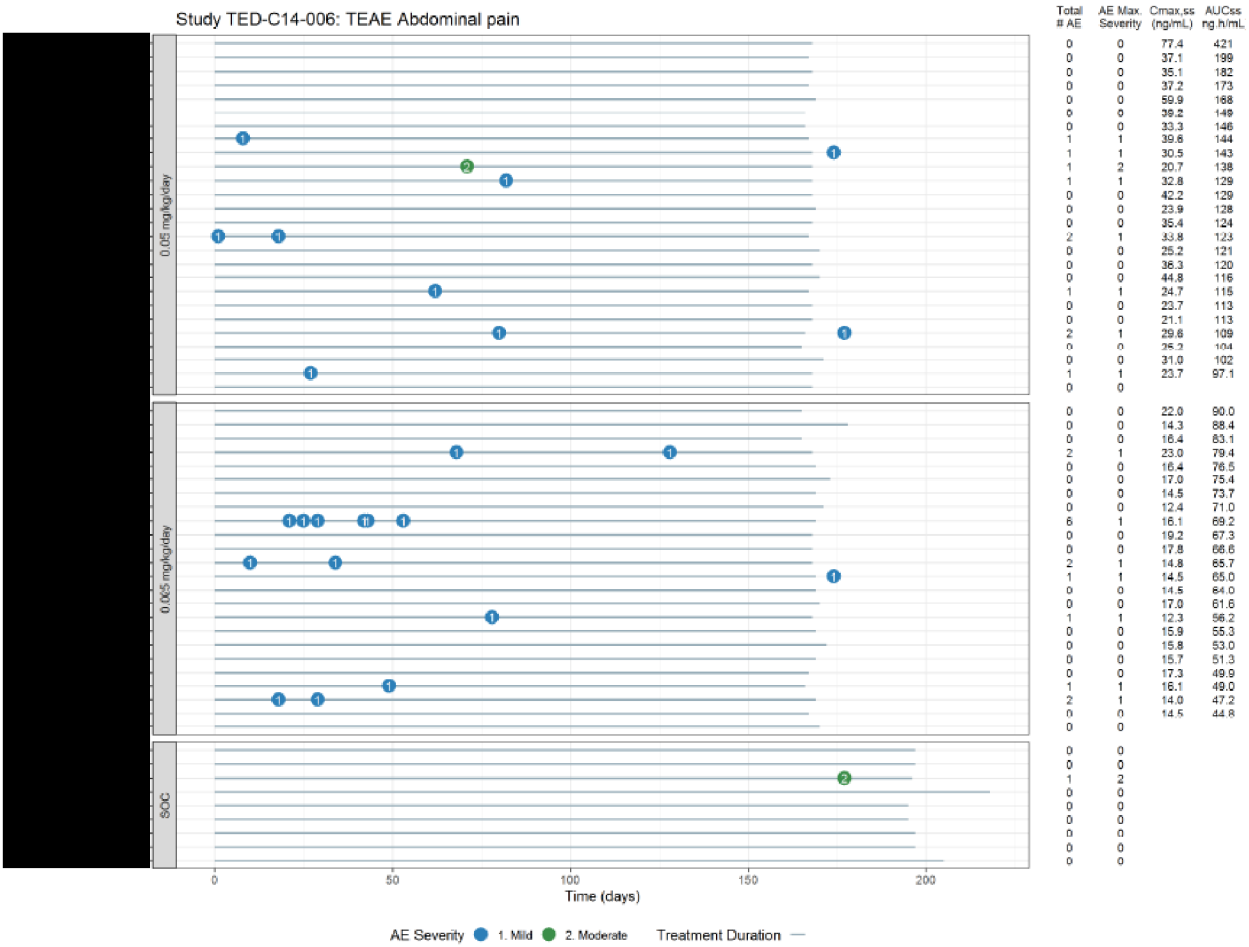
Based on these figures, a very low number of subjects experienced abdominal pain or vomiting. On the other hand, of the few subjects who experienced abdominal pain or vomiting, some presented repeated instances of events over time.

Figure 2 Occurrence of Abdominal Pain over Time and PK Parameters of Teduglutide – Study TED-C13-003



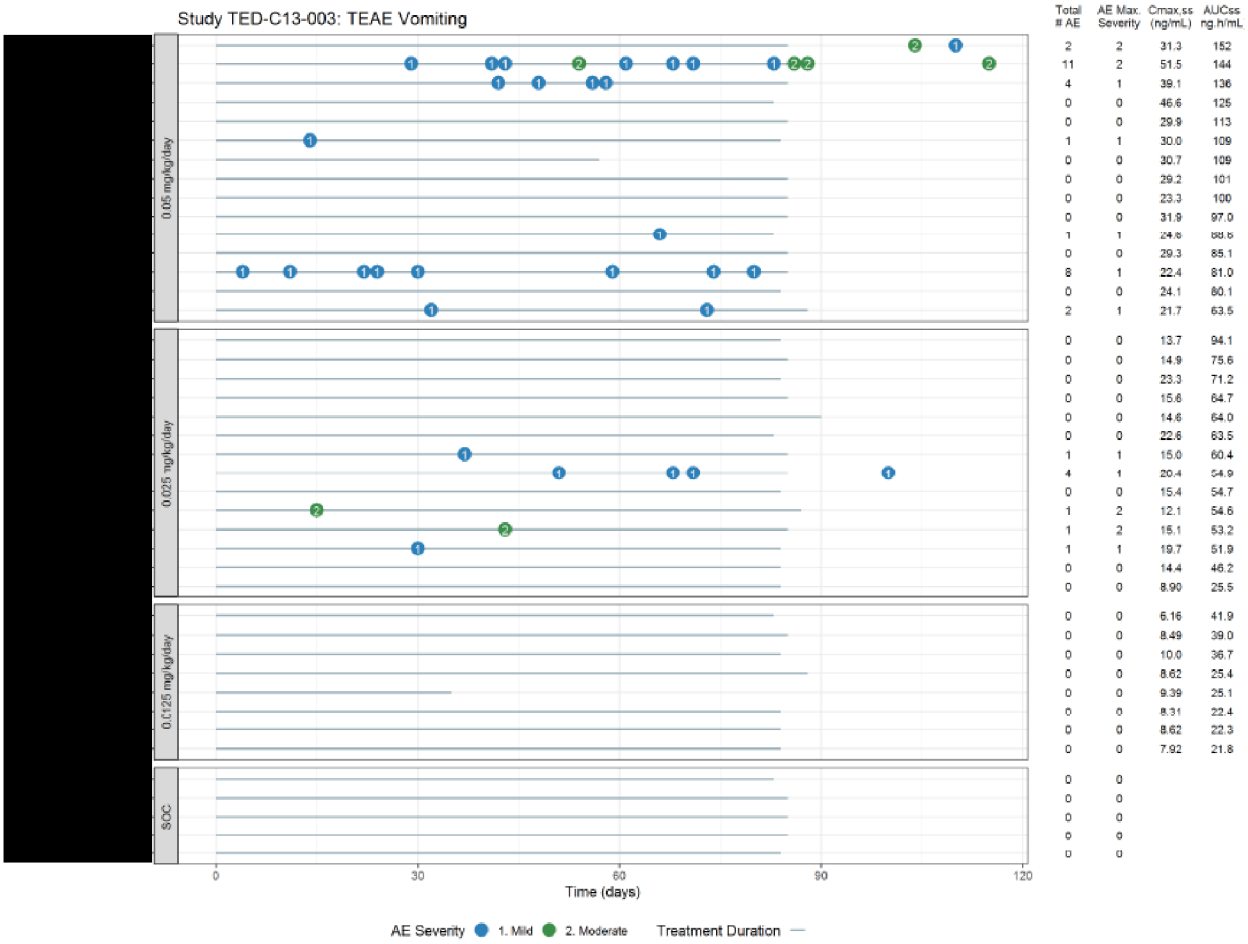
AE= adverse event; AUC_{ss} = area under the curve at steady state; $Cmax_{ss}$ = maximum concentration at steady state; Max= maximum; SOC= standard of care; TEAE= treatment emergent adverse event

Figure 3 Occurrence of Abdominal Pain over Time and PK Parameters of Teduglutide – Study TED-C14-006



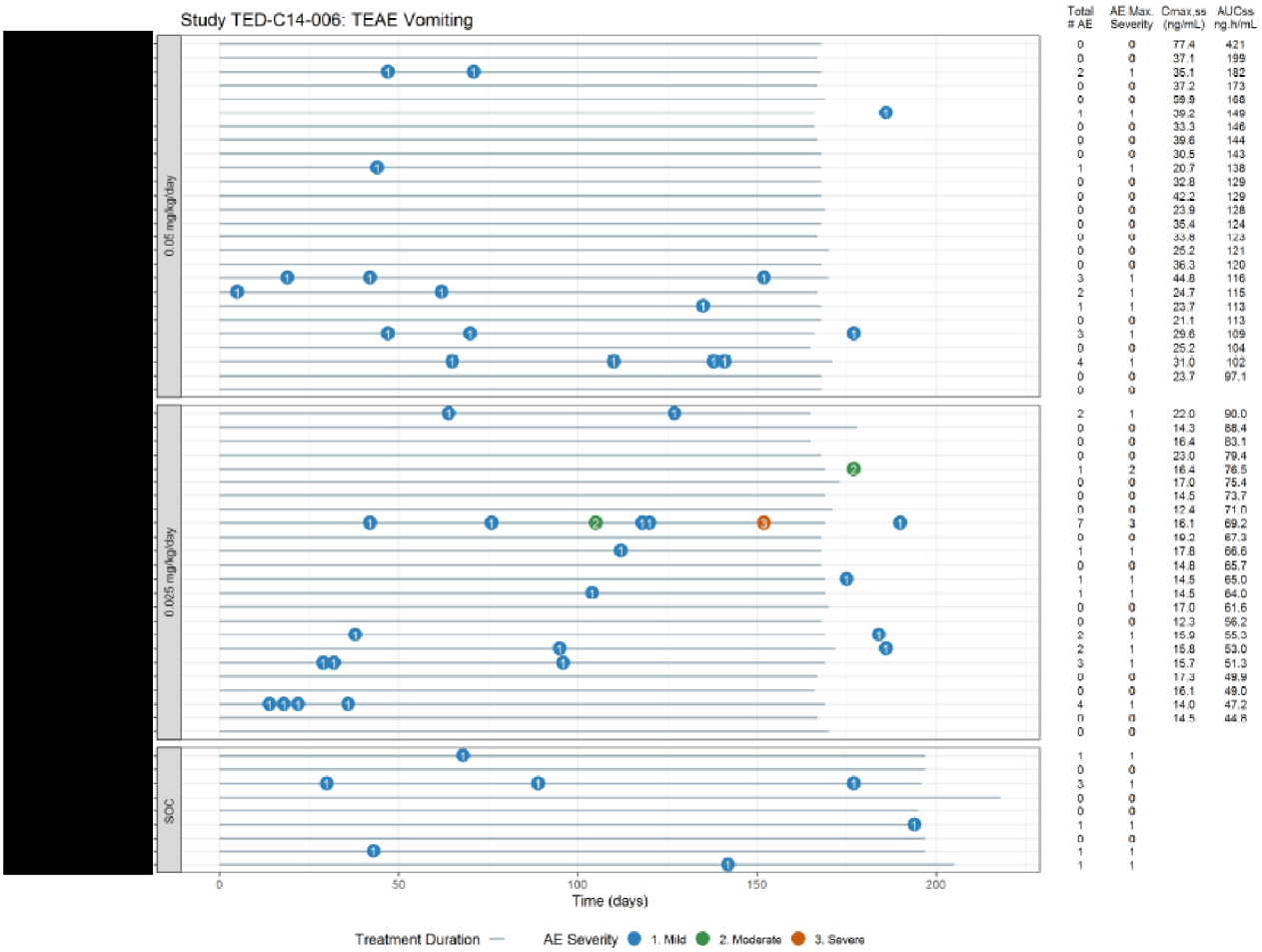
AE= adverse event; AUC_{ss} = area under the curve at steady state; $Cmax_{ss}$ = maximum concentration at steady state; Max= maximum; SOC= standard of care; TEAE= treatment emergent adverse event

Figure 4 Occurrence of Vomiting Pain over Time and PK Parameters of Teduglutide – Study TED-C13-003



AE= adverse event; AUC_{ss} = area under the curve at steady state; $Cmax_{ss}$ = maximum concentration at steady state; Max= maximum; SOC= standard of care; TEAE= treatment emergent adverse event

Figure 5 Occurrence of Vomiting Pain over Time and PK Parameters of Teduglutide – Study TED-C14-006



AE= adverse event; AUC_{ss} = area under the curve at steady state; $Cmax_{ss}$ = maximum concentration at steady state; Max= maximum; SOC= standard of care; TEAE= treatment emergent adverse event

The agency recommended the use of a logistic regression to assess the probability of TEAE. Logistic regression can only be used for binary outcomes. For example, the probability of subject to experience at least 1 TEAE can be assessed using logistic regression analyses.

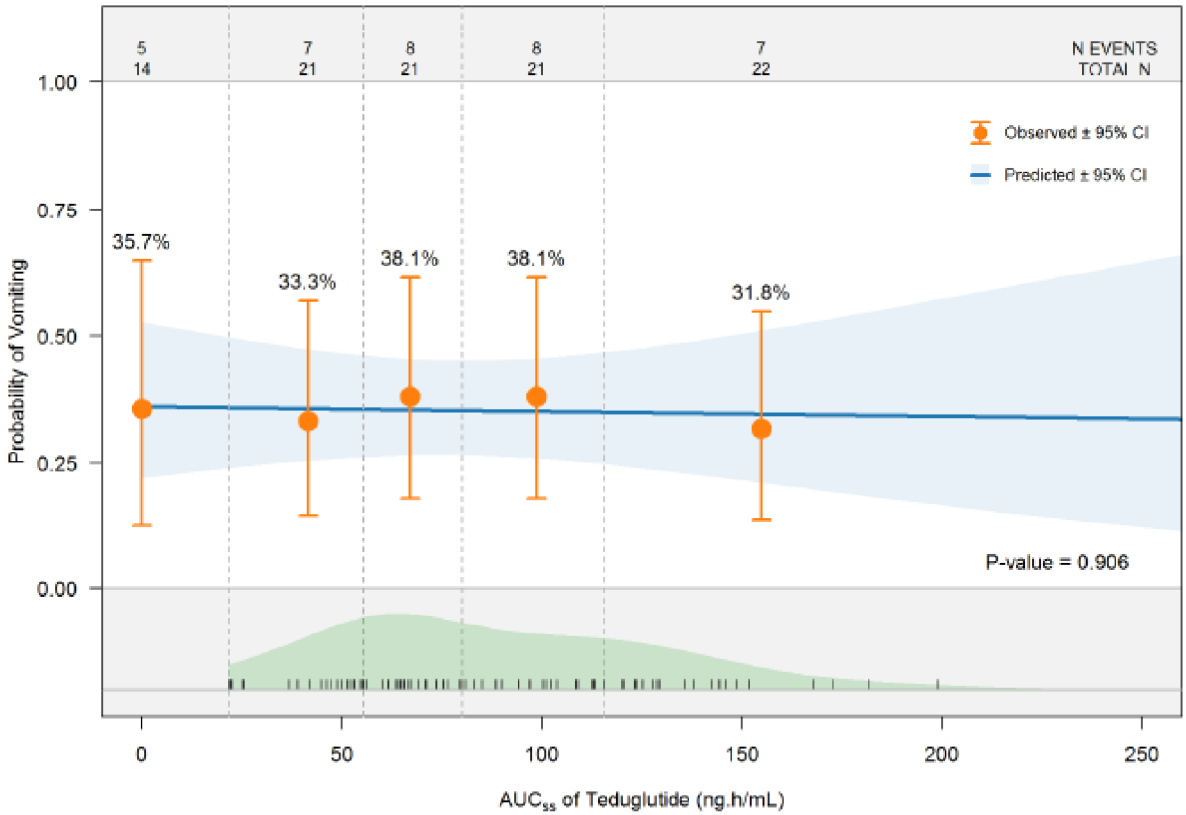
In order to take into account multiple TEAE over time, repeated time-to-event Cox models including teduglutide exposures and random effect (i.e. frailty model) were developed. Results derived with the repeated time-to-event Cox models with random effect were presented after the logistic regression analysis.

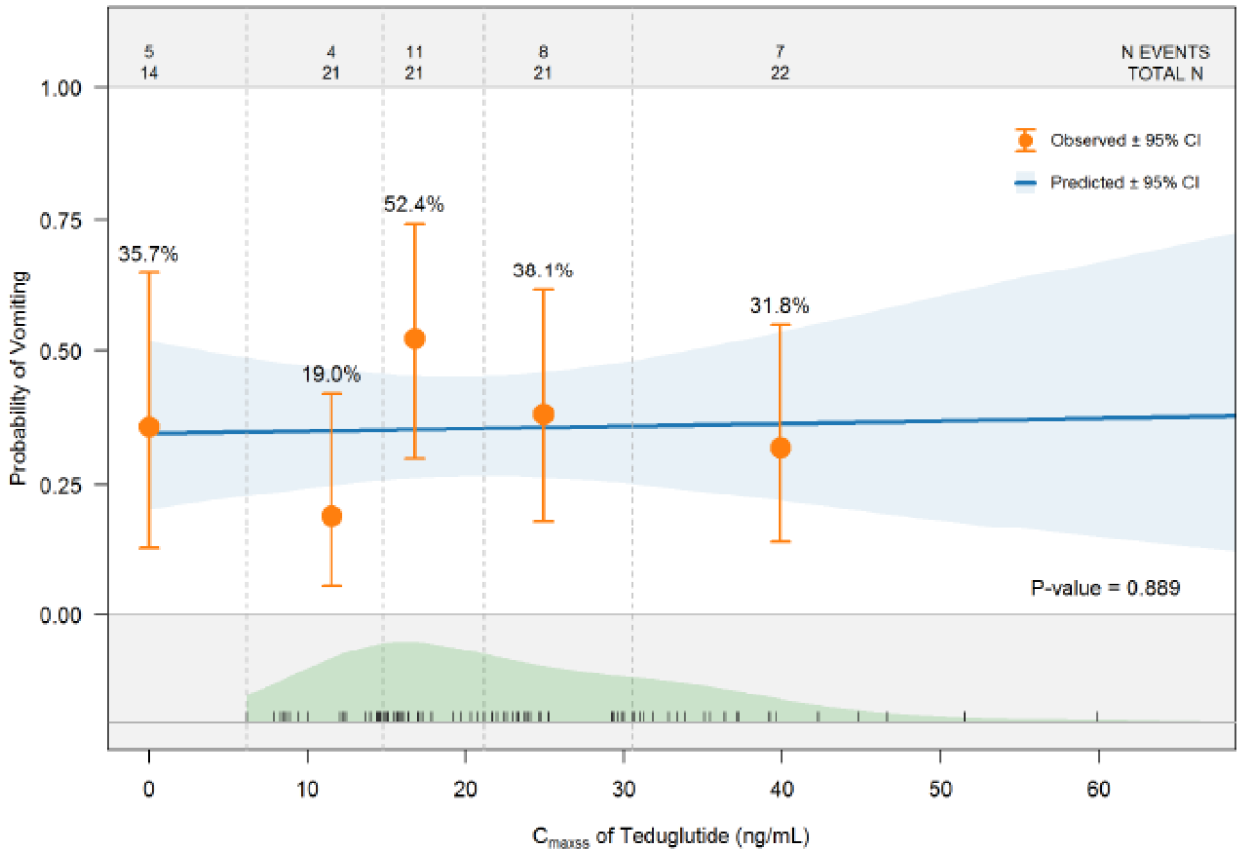
Logistic Regression Model (A Least 1 Instance of TEAE)

The relationship between teduglutide exposure (AUC_{ss} and $C_{max,ss}$) and the probability of vomiting is presented in Figure 6. No statistically significant relationship was observed ($p>0.05$).

The relationship between teduglutide exposure (AUC_{ss} and $C_{max,ss}$) and the probability of abdominal pain is presented in Figure 7. No statistically significant relationship was observed ($p>0.05$).

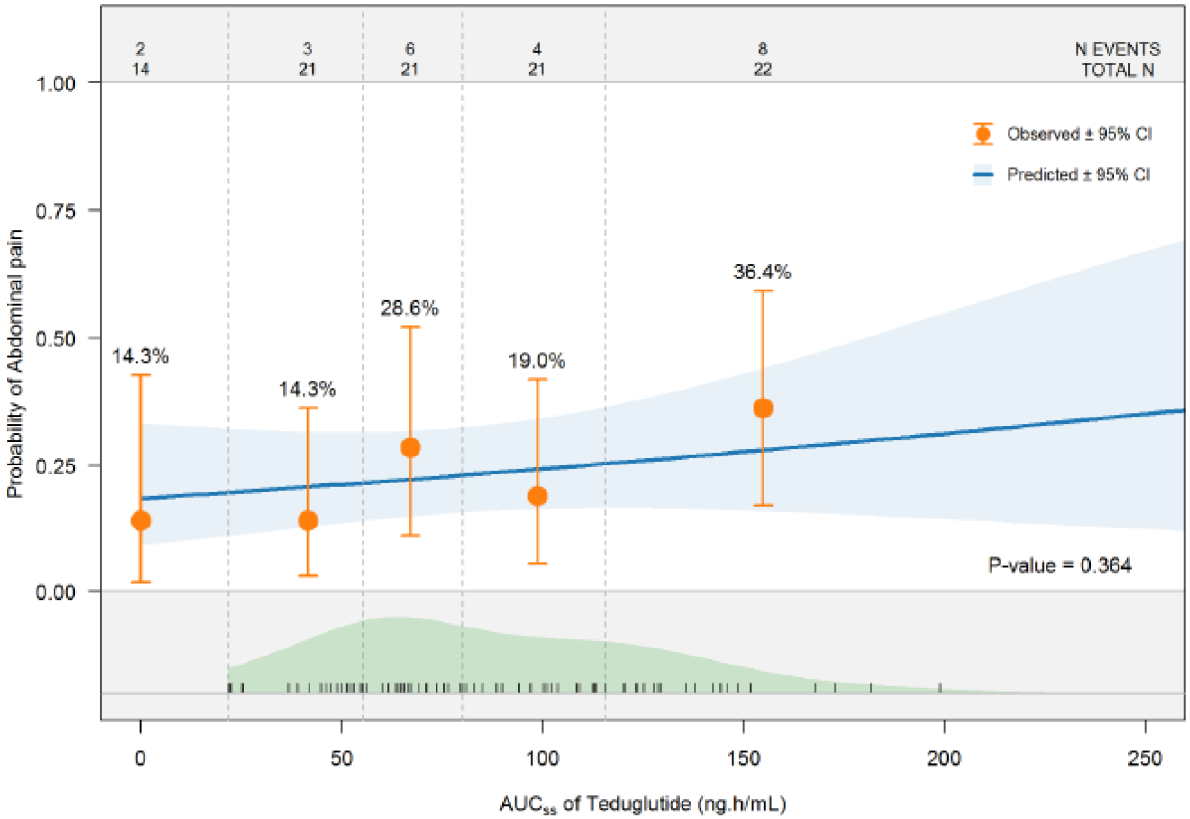
Figure 6 Logistic Regression - Relationship Between Teduglutide Exposure and Vomiting

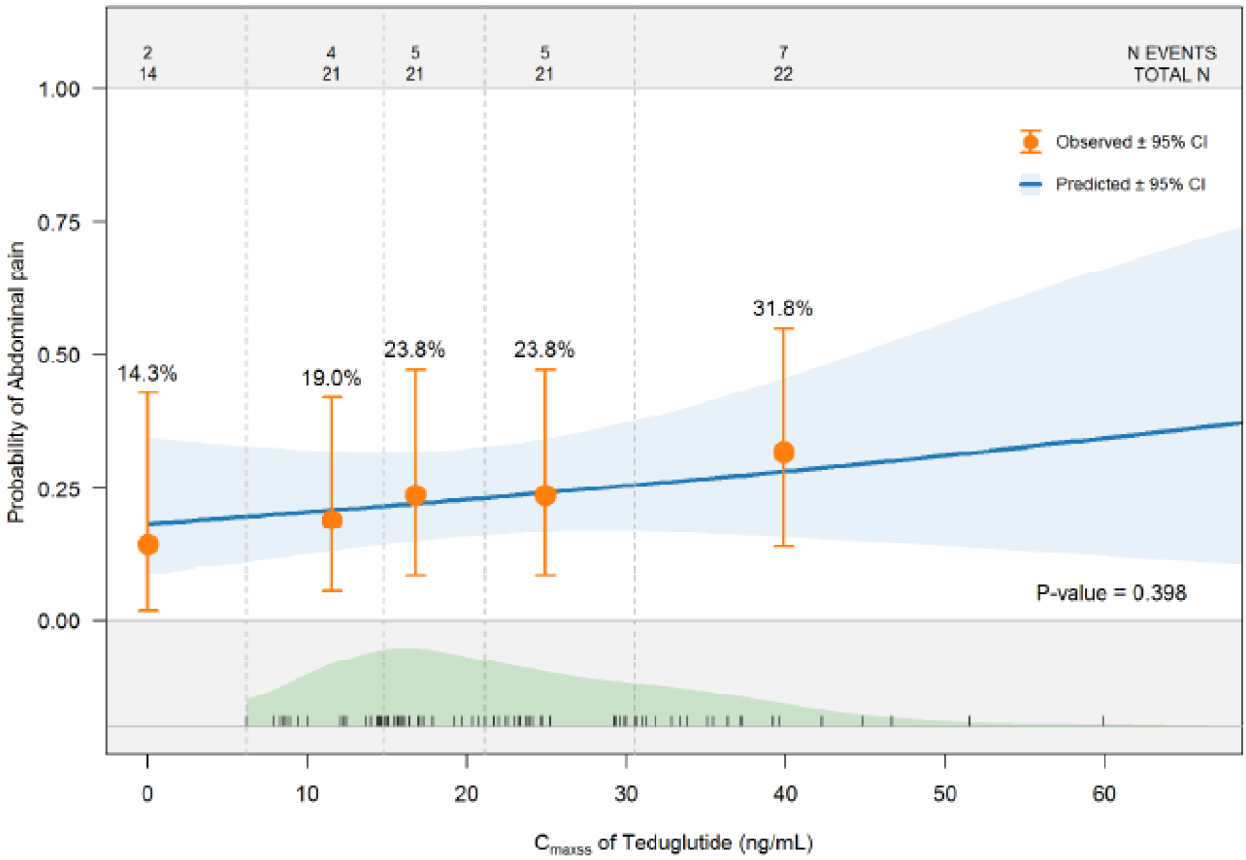




AUC_{ss} = area under the curve at steady state; CI= confidence interval; C_{maxss} = maximum concentration at steady state; N= number
Green area = Kernel density estimate of the distribution of exposure; Dark vertical bars = individual posthoc values in treated subjects

Figure 7 Logistic Regression - Relationship Between Teduglutide Exposure and Abdominal Pain





AUC_{ss} = area under the curve at steady state; CI= confidence interval; C_{maxss} = maximum concentration at steady state; N= number
Green area = Kernel density estimate of the distribution of exposure; Dark vertical bars = individual posthoc values in treated subjects

Time-to-Event Cox Model for Repeated Instances of Adverse Events

In order to take into account multiple TEAE over time, repeated time-to-event Cox models including teduglutide exposures and with random effect (frailty model) were developed. In addition, the model included a frailty (i.e., random effect) in order to take into account the correlation between repeated instances of TEAE over time.

The model used here can be expressed as

$$h_i(t) = h_0(t) Z_i \exp(\beta x_i)$$

where $h_i(t)$ is the hazard function for the TEAE at time t for the i^{th} subject, $h_0(t)$ is the baseline hazard, x_i is teduglutide dose or exposure for the i^{th} subject, β is the regression coefficient related to x_i, and Z_i is a subject-specific random effect known as the frailty term, assumed to follow a gamma distribution with mean equal to 1 and unknown variance to be estimated. The frailty term accounts for differences is susceptibility between subjects with the same level of exposure; i.e., some subjects have no events, while others have many. It is further assumed that the recurrent event times are independent conditional on the covariates and random effects.

Parameters derived with the time-to-event Cox models are presented in Table 6.

Table 6 Model Parameters - Time-to-Event Cox Models

Adverse Events	Parameters	Coefficient	SE(coefficient)	SE^2	Chi square	Degree of Freedom	p-value
Vomiting	AUCss	0.006399	0.004393	0.002793	2.12	1.00	0.150
	Frailty				162.82	66.79	<0.001
	$C_{max,ss}$	0.03824	0.01498	0.009017	6.52	1.00	**0.011**
	Frailty				137.28	61.89	<0.001
Abdominal Pain	AUCss	0.01025	0.00612	0.003298	2.8	1.00	0.094
	Frailty				127.4	64.52	<0.001
	$C_{max,ss}$	0.03652	0.02343	0.01168	2.43	1.00	0.120
	Frailty				130.18	65.11	<0.001

AUC_{ss} = area under the curve at steady state; $C_{max,ss}$ = maximum concentration at steady state; Frailty(id) = individual random effect; SE = standard error

A statistically significant association was observed between the $C_{max,ss}$ of teduglutide and the probability of vomiting (p=0.011). For abdominal pain, no statistically significant association was observed for exposure parameters (AUC_{ss} or $C_{max,ss}$). Individual random effects (frailty terms) were statistically significant in all models suggesting an important correlation between repeated instances of TEAE over time within patients.

Assessment of the MAH's response

The Applicant has presented appropriate statistics analyses, which emphasises the relation between the $C_{max,ss}$ of teduglutide and the probability of vomiting. For abdominal pain, no statistically significant association was found for exposure parameters. Individual random effects were also statistical significant suggesting an important correlation between repeatd instances of TEAE over time within patients.

Conclusion

The Question is considered resolved.

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

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

Question 7

The MAH has discussed the causalities between the teduglutide exposure and TESAEs as requested. Herein, two events of faecaloma. After further evaluation the MAH suggests that faecaloma may not to be the most accurate term to describe the event. The MAH should should therefore correct the term which should also be reflected in the SmPC section 4.8.

MAH's response

Based on follow up information received by the investigator on 24 July 2018, it was confirmed that faecaloma was not the most accurate term to describe the event. The term has, therefore, been updated to Feaces Hard. Furthermore, it has been confirmed that there was 1 SAE of Faecaloma not 2 counts as previously recorded (due to duplicate entry by the site). Therefore, 1 event of 'Faecaloma' (now updated to 'Faeces hard') was reported by 1 subject.

Analysis of Similar Events: As of 30 June 2018, there have been no SAE reports of Abnormal Faeces/ Faeces Hard identified in subjects exposed to active drug for any open US IND for the product. There have been 2 SAE reports of *Abnormal Faeces/Faeces Hard* identified in post-marketing setting. One of these 2 reports ("Hardening of her stool") was solicited and the other (Foul smelling bowel movements with no mention of the consistency of stool) was spontaneously reported. Causality by the investigator is unknown but deemed unlikely related by the Shire to SHP633 (teduglutide) due to alternate explanation for stool consistency and odor. The exposure from February 2013 - May 2018 data suggests approximately 698 subjects were exposed to active drug or blinded drug in Shire-sponsored studies and an estimated 3,907 person-years exposure in the post-marketing setting.

Based on the Analysis of Similar Events, there is insufficient evidence to support an update to SmPC to include *'Faeces hard'* in section 4.8.

Assessment of the MAH's response

The Applicant has changed the term "Faecaloma" to "Feaces Hard", which is endorsed. Furthermore, based on an Analysis of Similar Events, the Applicant found insufficient evidence to support an update to SmPC to include 'Faeces hard' in section 4.8, which is found acceptable.

Conclusion

The Question is considered resolved.

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

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

14. 3rd request for supplementary information

14.1. Major objections

1. The MAH argues that the POP PK model was based on plasma concentrations from 4 pediatric subjects aged 1-<2 years of age, and that "the coefficient of variability (CV%) of CL/F and Vc/F of teduglutide was very low in pediatric subjects 1 to < 2 years (6.7% and 14.8%, respectively)", which is acknowledged. Of notice, the Applicant has not provided information about the total number of plasma concentrations included in the full POP PK model from pediatric subjects aged 1-< 2 years. Furthermore, in the simulations of S.C. dose 0.05 mg/kg (Table 2 and 3), previously presented in the responses to questions 2. and 4., only one child 1-< 2 years was included. Additionally in Figure 6 in the response to question 6, only four plasma concentrations were presented representing the one child included. Thus data is still considered to limited to support the proposed changes to the SmPC. As staten in the assessment of the SmPC, the Applicant should reword the text in SmPC section 4.2, and in addition the Applicant should make the prescriber aware of the limited data in children < 2 years in the SmPC section 5.1. (**MO**).

14.2. Other concerns

2. The Applicant did not answer whether there might exist a social gradient between the teduglutide treatment arm and the SOC arm, that could include a selection bias. The Applicant should elaborate on this issue before the question can be considered fully resolved. (**OC**).

15. Assessment of the responses to the 3rd request for supplementary information

15.1. Major objections

Question 1

The MAH argues that the POP PK model was based on plasma concentrations from 4 pediatric subjects aged 1-<2 years of age, and that "the coefficient of variability (CV%) of CL/F and Vc/F of teduglutide was very low in pediatric subjects 1 to < 2 years (6.7% and 14.8%, respectively)", which is acknowledged. Of notice, the Applicant has not provided information about the total number of plasma concentrations included in the full POP PK model from pediatric subjects aged 1-< 2 years. Furthermore, in the simulations of S.C. dose 0.05 mg/kg (Table 2 and 3), previously presented in the responses to questions 2. and 4., only one child 1-< 2 years was included. Additionally in Figure 6 in the response to question 6, only four plasma concentrations were presented representing the one child included. Thus data is still considered to limited to support the proposed changes to the SmPC. As staten in the assessment of the SmPC, the Applicant should reword the text in SmPC section 4.2, and in addition the Applicant should make the prescriber aware of the limited data in children < 2 years in the SmPC section 5.1.

MAH's response

PK Samples Collected in Studies TED-C13-003 and TED-C14-006

The population PK model included PK data collected in pediatric subjects from two clinical studies (TED-C13-003 and TED-C14-006). The planned blood collection timepoints were as follow:

- TED-C13-003 (N=6 per subject; N= 219 samples in total):
    - Week 1: Pre-dose, and at 1 and 6 hours post-dose
    - Week 4: Pre-dose, and at 2 and 4 hours post-dose
- TED-C14-006 (N=4 per subject; N=187 samples in total):
    - Pre-dose, at 1, 2 and 4 hours post-dose at start of treatment

Study TED-C13-003 and Time-Independency Assessment

A total of 6 PK samples were collected for assessment of teduglutide PK in each patient 1-<2 years in study TED-C13-003. In which, a total of 3 patients 1-<2 years were enrolled.

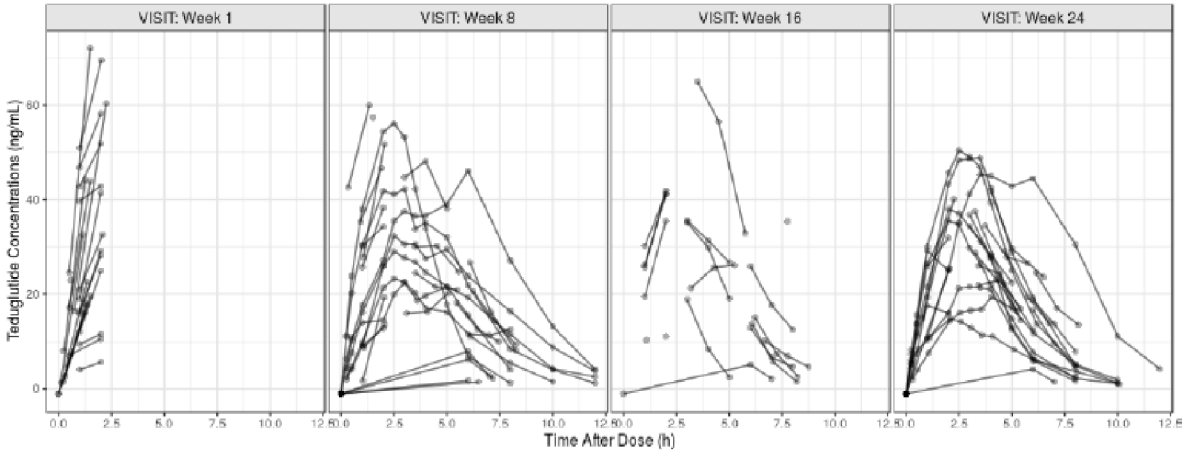
As a result, a total of 18 samples collected at Week 1 and Week 4 were available in patients 1-<2 years enrolled in study TED-C13-003.

The time-independent properties of teduglutide were previously demonstrated as part of a population PK analysis based on the clinical package. The time-independent properties of teduglutide in adult patients (study CL0600-004), older pediatric patients (2-17 years, TEDC13-003), and younger pediatric patients (1-<2 years, study TED-C13-003) are discussed below.

Time-Independency Analysis in Adult Patients with SBS

Individual observed concentration-time profiles of teduglutide in adult patients with SBS in study CL0600-004 (0.05 mg/kg dose only) are presented for each Visit in Figure 1.

Figure 1. Concentration-Time Profiles of Teduglutide in Adult Patients - Study CL0600-004 – By Visit on Linear Scale



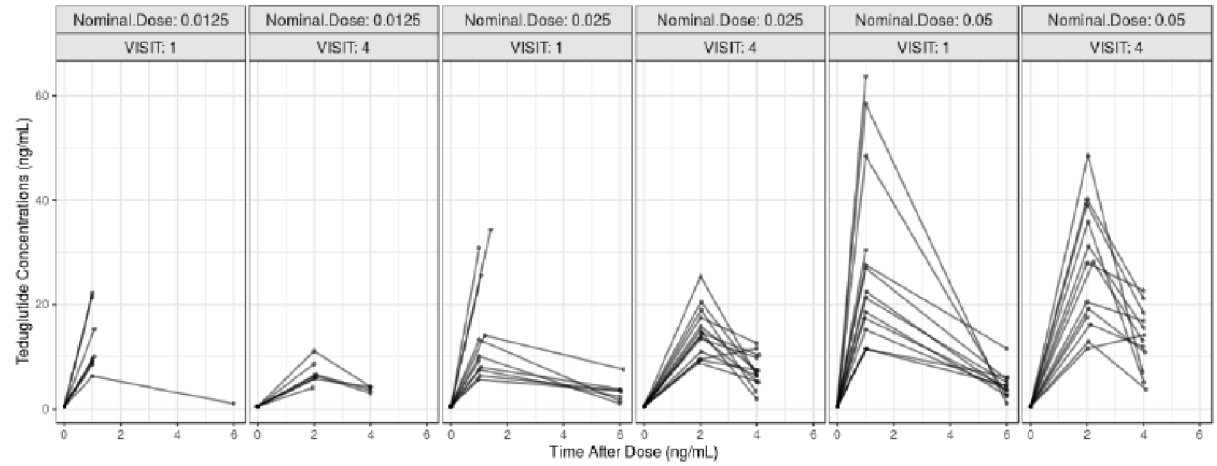
Note: Values below the limit of quantitation (1 ng/mL) were set to 0.5 ng/mL.

The PK properties of teduglutide did not change over time and no accumulation was observed following repeated administration of teduglutide SC daily in adult patients with SBS for up to 24 weeks. These results, along with those PK parameters derived as part of the population PK analysis, confirmed the time-independency in PK properties of teduglutide.

Time-Independency Analysis in Older Pediatric Patients (2–17 years) with SBS

Individual concentration-time profiles of teduglutide in older pediatric patients (2-17 years) at Week 1 and Week 4 in study TED-C13-003 (0.0125, 0.025 and 0.05 mg/kg) are presented in Figure 2.

Figure 2. Concentration-Time Profiles of Teduglutide in Older Pediatric Patients (2 - 17 years) - Study TED-C13-003 – Linear Scale



Note: Visit 1 (Day 1, Week 1), Visit 4 (Week 4). Values below the limit of quantitation (1 ng/mL) were set to 0.5 ng/mL.

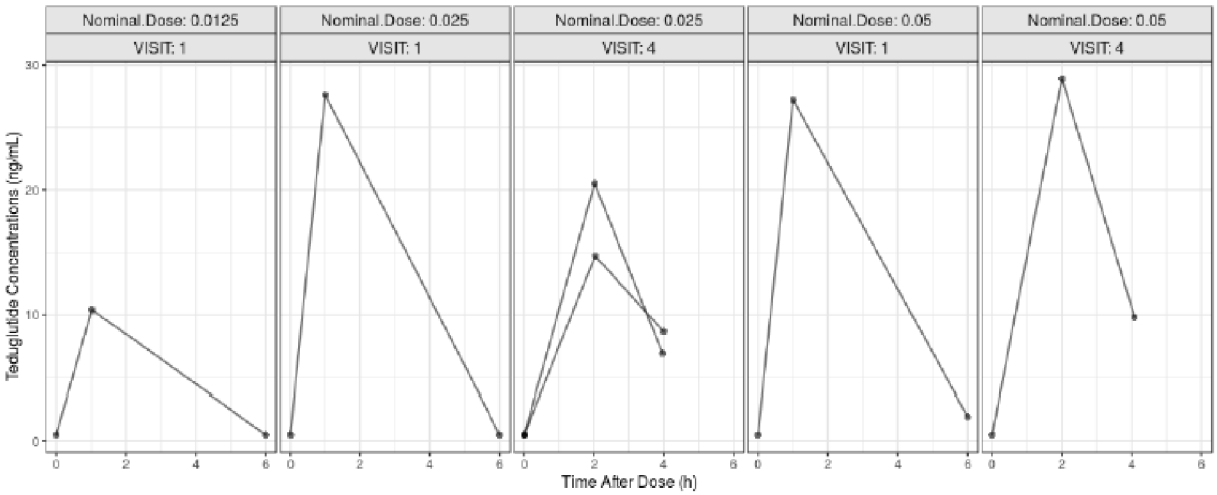
Similar to what was observed in adult patients, the PK properties of teduglutide did not change over time and no accumulation was observed following repeated administration of teduglutide SC daily in older pediatric patients (2-17 years) with SBS for up to 4 weeks.

These results, along with those PK parameters derived as part of the population PK analysis, further confirmed the time-independency in PK properties of teduglutide in older pediatric patients (2-17 years).

Time-Independency Analysis in Younger Pediatric Patients (1-< 2 Years) with SBS

Individual concentration-time profiles of teduglutide in younger pediatric patients (1-<2 years) at Week 1 and Week 4 in study TED-C13-003 (0.0125, 0.025 and 0.05 mg/kg) are presented in Figure 3.

Figure 3. Concentration-Time Profiles of Teduglutide in Younger Pediatric Patients (1 - <2 years) - Study TED-C13-003 – Linear Scale



Note: Visit 1 (Day 1, Week 1), Visit 4 (Week 4). Values below the limit of quantitation (1 ng/mL) were set to 0.5 ng/mL.

Note: Patient [redacted] received 0.0125 mg/kg at Visit 1 and 0.025 mg/kg at Visit 4.

Patient [redacted] received 0.05 mg/kg at Visit 1 and 4.

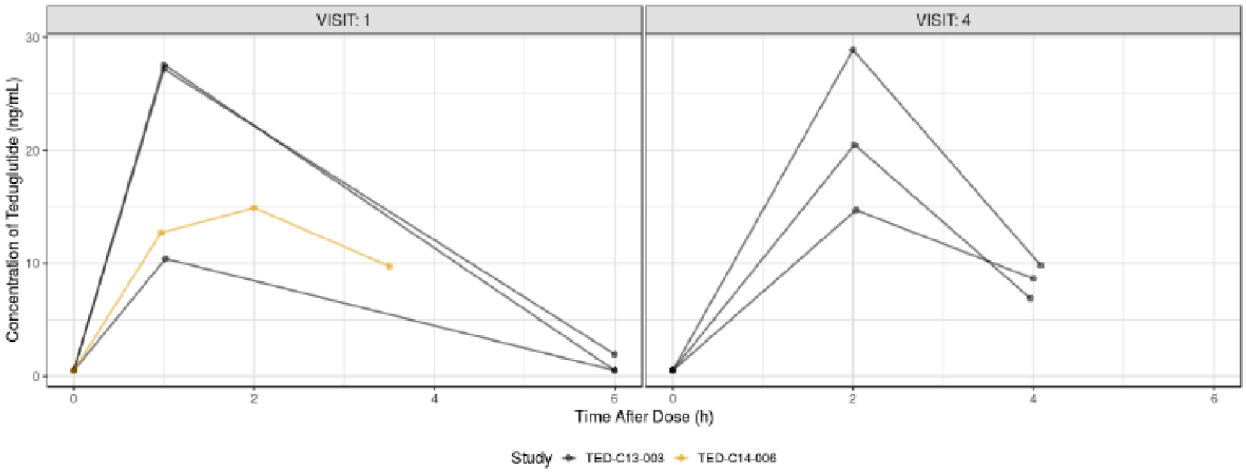
Patient [redacted] received 0.025 mg/kg at Visit 1 and 4.

Similar to what was observed in older pediatric patients (2-17 years), the PK properties of teduglutide did not change over time and no accumulation was observed following repeated administration of teduglutide SC daily in younger pediatric patients (1-<2 years). These results, along with those PK parameters derived as part of the population PK analysis, confirmed the time-independency in PK properties of teduglutide in younger pediatric patients (1-<2 years).

Study TED-C14-006

A total of 4 PK samples were collected for assessment of teduglutide concentration in a single patient in study TED-C14-006 (Day 1). The concentration-time profiles of teduglutide in a single patient 1-<2 years (0.05 mg/kg) relative to those observed in patient 1-<2 years from TED-C13-003 (all dose levels) are presented in Figure 4.

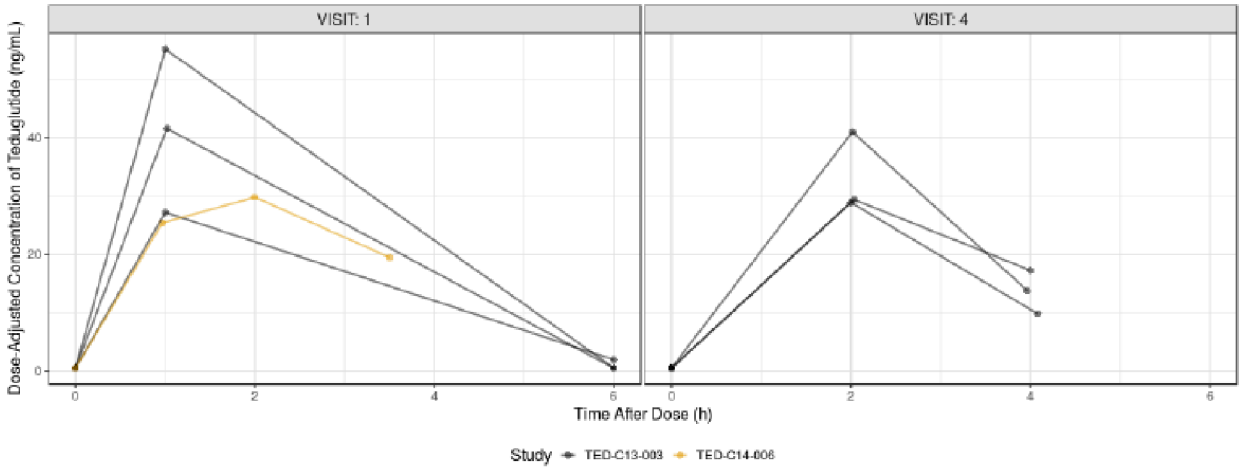
Figure 4. Concentration-Time Profiles of Teduglutide - Patient 1-<2 years in Study TED-C14-006 and TED-C13-003 Linear Scale



Note: Visit 1 (Day 1, Week 1), Visit 4 (Week 4). Values below the limit of quantitation (1 ng/mL) were set to 0.5 ng/mL.
Note: Patient [redacted] received 0.0125 mg/kg at Visit 1 and 0.025 mg/kg at Visit 4.
Patient [redacted] received 0.05 mg/kg at Visit 1 and 4.
Patient [redacted] received 0.025 mg/kg at Visit 1 and 4.

The concentration-time profiles of dose-adjusted teduglutide in a single patient 1-<2 years (0.05 mg/kg) relative to those (dose-adjusted teduglutide) observed in patient 1-<2 years from TED-C13-003 (all dose levels) are presented in Figure 5.

Figure 5. Dose-Adjusted Concentration-Time Profiles of Teduglutide - Patient 1-<2 years in Study TED-C14-006 and TED-C13-003 - Linear Scale



Note: Visit 1 (Day 1, Week 1), Visit 4 (Week 4). Values below the limit of quantitation (1 ng/mL) were set to 0.5 ng/mL.

Note: Patient [redacted] received 0.0125 mg/kg at Visit 1 and 0.025 mg/kg at Visit 4.

Patient [redacted] received 0.05 mg/kg at Visit 1 and 4.

Patient [redacted] received 0.025 mg/kg at Visit 1 and 4.

Note: Concentrations for the 0.025 and 0.0125 were adjusted for a 0.05 mg/kg dose (i.e., concentrations were multiplied by 2 and 4, respectively)

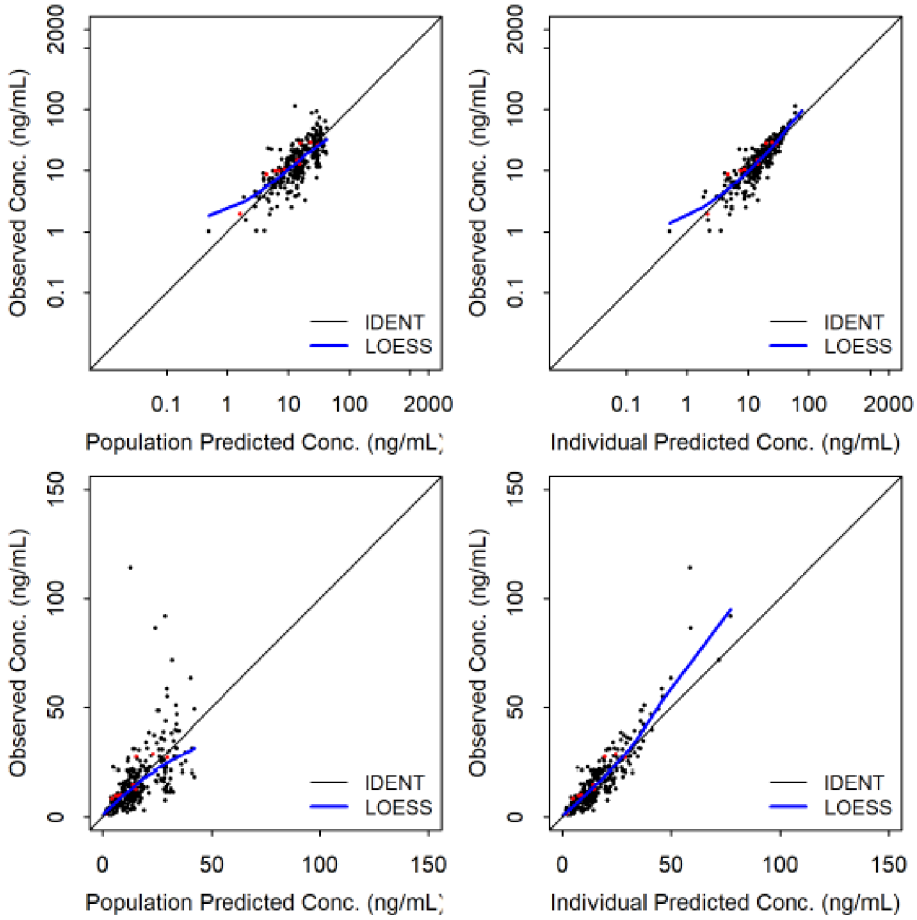
As expected, the PK concentrations of teduglutide in the single patient 1-<2 years were comparable to those observed in the same age patients (TED-C13-003).

Given the PK time-impendency properties of teduglutide in patients with SBS, data collected in one patient 1-<2 years in Study TED-C14-006 are reasonably combined with other 3 patients 1-<2 years for PK, efficacy and safety evaluation, supporting an extrapolation between pediatric patent groups and between pediatric patients and adult patients, especially for patients with SBS.

Population PK Analysis

The population PK model provided an adequate goodness-of-fit of teduglutide concentrations in pediatric patients enrolled in studies TED-C13-003 and TED-C14-006. Overall, PK parameters in patients 1-<2 years were well characterized with the population PK model as presented in Figure 6.

Figure 6. Goodness-of-Fit Plots: Final Population PK Model Including M3 Method – Study TED-C13-003 and TED-C14-006



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. Samples collected between the first dose and the lag timeof absorption had PRED and IPRED=0. Those samples are not presented on the log-scale plots. Red and black circles represent the observed concentrations in patients 1-<2 years and 2-17 years, respectively.

PK parameters of teduglutide in various age groups are presented in Table 1. Since time-independency has been confirmed across pediatric age groups and pediatric and adult populations, the population PK modeling and simulation approach has provided basis (along with other clinical observations) for the extrapolation between the populations.

Table 1. Descriptive Statistics of Teduglutide Parameters in Patients with SBS Following SC Dosing by Each Age Category (All dose levels)

Age Group	Statistic	CL/F (L/h)	Vc/F (L)	Ka (h^{-1})	Half-Life (h)
> 18 years	n	85	85	85	85
	Mean	13.5	23.3	0.359	1.28
	SD	4.76	8.77	0.0960	0.523
	CV%	35.3	37.7	26.7	40.9
	Median	12.8	22.3	0.349	1.24
	Min	5.14	2.06	0.174	0.150
	Max	39.7	48.9	0.543	3.21
12-17 years	n	7	7	7	7
	Mean	13.1	20.0	0.373	1.06
	SD	1.56	3.73	0.0916	0.166
	CV%	11.9	18.7	24.6	15.7
	Median	13.3	20.4	0.382	0.959
	Min	11.0	15.0	0.269	0.894
	Max	15.6	25.8	0.483	1.34
8-11 years	n	18	18	18	18
	Mean	9.97	11.9	0.452	0.823
	SD	1.67	3.38	0.113	0.186
	CV%	16.8	28.4	25.0	22.7
	Median	10.2	11.2	0.419	0.814
	Min	6.23	5.10	0.337	0.568
	Max	12.6	18.5	0.793	1.32
6-7 years	n	11	11	11	11
	Mean	7.52	7.28	0.550	0.678
	SD	1.38	1.81	0.106	0.166
	CV%	18.3	24.8	19.2	24.5
	Median	7.11	7.11	0.532	0.641
	Min	5.75	5.12	0.412	0.469
	Max	10.1	10.1	0.718	1.10

Age Group	Statistic	CL/F (L/h)	Vc/F (L)	Ka (h^{-1})	Half-Life (h)
4-5 years	n	20	20	20	20
	Mean	7.22	6.69	0.541	0.641
	SD	0.667	1.44	0.0864	0.122
	CV%	9.2	21.6	16.0	19.0
	Median	7.24	6.85	0.520	0.664
	Min	5.58	4.38	0.434	0.440
	Max	8.66	9.12	0.772	0.825
2-3 years	n	25	25	25	25
	Mean	6.23	5.01	0.649	0.602
	SD	1.77	1.31	0.130	0.254
	CV%	28.5	26.2	20.0	42.3
	Median	5.92	4.55	0.609	0.536
	Min	1.64	3.22	0.484	0.316
	Max	9.99	7.99	0.967	1.64
1-< 2 years	n	4	4	4	4
	Mean	5.37	4.19	0.717	0.542
	SD	0.360	0.620	0.0383	0.0913
	CV%	6.7	14.8	5.3	16.8
	Median	5.28	4.04	0.706	0.513
	Min	5.06	3.64	0.688	0.468
	Max	5.87	5.03	0.769	0.675

Conclusions

Based on the above discussions, similarity in dose-exposure response PK properties (time-independency), similarity in clinical manifestation and treatment of the disease, and clinical efficacy and safety observations between pediatric age groups and between pediatric and adult populations for up to 24 weeks of treatment, Shire believes that clinical observations obtained in four1-<2 year pediatric subjects (3 subjects were studied in TED-C13-003 and 1 subject was studied in TED-C14-006), although limited, are sufficient to support an extrapolation between populations and support safe and efficacious SC daily dose of 0.05 mg/kg in pediatric patients with SBS (1-<2 years) and to support the proposed changes to the SmPC.

Assessment of the MAH's response

The Applicant has argued that the clinical observations obtained in: "*obtained in four 1-<2 year pediatric subjects (3 subjects were studied in TED-C13-003 and 1 subject was studied in TED-C14-006),*" is sufficient to support extrapolation between populations. However, such an extrapolation is based on several assumptions, and thus paediatric data from four patients in the specifically vulnerable age group <2 years is still considered too limited.

Thus, the following wording in section 4.2 in the SmPC could be acceptable:

"A treatment period of 6 months is recommended after which treatment effect should be evaluated. In children below the age of two years, treatment should be evaluated after 12 weeks. There are no data available in paediatric patients after 6 months."

The Applicant is though encouraged to introduce the data and results for the respective age group in the SmPC section 5.1 in accordance to the SmPC guideline.

Conclusion

The question is partly solved.

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

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

15.2. Other concerns

Question 2

The Applicant did not answer whether there might exist a social gradient between the teduglutide treatment arm and the SOC arm, that could include a selection bias. The Applicant should elaborate on this issue before the question can be considered fully resolved.

MAH's response

The MAH considers that the likelihood of social factors resulting in a selection bias in the teduglutide treatment arm and the SOC arm of study TED-C14-006 to be in line with other drug development programs and unlikely to have significantly influenced the safety or efficacy conclusions.

Historically, certain racial or ethnic minorities have been more likely to be suspicious of participating in clinical trials for various reasons, including: historical instances of exploitation, lack of access to affordable healthcare insurance which limited interactions with healthcare professionals or led to seeking care at under-resourced hospitals, and work in hourly jobs that provide less scheduling flexibility. Despite this, the racial and ethnic distributions in the overall study population were reflective of the countries in which the study was conducted: 24% of total subjects were Hispanic or Latino, 12% of total subjects were Black or African American, 5% of total subjects were Asian, and 5% of total subjects had a race of "Other".

It is acknowledged that the racial and ethnic distribution of subjects was more diverse in the SOC arm, but such differences do not necessarily indicate a gradient in social determinants of health, which include income, level of education, residential segregation, social support, transportation options, public safety, native language, and literacy. These variables were not captured in the TED-C14-006 study.

Study investigators were expected to present the choice of treatment arm in the same manner to all subjects. The support provided for transportation and reimbursement for lodging and meals for study-related visits was the same for both study arms and investigators were to follow the same nutritional support adjustment algorithm for all subjects, regardless of treatment arm.

An integrated analysis of safety data from the TED-C13-003 and the TED-C14-006 studies compared the frequencies of TEAEs, SAEs, anti-teduglutide antibodies, as well as markedly abnormal chemistry and hematology values according to "white" and "non-white" race. No clear racial differences were observed in any of these safety outcomes.

In conclusion, it is unknown but unlikely that there was a difference between treatment arms in social determinants of health. Furthermore, it is unlikely that any social gradient, if present, would have affected the evaluation of safety or efficacy in study TED-C14-006.

Assessment of the MAH's response

The Applicant has argued that it is unlikely that a social gradient has effected the evaluation of efficacy or safety in the study. However, due to the study-design with a non-random selection into the study-arms, some children would probably be less likely to be included in the treatment arms than others. The Applicant has clarified that study investigators were expected to present the choice of treatment arm in the same manner to all subjects, and that the support provided for transportation and reimbursement for lodging and meals for study-related visits was the same for both study arms etc. It is acknowledged that these initiatives most likely has reduced the magnitude of the selection bias, which is though not eliminated. However, the issue will not be further pursued.

Conclusion

The Question is considered solved.

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

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

16. 4th request for supplementary information

- The MAH should update the wording in the SmPC section 4.2 to the following:

  "A treatment period of 6 months is recommended after which treatment effect should be evaluated. In children below the age of two years, treatment should be evaluated after 12 weeks. There are no data available in paediatric patients after 6 months."

- The Applicant should introduce the data and results for the respective age group in the SmPC section 5.1 in accordance to the SmPC guideline.

17. Assessment of the responses to the 4th request for supplementary information

Question 1

The MAH should update the wording in the SmPC section 4.2 to the following:

"A treatment period of 6 months is recommended after which treatment effect should be evaluated. In children below the age of two years, treatment should be evaluated after 12 weeks. There are no data available in paediatric patients after 6 months."

MAH response

The MAH accepts revisions to the text as requested by the assessor.

Assessment of the MAH's response

Issue resolved.

Conclusion

The Question resolved.

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

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

Question 2

The Applicant should introduce the data and results for the respective age group in the SmPC section 5.1 in accordance to the SmPC guideline.

MAH response

The MAH's opinion is that the sample sizes are too small to draw meaningful statistical comparisons across age groups, and proposes not to present results divided by age groups. In order to address the assessor's concern, the sponsor proposes the following revisions to the text, which provide an accurate statement of the efficacy findings, including limitations of the paediatric database:

"Paediatric population

The efficacy data presented are derived from 2 controlled studies in paediatric patients up to 24 weeks duration. These studies included 101 patients in the following age groups: 5 patients 1-2 years, 56 patients 2 to <6 years, 32 patients 6 to <12 years, 7 patients 12 to <17 years, and 1 patient 17 to <18 years. Despite the limited sample size, clinically meaningful reductions in the requirement for parenteral support were observed across all age groups."

Assessment of the MAH's response

The MAH finds that the sample size is too small to draw meaningful statistical comparisons across age groups, and the MAH thus suggest the text revision as follows marked with tracked changes:

The efficacy data presented are derived from 2 controlled studies in paediatric patients up to 24 weeks duration. These studies included 101 patients in the following age groups: 5 patients 1-2 years, 56 patients 2 to <6 years, 32 patients 6 to <12 years, 7 patients 12 to <17 years, and 1 patient 17 to <18 years. Despite the limited sample size, clinically meaningful, reductions in the requirement for parental support were observed across all age groups."

In order to stress that no formal statistical comparison was made, the text added should be revised as follows (marked in blue):

"Despite the limited sample size, which did not allow meaningful statistical comparisons, clinically meaningful, numerical reductions in the requirement for parental support were observed across all age groups."

Conclusion

The Question is considered solved provided that the text is amended as indicated.

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

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

MAH response

The MAH accepts revisions to the text as requested by the assessor.

Assessment of the MAH's response

Issue resolved.

Conclusion

The Question resolved.

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

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

18. Attachments

1. Product information (changes highlighted) as adopted by the CHMP on 13 December 2018

Reminders to the MAH

1. The MAH is reminded to submit an eCTD closing sequence with the final documents provided by Eudralink during the procedure (including final PI translations, if applicable) within 15 days after the Commission Decision, if there will be one within 2 months from adoption of the CHMP Opinion, or prior to the next regulatory activity, whichever is first. If the Commission Decision will be adopted within 12 months from CHMP Opinion, the closing sequence should be submitted within 30 days after the Opinion. For additional guidance see chapter 4.1 of the *Harmonised Technical Guidance for eCTD Submissions in the EU*.

2. In accordance with Article 13(3) of Regulation (EC) No 726/2004 the Agency makes available a European Public Assessment Report (EPAR) on the medicinal product assessed by the Committee for Medicinal Products for Human Use. The EPAR is first published after the granting of the initial marketing authorisation (MA) and is continuously updated during the lifecycle of the medicinal product. In particular, following a major change to the MA, the Agency further publishes the assessment report of the CHMP and the reasons for its opinion in favour of granting the change to the authorisation, after deletion of any information of a commercially confidential nature.

   Should you consider that the CHMP assessment report contains commercially confidential information, **please provide the EMA Procedure Assistant with your proposal for deletion of commercially confidential information** (CCI) in "track changes" and with detailed justification **within 15 days from adoption of the CHMP Opinion**. The principles to be applied for the deletion of CCI are published on the EMA website at http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/03/WC500124536.pdf.