14 October 2021
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Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Revestive

teduglutide

Procedure no: EMEA/H/C/002345/P46/012

Note

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

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1. Introduction

On the 4th of May, the MAH submitted a completed paediatric study SHP633-304, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

Study SHP633-304 was a Phase 3, Prospective, Open-Label, Long-Term Safety and Efficacy Study of Teduglutide in Pediatric Patients with Short Bowel Syndrome Who Completed TED-C14-006 or SHP633-301. The Study was conducted as part of the product development program and was completed on 05 Nov 2020.

There are no regulatory consequences identified by the MAH as a result of this study.

2.2. Information on the pharmaceutical formulation used in the study

This was an open-label study.

If teduglutide treatment eligibility was established, teduglutide 0.05 mg/kg was administered by subcutaneous (SC) injection once daily into 1 of the 4 quadrants of the abdomen (but not near a stoma) or into either the thigh or arm.

Teduglutide was available as 1.25 mg and 5 mg powder and solvent for solution for injection.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

Study SHP633-304 A Prospective, Open-Label, Long-Term Safety and Efficacy Study of Teduglutide in Pediatric Patients with Short Bowel Syndrome Who Completed TED-C14-006 or SHP633-301

2.3.2. Clinical study

Study SHP633-304

A Prospective, Open-Label, Long-Term Safety and Efficacy Study of Teduglutide in Pediatric Patients with Short Bowel Syndrome Who Completed TED-C14-006 or SHP633-301

Description

Methods

Objective(s)

The primary objective of the study is to evaluate the long-term safety and tolerability of teduglutide treatment in pediatric subjects with Short Bowel Syndrome (SBS) who completed TED-C14-006 or SHP633-301.

The secondary objective of this study is to evaluate the long-term efficacy of teduglutide

Study design

SHP633-304 was a Phase 3, prospective, open-label, long-term extension study to evaluate the safety and efficacy of teduglutide in pediatric subjects, including infants, with SBS who completed their core study, TED-C14-006 or SHP633-301, and who were dependent on Parenteral support (PS). Children in Study TED-C14-006 were 1 through 17 years of age; infants in Study SHP633-301 were 4 to 12 months corrected gestational age (a premature baby's chronological age minus the number of weeks or months he/she was born early). This extension study evaluated the long-term safety and durability of efficacy in subjects who had received 24 weeks of teduglutide treatment in their core study, as well as the need for additional teduglutide treatment in those subjects, and allowed for first-time treatment of teduglutide-naïve subjects who had participated in the standard of care treatment arm in their core study.

Figure 1 Study Design Schematic

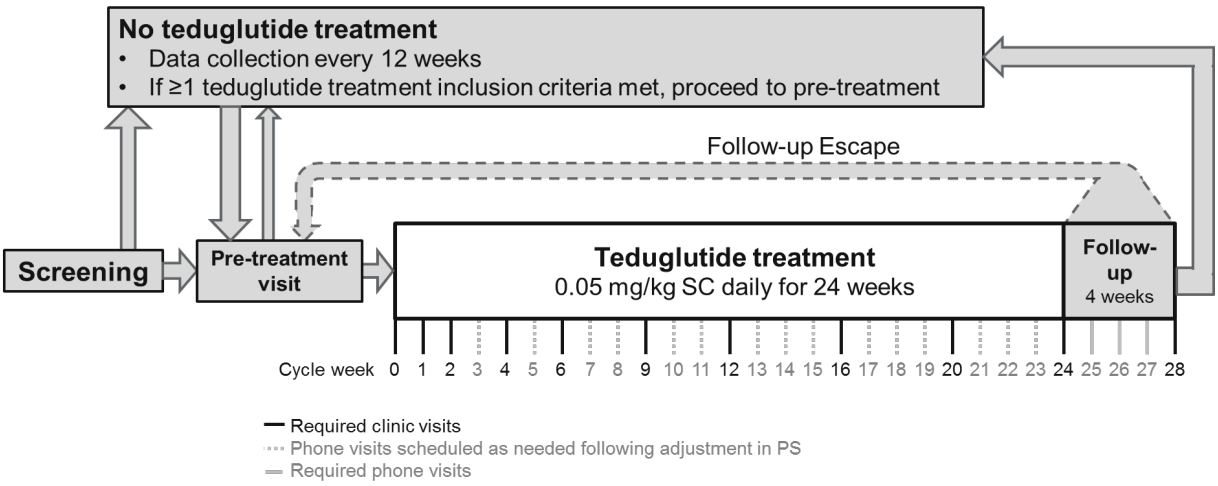

Figure legend: Safety and efficacy data for subjects not receiving teduglutide treatment were captured approximately every 12 weeks, but subjects could proceed to a pretreatment visit at any time to assess eligibility for teduglutide therapy. Eligible subjects entered a 28-week teduglutide cycle. During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

Study population /Sample size

This extension study had 2 sets of eligibility criteria - one for study eligibility and the other for treatment eligibility. Teduglutide treatment eligibility did not impact study eligibility.

Study inclusion criteria

Each subject had to meet all the following criteria to be eligible for the study:

1. Provide written informed consent (subject, parent or legal guardian and, as appropriate, subject informed assent) to participate in the study before completing any study-related procedures.
2. Complete their core study (including subjects in the standard of care treatment arm).
3. Understand and be willing and able to fully adhere to study requirements as defined in this protocol.

Study exclusion criteria

There were no study exclusion criteria for this study.

Treatment inclusion criteria

1. Subject was teduglutide-naive, receiving PS, and unable to significantly reduce PS or advance enteral feeds (e.g., 10% or less change in PS or advance in feeds) for at least 3 months prior to and during the teduglutide pretreatment visit, as assessed by the investigator. Transient instability for events such as interruption of central access or treatment for sepsis was allowed if the PS returned to within 10% of baseline prior to the event.
2. Subject was previously treated with teduglutide and at least 1 of the following criteria was satisfied:
    a. Increasing PS requirements following teduglutide discontinuation
    b. Decreased PS requirement during prior teduglutide treatment, followed by cessation of improvement after teduglutide discontinuation
    c. Deteriorating nutritional status (e.g., weight loss or growth failure) despite maximal tolerated enteral nutrition (EN) following teduglutide discontinuation
    d. Deteriorating fluid or electrolyte status despite maximal tolerated enteral fluid and electrolyte intake following teduglutide discontinuation
    e. Severe diarrhea related to teduglutide discontinuation

Treatment exclusion criteria

1. Body weight less than 10 kg at the pretreatment visit
2. Unresected gastrointestinal (GI) polyp, known polyposis condition, premalignant change, or malignancy, in the GI tract
3. History of cancer in the previous 5 years except surgically curative skin cancers
4. Serial transverse enteroplasty or other major intestinal surgery within 3 months preceding the teduglutide pretreatment visit. Insertion of a feeding tube, anastomotic ulcer repair, minor intestinal resections no more than 10 cm, and endoscopic procedures are allowed
5. Intestinal or other major surgery planned or scheduled to occur during the 28-week cycle

6. Clinically significant intestinal stricture or obstruction
7. Clinically significant, active or recurrent pancreatic or biliary disease
8. Active, severe, or unstable, clinically significant hepatic impairment or injury, including the following laboratory values at the pretreatment visit:
    a. Total bilirubin at least 2 × upper limit of normal (ULN)
    b. Aspartate aminotransferase (AST) at least 7 × ULN
    c. Alanine aminotransferase (ALT) at least 7 × ULN
9. Renal dysfunction shown by results of an estimated glomerular filtration rate (eGFR) below 50 mL/min/1.73 m2 at the pretreatment visit
10. Unstable cardiac disease, congenital heart disease or cyanotic disease, with the exception of subjects who had undergone ventricular or atrial septal defect repair, or patent ductus arteriosus ligation
11. Participation in a clinical study using an experimental drug (other than glutamine, Omegaven, or Smoflipid) within 3 months or 5.5 half-lives of the experimental drug, whichever is longer, prior to the pretreatment visit and for the duration of the 28-week cycle
12. Treatment with analogs of glucagon-like peptide-1 (GLP-1), GLP-2 (not including teduglutide), insulin-like growth factor-1 (IGF-1), or growth hormone, within 3 months preceding the teduglutide pretreatment visit.
13. Treatment with octreotide or dipeptidyl peptidase 4 (DPP-4) inhibitors within 3 months prior to the pretreatment visit
14. Known or suspected intolerance or hypersensitivity to the investigational product, closely related compounds, or any of the stated ingredients
15. Known history of alcohol or other substance abuse within 1 year prior to the pretreatment visit
16. Pregnant or lactating female subjects
17. Sexually active female subjects of child-bearing potential unwilling to use approved contraception during teduglutide treatment and for 30 days after the treatment period
18. Any condition, disease, illness, or circumstance that in the investigator’s opinion puts the subject at any undue risk, prevents completion of the study, or interferes with analysis of the study results.

Follow-up period escape criteria

At the discretion of the investigator, the follow-up periods could be interrupted and the subject could proceed directly to a pretreatment visit, if at least 1 of the following criteria was met:

1. Increasing PS requirements following teduglutide discontinuation
2. Deteriorating nutritional status (e.g., weight loss or growth failure) despite maximal tolerated EN following teduglutide discontinuation
3. Deteriorating fluid or electrolyte status despite maximal tolerated enteral fluid and electrolyte intake following teduglutide discontinuation
4. Severe diarrhea related to teduglutide discontinuation

Sample size

The number of subjects in this study is not based on statistical power considerations as this is an extension study of the core studies, TED-C14-006 and SHP633-301. The maximum number of subjects was determined by the enrollment in TED-C14-006 and SHP633-301.

CHMP's comment

The numbers of enrollment in each of the core studies, the numbers of subjects eligible and ineligible, respectively, for the extension study at the end of the core studies, and the reasons for eligibility and ineligibility, respectively, should be provided **(OC).**

Treatments

This was an open-label study. Eligibility to teduglutide treatment was dependent on the subject's disease course as defined by the teduglutide treatment eligibility criteria.

If teduglutide treatment eligibility was established, teduglutide 0.05 mg/kg was administered by subcutaneous (SC) injection once daily into 1 of the 4 quadrants of the abdomen (but not near a stoma) or into either the thigh or arm.

Teduglutide was available as 1.25 mg and 5 mg powder and solvent for solution for injection.

For all subjects at all visits, nutritional support adjustment in volume and calories should be considered. To maintain consistency across centers, all attempts were made to follow the nutritional support adjustment guidelines (developed with SBS expert input and provided in the protocol) for decisions regarding PS reduction and advances in enteral feeds based on weight gain, urine and stool output, and clinical stability. Departure from the guidelines, however, was not considered a protocol deviation.

Outcomes/endpoints

The efficacy endpoints were analyzed in 2 ways: 1) based on the subject diary data, and 2) based on the investigator-prescribed data. Parenteral support was reported in both subject diary data and the investigator-prescribed data in the eCRF. Parenteral support prescription data collected include prescribed weekly total kilocalories, volume, number of days per week, and average hours per day. Parenteral support diary data were collected daily for 2 weeks prior to all scheduled visits in the intake diary eCRFs. The data collected include actual PS total infusion duration, total volume and total kilocalories.

Efficacy endpoints were analyzed at the end of each teduglutide treatment period (Week 24 or end of treatment [EOT]), and at each study visit, relative to the baseline of the core study and/or first exposure to teduglutide. The following efficacy endpoints were analyzed:

- Reduction in PS volume of at least 20%, 50% and 75% at the end of each teduglutide treatment period
- Change and percentage change in PS volume and intake calories
- Enteral autonomy (complete weaning off PS)
- Change in hours per day and days per week of PS

Safety analyses

Exposure, Treatment Emergent Adverse Events / Serious Adverse Events, Clinical Laboratory Evaluations, Gastrointestinal-Specific Testing, Physical Examination, Vital Signs including Weight, Height, BMI, head circumference and Z-scores for these, Faecal and Urine Outputs.

Statistical Methods

The all subjects screened (SRN) set contains all subjects who provided signed informed consent for the study.

The safety population includes all enrolled subjects in the study. Safety population will be used for both safety and efficacy analyses.

Subjects are identified by the treatments received in the core and extension studies, as follows:

- NTT/NTT – subjects who never received teduglutide in the core or extension study
- NTT/TED (teduglutide) – subjects who did not receive teduglutide in the core study but who received teduglutide in the extension study
- TED/NTT – subjects who received teduglutide in the core study but who did not receive teduglutide in this extension study
- TED/TED – subjects who received teduglutide in both the core study and the extension study

The ANY TED group comprised all subjects in the NTT/TED, TED/NTT, and TED/TED treatment groups.

Due to the limited size of the study population, descriptive statistics were used with a goal of summarizing the sample. As such, no claims of significance were made for any of the data.

Continuous variables, including those assessed on a discrete scale, were summarized using descriptive statistics including number of subjects, mean, median, standard deviation, maximum, and minimum. For categorical variables, statistical summaries included number of subjects and percentages.

For summary purposes and unless otherwise specified, baseline was defined as the last nonmissing measurement on or prior to the baseline visit of the core study. The data were summarized only when data was not collected in the core study, and no baseline comparisons were made.

The safety population was used for the efficacy analysis of data. There were subjects from the TED-C14-006 and SHP633-301 studies that enrolled into this SHP633-304 study. The main SAP analysis discusses the subjects from both studies.

An independent DMC reviewed the data on a routine basis for safety assessment. An interim analysis of 6 months of data was planned and conducted for this study, which included data collected through the data cutoff date of 02 Feb 2018. The data included at least 6 months (24 weeks) of follow-up for 42 subjects and at least 4 months (16 weeks) of follow-up for 13 subjects. The results of this interim analysis were issued in a 6-month interim clinical study report dated 05 Jul 2018.

Among subjects from SHP633-301, a subset of analysis was done for the following: disposition, protocol deviations, demographics, concomitant medications, compliance reduction in actual PS volume, reduction in prescribed volume, changes in actual PS volume, changes in prescribed volume, change in actual PS caloric intake, and change in prescribed PS caloric intake. The Applicant states there were no new efficacy or safety findings from the subset analysis.

No subgroup analysis was performed for this study.

CHMP's comment

Comparisons of results observed in this extension study are made against the core study baseline, i.e. the baseline data in the TED-C14-006 and SHP633-301 studies, respectively.

The core study 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 had LPLV 18 August 2017 and a variation was submitted 16 March 2018 (CTD sequence 0112). The results of study TED-C14-006 were implemented in the SmPC in 2018.

The core study SHP633-301, a study to evaluate the safety, efficacy/pharmacodynamics (PD), and pharmacokinetics (PK) of teduglutide in infants 4 to 12 months corrected gestational age (a premature baby's chronological age minus the number of weeks or months he/she was born early) with SBS and who are dependent on parenteral support (PIP Study 8) had LPLV 24 September 2020 and the results submitted 24 March 2021(CTD sequence 0144) and are currently under regulatory review.

The present extension study included 6 infants 4 to 12 months corrected gestational age out of 10 initially included in the core study SHP633-301. The Applicant states that there were no new efficacy or safety findings from the subset analysis of these subjects. However, since the core study SHP633-301 is currently under regulatory review, no separate assessment of results compared to the core study SHP633-301 baseline in these 6 infants can be made in the extension study at this time.

As no subgroup analysis was performed this assessment concerns the results provided for the overall study population only.

As stated by the Applicant, descriptive statistics were used with a goal of summarizing the sample. As such, no claims of significance were made for any of the data. This is accepted.

The interim clinical study report has not been reviewed in the present assessment.

Results

Recruitment/ Number analysed

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

Table 8 Subject Disposition-Safety Population

Category	NTT/NTT	NTT/TED	TED/NTT	TED/TED	Any TED	Total
Screened subjects, n						61
Enrolled subjects, n	7	3	1	50	54	61
Completed treatment, n (%)	0	3 (100.0)	0	31 (62.0)	34 (63.0)	34 (55.7)
Completed study, n (%)	6 (85.7)	3 (100.0)	0	38 (76.0)	41 (75.9)	47 (77.0)
Early treatment discontinuation, n (%)	0	0	0	19 (38.0)	19 (35.2)	19 (31.1)
Adverse event n (%)	0	0	0	3 (6.0)	3 (5.6)	3 (4.9)

Category	NTT/NTT	NTT/TED	TED/NTT	TED/TED	Any TED	Total
Withdrawal by parent/guardian n (%)	0	0	0	1 (2.0)	1 (1.9)	1 (1.6)
Physician decision n (%)	0	0	0	3 (6.0)	3 (5.6)	3 (4.9)
Lost to follow-up n (%)	0	0	0	1 (2.0)	1 (1.9)	1 (1.6)
Other n (%)	0	0	0	11 (22.0)	11 (20.4)	11 (18.0)
Early study discontinuation, n (%)	1 (14.3)	0	1 (100.0)	12 (24.0)	13 (24.1)	14 (23.0)
Adverse event n (%)	0	0	0	1 (2.0)	1 (1.9)	1 (1.6)
Withdrawal by subject	0	0	0	1 (2.0)	1 (1.9)	1 (1.6)
Withdrawal by parent/guardian n (%)	0	0	0	0	0	0
Physician decision n (%)	0	0	1 (100.0)	1 (2.0)	2 (3.7)	2 (3.3)
Lost to follow-up, n (%)	1 (14.3)	0	0	1 (2.0)	1 (1.9)	2 (3.3)
Death, n (%)	0	0	0	1 (2.0)	1 (1.9)	1 (1.6)
Other n (%)	0	0	0	7 (14.0)	7 (13.0)	7 (11.5)

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

Baseline data

The majority (50/61) of the subjects received teduglutide in both the core study and this extension study (TED/TED group). There were 7 subjects who had never received teduglutide (NTT/NTT group), 3 subjects who did not receive teduglutide in their core study but who had received teduglutide in this extension study (NTT/TED group), and 1 subject who received teduglutide in the core study but who had not received teduglutide in this extension study (TED/NTT). In addition, the ANY TED subjects were comprised of the NTT/TED, TED/NTT, and TED/TED treatment groups.

The mean age at core study baseline was 5.5±3.86 years and the majority of subjects were in the 1 to less than 12 years age group (83.6%). Six children under 1 year of age were enrolled. There were 3 subjects in the 12 to less than 17 years age group and 1 subject in the 17 to less than 18 years age group. The majority of subjects were male (41/61 [67.2%]), white (42/61[68.9%]), and not Hispanic or Latino (40/61 [65.6%]).

Table 11 Demographics and Baseline Characteristics–Safety Population

Category	NTT/NTT (N=7)	NTT/TED (N=3)	TED/NTT (N=1)	TED/TED (N=50)	Any TED (N=54)	Total (N=61)
Age at core study baseline (years), mean (SD)	5.8 (5.43)	1.5 (0.80)	[redacted]	5.7 (3.69)	5.5 (3.68)	5.5 (3.86)
Age Group, n (%)						
Less than 1 year	1 (14.3)	1 (33.3)		4 (8.0)	5 (9.3)	6 (9.8)
1 to less than 12 years	5 (71.4)	2 (66.7)		43 (86.0)	46 (85.2)	51 (83.6)
12 to less than 17 years	0	0		3 (6.0)	3 (5.6)	3 (4.9)
17 to less than 18 years	1 (14.3)	0		0	0	1 (1.6)
Sex, n (%)						
Male	4 (57.1)	2 (66.7)		34 (68.0)	37 (68.5)	41 (67.2)
Female	3 (42.9)	1 (33.3)		16 (32.0)	17 (31.5)	20 (32.8)
Premenarchal	2 (28.6)	1 (33.3)		15 (30.0)	16 (29.6)	18 (29.5)
Child-bearing potential	1 (14.3)	0		1 (2.0)	1 (1.9)	2 (3.3)
Race, n (%)						
White	3 (42.9)	0		38 (76.0)	39 (72.2)	42 (68.9)
Black or African American	1 (14.3)	0		6 (12.0)	6 (11.1)	7 (11.5)
Asian	1 (14.3)	1 (33.3)		1 (2.0)	2 (3.7)	3 (4.9)
Other	1 (14.3)	1 (33.3)		1 (2.0)	2 (3.7)	3 (4.9)
Not allowed based on local regulations	1 (14.3)	1 (33.3)		4 (8.0)	5 (9.3)	6 (9.8)
Ethnicity, n (%)						
Hispanic or Latino	3 (42.9)	1 (33.3)		10 (20.0)	11 (20.4)	14 (23.0)
Not Hispanic or Latino	3 (42.9)	1 (33.3)		35 (70.0)	37 (68.5)	40 (65.6)
Not allowed based on local regulations	1 (14.3)	1 (33.3)		5 (10.0)	6 (11.1)	7 (11.5)
Weight z-score at core study baseline, mean (SD)	0.07 (0.799)	-1.29 (1.323)	-2.55 (-)	-0.75 (1.040)	-0.81 (1.068)	-0.71 (1.073)
Height z-score at core study baseline, mean (SD)	-0.14 (1.727)	-0.97 (1.255)	-2.47 (-)	-1.16 (1.274)	-1.17 (1.263)	-1.05 (1.348)
BMI z-score at core study baseline, mean (SD)	0.23 (0.467)	-0.89 (1.266)	-0.81 (-)	-0.01 (1.003)	-0.08 (1.021)	-0.04 (0.976)
Head circumference z-score at core study baseline, mean (SD)	-0.75 (-)	-1.34 (0.517)	0	-0.25 (1.289)	-0.42 (1.254)	-0.44 (1.208)

Note: Body mass index (BMI) is calculated as body weight in kg divided by height in meters squared, when both body weight and height are collected.
Note: Percentages are based on the number of subjects in the safety population for the defined treatment groups.
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 at least 2 years old) and World Health Organization (age less than 2 years old) Z-score calculation charts are used for calculation.
Note: Baseline is defined as the core study baseline value.
Source: [redacted]

CHMP's comment

A total of 61 subjects were screened and enrolled. These 61 subjects constituted the safety population. All analyses were based on the safety population

Six subjects < 1 year of age were enrolled from the core study SHP633-301 from which it can be deducted that 61-6 = 55 subjects 1 – 18 years of age were enrolled from the core study TED-C14-006.

The numbers of enrollment in each of the core studies, the numbers of subjects eligible and ineligible, respectively, for the extension study at the end of the core studies, and the reasons for eligibility and ineligibility, respectively, should be provided **(OC)**.

A total of 8 subjects who did not receive teduglutide in the extension study: 7 subjects in the NTT/NTT group and 1 subject in the TED/NTT group. The applicant should discuss the reason for why teduglutide apparently was not needed in the 8 subjects in the NTT/NTT and TED/NTT groups **(OC)**.

Efficacy results

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

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

in the NTT/NTT, TED/NTT, and TED/TED groups and as the extension study baseline for the NTT/TED group; diary data are presented.

CHMP's comment

The efficacy summary focuses on the subject diary data. The applicant states the diary data was considered a more representative measure of efficacy than the investigator prescribed data. This is accepted.

Furthermore, as stated in the CSR, it was decided that the focus of discussion in the CSR text would compare data from approximately 2 years of subject participation in the TED/TED vs NTT/NTT groups. Therefore, the summary of teduglutide treatment efficacy focuses on the end of teduglutide treatment in Cycle 4 for the TED/TED group compared with the end of Visit NT 8 for the NTT/NTT group.

However, this time period seems arbitrary and the rationale for this decision needs further discussion. **(OC).**

Reduction in parenteral support volume

Subject diary data

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

Table 13 Reductions of At Least 20%, 50%, and 75% in Parenteral Support Volume-Diary Data-Safety Population

Visit	Reductions in Diary PS Volume (mL/kg/day), n (%)		
	At Least 20%	At Least 50%	At Least 75%
Teduglutide Treatment (TED/TED Group) (N=50)			
Cycle 1 Day 1 (n=50)	23 (46.0)	10 (20.0)	5 (10.0)
Cycle 4 EOT (n=27)	20 (74.1)	13 (48.1)	7 (25.9)
No-Teduglutide Treatment (NTT/NTT Group) (N=7)			
NT1 (n=6)	1 (16.7)	0	0
NT8 (n=5)	2 (40.0)	1 (20.0)	1 (20.0)

EOT=end of treatment; NT=no-teduglutide; PS=parenteral support
Note: NTT/NTT - subjects who did not receive teduglutide in either their core study or this extension study; TED/TED - subjects who received teduglutide in their core study and this extension study.
Note: Baseline is defined as the core study baseline visit.
Source: [redacted]

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

CHMP's comment

While the changes in PS volume are measured against the respective core studies' baselines, the proportion of subjects achieving at least 20%, 50% and 75% reduction in PS, respectively, are calculated on the basis of the number of patients being seen at the visits Cycle 1 Day 1 (n=50) / NT1 (n=6) and Cycle 4 EOT (n=27) / NT8 (n=5), respectively.

However, these proportions do not consider the changes in PS, if any, from the core studies' baselines in the subjects not being seen at the respective visits. Therefore, the change in proportions achieving at least 20%, 50% and 75% reduction in PS, respectively, as described cannot be considered conclusive evidence of efficacy.

Furthermore, the difference between the TED/TED and the NTT/NTT groups with respect to the change in proportions achieving at least 20%, 50% and 75% reduction in PS, respectively, is difficult to interpret because the apparent smaller change in proportions in the NTT/NTT group compared to the TED/TED group may be confounded by the fact that teduglutide apparently was not needed in the 8 subjects in the NTT/NTT and TED/NTT groups.

With respect to the mean change in diary PS volume, the means estimated at the core studies' baselines, at Cycle 1 Day 1 /NT1 and at Cycle 4 EOT / NT8, respectively, were estimated on the basis of different numbers of subjects, who were seen at these respective visits. These means do not consider the mean changes in PS volume, if any, in the subjects not seen at these visits. Therefore, the change in means of PS volume as described cannot be considered conclusive evidence of efficacy.

Furthermore, the difference between the TED/TED and the NTT/NTT groups with respect to the mean changes in PS volume is difficult to interpret because the apparent smaller change in means of PS volume in the NTT/NTT group compared to the TED/TED group may be confounded by the fact that teduglutide apparently was not needed in the 8 subjects in the NTT/NTT and TED/NTT groups.

It is noted that there are no regulatory consequences identified by the MAH as a result of this study. The extension study was primarily designed for long-term safety assessment, whereas the efficacy assessment is only a secondary objective. As the above-mentioned efficacy endpoints are presented they are considered descriptive and supportive for the existing data on efficacy only.

Enteral autonomy

Twelve subjects (24.0%) in the TED/TED group and 1 subject (14.3%) in the NTT/NTT group achieved enteral autonomy during various cycles; once achieved, this was maintained to the end of the study in all but 1 case, in which the subject fluctuated briefly in Cycle 2.

CHMP's comment

Achievement of sustained enteral autonomy in a number of subjects is a more straightforward endpoint because both core studies required per design that all subjects were dependent on parenteral support to be eligible to enroll in the core studies. On this background this outcome is readily interpretable as a beneficial effect, although other factors than the teduglutide treatment may have contributed since the extension study is not a randomized controlled study.

Of note, since a number of patients in the core study TED-C14-006 achieved enteral autonomy during the core study, it should be clarified if all subjects enrolled in the extension study were dependent on parenteral support **(OC)**.

Reduction in Parenteral Support Calories

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

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

CHMP comment

With respect to the mean change in PS calories, the means estimated at the core studies' baselines, at Cycle 1 Day 1 /NT1 and at Cycle 4 EOT / NT8, respectively, were estimated on the basis of different numbers of subjects, who were seen at these respective visits. These means do not consider the mean changes in PS calories, if any, in the subjects not seen at these visits. Therefore, the change in means of PS calories as described cannot be considered conclusive evidence of efficacy.

Furthermore, the difference between the TED/TED and the NTT/NTT groups with respect to the mean changes in PS calories is difficult to interpret because the apparent smaller changes (small increase at NT1, small decrease at NT8) in means of PS calories in the NTT/NTT group compared to the TED/TED group may be confounded by the fact that teduglutide apparently was not needed in the 8 subjects in the NTT/NTT and TED/NTT groups.

It is noted that there are no regulatory consequences identified by the MAH as a result of this study. The extension study was primarily designed for long-term safety assessment, whereas the efficacy assessment is only a secondary objective. As the above-mentioned efficacy endpoints are presented they are considered descriptive and supportive for the existing data on efficacy only.

Reduction in Parenteral Support Infusion Time

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

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

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

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

CHMP comment

With respect to the mean change in PS infusion time (hours/day and days/week), the means estimated at the core studies' baselines, at Cycle 1 Day 1 /NT1 and at Cycle 4 EOT / NT8, respectively, were estimated on the basis of different numbers of subjects, who were seen at these respective visits. These means do not consider the mean changes in PS infusion time, if any, in the subjects not seen at these visits. Therefore, the change in means of PS infusion time as described cannot be considered conclusive evidence of efficacy.

Furthermore, the difference between the TED/TED and the NTT/NTT groups with respect to the mean changes in PS infusion time is difficult to interpret because the apparent smaller changes in means of PS infusion time in the NTT/NTT group compared to the TED/TED group may be confounded by the fact that teduglutide apparently was not needed in the 8 subjects in the NTT/NTT and TED/NTT groups.

The finding that the described reductions in PS volume and infusion time are correlated is expected, but may still not be considered conclusive evidence of efficacy as both observations are subject to the same limitations as commented.

It is noted that there are no regulatory consequences identified by the MAH as a result of this study. The extension study was primarily designed for long-term safety assessment, whereas the efficacy assessment is only a secondary objective. As the above-mentioned efficacy endpoints are presented they are considered descriptive and supportive for the existing data on efficacy only.

Quality of Life Findings

From parent reports, the PedsQL Generic Core Subscale Scores total score (Table 17) and the PedsQL Gastrointestinal Symptoms Module diarrhea subscale score (Table 19) showed improvement (positive changes) from baseline to Cycle 4 EOT for the teduglutide treatment (TED/TED) group compared with slight decreases in scores from baseline to NT8 for the no teduglutide NTT group. Self-reported data showed improvement in the PedsQL Gastrointestinal Symptoms Module food and drink limits subscale score (Table 18) for the TED/TED group compared with the NTT/NTT group. Self-reported data also showed improvement in the total score (Table 17) for the TED/TED group, however similar improvement was shown in the NTT/NTT group.

Table 17 PedsQL Generic Core Total Scores - NTT/NTT and TED/TED Groups

	NTT/NTT Group (N=7)	TED/TED Group (N=50)
	Parent Reports	
	Baseline	
n	4	32
mean (SD)	58.46 (9.013)	70.72 (15.660)
	Change From Baseline	
	NT1	**Cycle 1 Week 12**
n	0	30
mean (SD)	0	2.49 (16.756)
	NT8	**Cycle 4 Week 24**
n	3	15
mean (SD)	-0.78 (25.566)	4.63 (16.376)
	Self Reports	
	Baseline	
n	1	18
mean (SD)	56.52 (-)	70.83 (17.877)
	Change From Baseline	
	NT1	**Cycle 1 Week 12**
n	0	17
mean (SD)	0	-2.17 (13.657)
	NT8	**Cycle 4 Week 24**
n	1	6
mean (SD)	7.11 (-)	9.36 (5.046)

Note: In The PedsQL Generic Core Scale, the scores are reversed scored and linearly transformed to a 0 to100 scale as follows: 0=100, 1=75, 2=50, 3=25, and 4=0. As such, a positive change from baseline indicated clinical improvement.
Note: The subscale score is calculated as the sum of the items over the number of items answered in the scale.
Note: TED/TED - subjects who received teduglutide in their core study and in the extension study.
Note: NTT/NTT - subjects who did not receive teduglutide in either their core study or this extension study.
Source: [redacted]

Table 18 PedsQL Gastrointestinal Symptoms – Food and Drink Subscale Scores – NTT/NTT and TED/TED Groups

	NTT/NTT Group (N=7)	TED/TED Group (N=50)
	Parent Reports	
	Baseline	
n	5	42
mean (SD)	33.33 (35.722)	50.00 (33.813)
	Change From Baseline	
	NT1	**Cycle 1 Week 12**
n	0	41
mean (SD)	0	2.74 (28.007)
	NT8	**Cycle 4 Week 24**
n	4	22
mean (SD)	20.83 (29.853)	18.56 (33.227)
	Self Reports	
	Baseline	
n	1	24
mean (SD)	75.00 (-)	55.90 (27.499)
	Change From Baseline	
	NT1	**Cycle 1 Week 12**
n	0	24
mean (SD)	0	8.33 (27.584)
	NT8	**Cycle 4 Week 24**
n	1	11
mean (SD)	-8.33 (-)	23.11 (19.397)

Note: In the PedsQL Gastrointestinal Symptom Module, the scores are reversed scored and linearly transformed to a 0 to 100 scale as follows: 0=100, 1=75, 2=50, 3=25, and 4=0. As such, a positive change from baseline indicated clinical improvement.
Note: The subscale score is calculated as the sum of the items over the number of items answered in the scale.
Note: TED/TED - subjects who received teduglutide in their core study and in the extension study.
Note: NTT/NTT - subjects who did not receive teduglutide in either their core study or this extension study.
Source: [redacted]

Table 19 PedsQL Gastrointestinal Symptoms – Diarrhea Subscale Scores – NTT/NTT and TED/TED Groups

	NTT/NTT Group (N=7)	TED/TED Group (N=50)
	Parent Reports	
	Baseline	
n	4	39
mean (SD)	58.46 (9.013)	50.73 (22.959)
	Change From Baseline	
	NT1	**Cycle 1 Week 12**
n	0	36
mean (SD)	0	1.09 (16.878)
	NT8	**Cycle 4 Week 24/EOT**
n	3	20
mean (SD)	-0.78 (25.566)	8.57 (23.702)
	Self Reports	
	Baseline	
n	1	22
mean (SD)	53.57 (-)	65.58 (20.189)
	Change From Baseline	
	NT1	**Cycle 1 Week 12**
n	0	21
mean (SD)	0	-0.85 (22.443)
	NT8	**Cycle 4 Week 24/EOT**
n	1	9
mean (SD)	-3.57 (-)	-6.15 (22.072)

Note: In the PedsQL Gastrointestinal Symptom Module, the scores are reversed scored and linearly transformed to a 0 to 100 scale as follows: 0=100, 1=75, 2=50, 3=25, and 4=0. As such, a positive change from baseline indicated clinical improvement.
Note: The subscale score is calculated as the sum of the items over the number of items answered in the scale.
Note: TED/TED - subjects who received teduglutide in their core study and in the extension study.
Note: NTT/NTT - subjects who did not receive teduglutide in either their core study or this extension study.
Source: [redacted]

Assessor's comment

The Quality of Life measures mean changes from baseline are estimated on the basis of different numbers of subject at baseline, at Cycle 1 week 12 / NT1 and Cycle 4 week24/EOT / NT8, respectively.

These means do not consider the mean changes in Quality of Life measures, if any, in the subjects not seen at these visits. Therefore, the change in means of Quality of Life measures as described cannot be considered conclusive evidence of efficacy.

Furthermore, the difference between the TED/TED and the NTT/NTT groups with respect to the mean changes in Quality of Life measures is difficult to interpret because the apparent smaller and opposite direction changes in some of the means of Quality of Life measures in the NTT/NTT group compared to the TED/TED group may be confounded by the fact that teduglutide apparently was not needed in the 8 subjects in the NTT/NTT and TED/NTT groups.

It is noted that there are no regulatory consequences identified by the MAH as a result of this study. The extension study was primarily designed for long-term safety assessment, whereas the efficacy assessment is only a secondary objective. As the above-mentioned efficacy endpoints are presented they are considered descriptive and supportive for the existing data on efficacy only.

Safety results

Exposure

The number of treatment cycles is presented for the safety population in Table 14.3.1.2. The mean number of cycles received was 3.0±2.00 cycles for the NTT/TED group and 3.5±1.61 cycles for the TED/TED group.

Exposure to teduglutide is presented for the safety population in Table 14.3.1.1. For the ANY TED group (N=54), the mean duration of exposure to teduglutide (core + extension) was 100.99±43.103 weeks (range = 24.0 to 165.3 weeks).

All subjects who completed their core study enrolled in this extension study. A total of 37 of the 51 subjects who had received teduglutide treatment in their core study started a teduglutide treatment cycle within 4 weeks after enrolling in this extension study

Table 14.3.1.2
Number of Treatment Cycles
Safety Population

Parameter	Statistic	NTT/TED (N=3)	TED/TED (N=50)	ANY TED (N=53)
Number of Cycles Entered				
	n	3	50	53
	Mean (SD)	3.0 (2.00)	3.5 (1.61)	3.5 (1.61)
	Median	3.0	4.0	4.0
	Min, Max	1, 5	1, 6	1, 6
0	n (%)	0	0	0
1	n (%)	1 (33.3)	7 (14.0)	8 (15.1)
2	n (%)	0	10 (20.0)	10 (18.9)
3	n (%)	1 (33.3)	6 (12.0)	7 (13.2)
4	n (%)	0	7 (14.0)	7 (13.2)
5	n (%)	1 (33.3)	17 (34.0)	18 (34.0)
>5	n (%)	0	3 (6.0)	3 (5.7)

Table 14.3.1.1
Extent of Exposure
Safety Population

Parameter	Statistic	NTT/TED (N=3)	TED/NTT (N=1)	TED/TED (N=50)	ANY TED (N=54)
Total (CORE + Extension) Extent of Exposure (weeks)					
	n	3	1	50	54
	Mean (SD)	89.95 (51.492)	24.00 (-)	103.19 (42.047)	100.99 (43.103)
	Median	63.57	24.00	112.93	106.22
	Min, Max	57.0, 149.3	24.0, 24.0	28.3, 165.3	24.0, 165.3

CHMP's comment

The long-term exposure of 3.5±1.61 cycles or 103.19±42.047 weeks (range = 28.3 to 165.3 weeks). for the 50 subjects in the TED/TED group and similar for the ANY TED group is adequate for safety evaluation.

Adverse events

Overall, treatment-emergent adverse events (TEAEs) were reported in 85.7% to 100% of subjects across treatment groups (Table 1). There was a total of 31 treatment-related TEAEs in 16 subjects (32.0%) in the TED/TED group. Treatment-emergent serious adverse events (TESAEs) were reported in 57.1% to 100% of subjects across treatment groups. In the TED/TED group: 4 subjects (8.0%)

reported a total of 5 treatment-related TESAEs; 3 subjects (6.0%) reported a TEAE that led to treatment discontinuation; 3 subjects (6.0%) subjects reported a TEAE that led to study discontinuation; and 2 subjects (4.0%) subjects died during the study. No AEs of special interest were reported.

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

	NTT/NTT (N=7)		NTT/TED (N=3)		TED/NTT (N=1)		TED/TED (N=50)		ANY TED (N=54)	
Category	n(%)	m	n(%)	m	n(%)	m	n(%)	m	n(%)	m
Any TEAE	6 (85.7)	106	3 (100.0)	67	1 (100.0)	23	50 (100.0)	1152	54 (100.0)	1242
TEAE highest severity[a]										
Mild	0		2 (66.7)		0		10 (20.0)		12 (22.2)	
Moderate	5 (71.4)		0		0		18 (36.0)		18 (33.3)	
Severe	1 (14.3)		1 (33.3)		1 (100.0)		22 (44.0)		24 (44.4)	
TEAE relationship[b]										
Not related	-		1 (33.3)	65	1 (100.0)	23	34 (68.0)	1121	36 (66.7)	1209
Related	-		2 (66.7)	2	0	0	16 (32.0)	31	18 (33.3)	33
Any TESAE	4 (57.1)	24	2 (66.7)	16	1 (100.0)	6	41 (82.0)	193	44 (81.5)	215
TESAE relationship[b]										
Not related	-	-	2 (66.7)	16	1 (100.0)	6	37 (74.0)	188	40 (74.1)	210
Related	-	-	0	0	0	0	4 (8.0)	5	4 (7.4)	5
AE leading to treatment discontinuation	-	-	0	0	-		3 (6.0)	4	3 (5.6)	4
AE leading to study discontinuation	0	0	0	0	0	0	3 (6.0)	3	3 (5.6)	3
TEAE leading to death	0	0	0	0	0	0	2 (4.0)	2	2 (3.7)	2
AE of special interest[c]	0	0	0	0	0	0	0	0	0	0

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

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

[b] Only higher relationship per subject is counted for incidence and percentage, but AEs with different relationships per subject can be counted multiple times for the number of events.

[c] Adverse events of special interest were defined as growth of pre-existing polyps of the colon, benign neoplasia of the GI tract including the hepatobiliary system, and tumor promoting ability (eg, benign and/or malignant neoplasia of any kind, not limited to those of the GI or hepatobiliary system).

Note: Percentages are based on the number of subjects enrolled in each treatment group.

Note: Treatment-emergent adverse events are defined as adverse events that started or worsened on or after the date of first dose for treatment groups TED/TED, TED/NTT, NTT/TED and ANY TED and adverse events that started or worsened on or after the core study baseline visit for NTT/NTT.

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

Source: [redacted]

For the subjects ever treated with teduglutide (ANY TED group), the most frequent TEAEs were vomiting (30 subjects [55.6%]), pyrexia (31 subjects [57.4%]), and abdominal pain, upper respiratory tract infection, and cough (18 subjects ([33.3%] for each). There were 40 events in 16 subjects (29.6%) treated with teduglutide in the SOC 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 subjects never treated with teduglutide (NTT/NTT group), the most frequent TEAEs were vomiting and upper respiratory tract infection (4 subjects [57.1%] for each). Although the percentage of subjects with TEAEs was similar in the ANY TED subjects (100.0%) and the NTT/NTT subjects (85.7%), the average number of events per subject was much higher in the TED/TED group compared to the NTT/NTT group.

CHMP's comment

TEAE was reported in 100% of patients receiving teduglutide and 85.7% of patients not receiving teduglutide. TESAE was reported in 81.5% of patients receiving any teduglutide and 57.1% of patients not receiving teduglutide. This reflects the general health condition of this patient population, as only a smaller proportion of TEAEs overall was considered related to teduglutide, e.g. 31 treatment-related TEAEs in 16 subjects (32.0%) and 5 TESAEs in 4 subjects (8.0%) in the TED/TED group. Only few TEAEs led to treatment discontinuation. The most frequent TEAEs were vomiting, pyrexia, abdominal pain, upper respiratory tract infection and cough. These are all known frequent adverse events described in the SmPC.

Adverse events by relationship

A total of 31 related TEAEs were reported in 16 subjects (32.0%) in the TED/TED group, 2 related events in 2 subjects in the NTT/TED group, and no related TEAEs in the NTT/NTT or TED/NTT groups. All related TEAEs, with the exception of 6 events of injection site erythema in 1 subject and 2 events of psychomotor hyperactivity in 1 subject, were single events reported by a single subject.

CHMP's comment

Only a smaller proportion of TEAEs overall was considered related to teduglutide.

Deaths

Two deaths were reported in the study, both in the TED/TED group.

- One subject was a male with a medical history including midgut volvulus, and hip subluxation, who died due to the worsening of SBS after the subject's family elected to pursue end of life care and home hospice due to the inability to wean off PS, comorbid conditions not related to study drug, and impaired quality of life related to both SBS and comorbid conditions. The subject died due to withdrawal of enteral and parenteral fluid and nutritional support. The worsening of SBS was severe in intensity and not related to teduglutide.
- The other subject was a male who developed SBS due to late-onset necrotizing enterocolitis. The subject experienced a severe SAE of cerebral ischaemia (ischemic stroke). The reason for the stroke was unknown. Approximately 6 months later, a second severe SAE of ischemic stroke occurred. The subject gradually developed severe polyuremia and multisystem organ failure and died due to central nervous system vasculitis and ischemic stroke. The events were not related to teduglutide.

CHMP's comment

Two deaths occurred in the study. This is not unexpected in this patient population. Both deaths were considered related to the underlying health condition and not to teduglutide. This is accepted.

Serious adverse events

Serious adverse events that occurred in at least 2 subjects who received teduglutide are summarized in Table 3.

The percentage of subjects with TESAEs was higher in ANY TED subjects (81.5%) than in NTT/NTT subjects (57.1%). For all subjects treated with teduglutide (ANY TED group), the SOCs with the highest percentage of subjects reporting TESAEs were infections and infestations (55.6%), general disorders and administration site conditions (37.0%), and gastrointestinal disorders and metabolism and nutritional disorders (20.4% each). The majority of TESAEs were single events reported by a single subject. Treatment-emergent serious adverse events reported at least 3 times included 32 events of pyrexia, 25 events of device related infection, 8 events of metabolic acidosis, 7 events of dehydration, 6 events each of influenza and device breakage, 5 events of vomiting, 4 events of device related sepsis, and 3 events each of abdominal pain, urinary tract infection, femur fracture, device occlusion, and device dislocation.

For the NTT/NTT group, the TESAEs that were reported at least twice included 5 events of acidosis, 3 events of staphylococcal bacteraemia, and 2 events each for gastroenteritis viral, Malassezia infection, and device malfunction.

Four subjects in the TED/TED group reported 5 treatment-related TESAEs. One subject had moderate ileus, 1 had severe lactic acidosis, 1 had moderate metabolic acidosis, and 1 had moderate renal tubular acidosis and moderate tubulointerstitial nephritis. In the NTT/NTT group, no treatment-related TESAEs were reported.

Table 3 Treatment-Emergent Serious Adverse Events By System Organ Class and Preferred Term in At Least 2 Subjects Who Received Teduglutide - Safety Population

System Organ Class	NTT/NTT (N=7)		NTT/TED (N=3)		TED/NTT (N=1)		TED/TED (N=50)		Any TED (N=54)	
Preferred Term	n (%)	m	n (%)	m	n (%)	m	n (%)	m	n (%)	m
Any TESAE	4 (57.1)	24	2 (66.7)	16	1 (100.0)	6	41 (82.0)	193	44 (81.5)	215
Gastrointestinal Disorders			1 (33.3)	8			10 (20.0)	14	11 (20.4)	22
Vomiting			1 (33.3)	2			2 (4.0)	3	3 (5.6)	5
Abdominal pain			1 (33.3)	2			1 (2.0)	1	2 (3.7)	3
Diarrhoea							2 (4.0)	2	2 (3.7)	2
General Disorders and Administration Site Conditions			2 (66.7)	2			18 (36.0)	34	20 (37.0)	36
Pyrexia			1 (33.3)	1			16 (32.0)	31	17 (31.5)	32
Complication associated with device			1 (33.3)	1			1 (2.0)	1	2 (3.7)	2
Hepatobiliary Disorders							3 (6.0)	3	3 (5.6)	3
Cholelithiasis							2 (4.0)	2	2 (3.7)	2
Infections and Infestations	4 (57.1)	14	1 (33.3)	5			29 (58.0)	73	30 (55.6)	78
Device related infection							15 (30.0)	25	15 (27.8)	25
Influenza							6 (12.0)	6	6 (11.1)	6
Device related sepsis	1 (14.3)	1					4 (8.0)	4	4 (7.4)	4
Urinary tract infection							3 (6.0)	3	3 (5.6)	3
Cellulitis							2 (4.0)	2	2 (3.7)	2
Rhinovirus infection			1 (33.3)	1			1 (2.0)	1	2 (3.7)	2
Sepsis	1 (14.3)	1					2 (4.0)	2	2 (3.7)	2
Upper respiratory tract infection	1 (14.3)	1					2 (4.0)	2	2 (3.7)	2
Viral infection							2 (4.0)	2	2 (3.7)	2
Injury, Poisoning and Procedural Complications	1 (14.3)	1					5 (10.0)	6	5 (9.3)	6
Femur fracture							2 (4.0)	3	2 (3.7)	3
Metabolism and Nutrition Disorders	1 (14.3)	5			1 (100.0)	4	10 (20.0)	23	11 (20.4)	27
Metabolic acidosis					1 (100.0)	4	4 (8.0)	4	5 (9.3)	8
Dehydration							2 (4.0)	7	2 (3.7)	7
Feeding intolerance							2 (4.0)	2	2 (3.7)	2
Product Issues	2 (28.6)	3					9 (18.0)	13	9 (16.7)	13
Device breakage	1 (14.3)	1					5 (10.0)	6	5 (9.3)	6
Device occlusion							3 (6.0)	3	3 (5.6)	3
Device dislocation							2 (4.0)	3	2 (3.7)	3

m=number of events; n=number of subjects experiencing the event; TESAE = treatment-emergent serious adverse event
TESAE, defined as serious treatment emergent events occurring from the time of the signing of the informed consent form (ICF) for this extension study through last study visit.
Note: Percentages are based on the number of subjects enrolled in each treatment group.
Note: TEAEs are defined as adverse events that started or worsened on or after the date of first dose for treatment groups TED/TED, TED/NTT, NTT/TED and ANY TED and adverse events that started or worsened on or after the core study baseline visit for NTT/NTT.
Note: Subjects are counted no more than once for incidence, but can be counted multiple times for the number of events.
Note: System organ classes and preferred terms were coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 19.1.
Source: [redacted]

Three TED/TED subjects (4.9%) discontinued treatment early due to TESAEs, but 1 remained in the study. One subject discontinued treatment and the study due to a moderate TESAE of enterocutaneous fistula. The fistula was resolved after 12 days. Other subject interrupted treatment due to mild vomiting which lasted for approximately 3 months, and discontinued treatment due to a moderate TESAE of renal tubular acidosis, but remained in the study. The third subject discontinued from treatment due to a TESAE of ischemic stroke, and subsequently died due to a second ischemic stroke.

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

In this study, the deaths, TESAEs, discontinuations due to TEAEs, and AESIs were consistent with the prior pediatric studies of teduglutide and previous experience with teduglutide in adult subjects with SBS.

Two subjects died during the study. Neither subject died from a teduglutide related TESAE. Per the investigator, 1 subject's family elected to pursue end of life care and home hospice due to the inability to wean off PS, comorbid conditions not related to study drug, and impaired quality of life related to both SBS and comorbid conditions.

The other subject died from severe TESAEs of ischemic stroke. The percentage of subjects with TESAEs was higher in ANY TED subjects (81.5%) than in NTT/NTT subjects (57.1%). For all the subjects treated with teduglutide, the majority of TESAEs were single events reported by a single subject.

Treatment discontinuations included 3 subjects who discontinued due to TESAEs which were not treatment related.

There were no AESI identified during the study.

CHMP's comment

The Applicant's analysis and discussion of deaths, serious adverse events and other significant adverse events are accepted, i.e. in this study, the deaths, TESAEs, discontinuations due to TEAEs, and AESIs were consistent with the prior pediatric studies of teduglutide and previous experience with teduglutide in adult subjects with SBS.

Of note, no AESIs, meaning no Adverse events of special interest, which were defined as growth of pre-existing polyps of the colon, benign neoplasia of the GI tract including the hepatobiliary system, and tumour promoting ability (e.g., benign and/or malignant neoplasia of any kind, not limited to those of the GI or hepatobiliary system) were identified during the study.

Serum Chemistry

Postbaseline markedly abnormal laboratory values for serum chemistry reported during the teduglutide treatment cycles for the 50 TED/TED subjects included 11 (22.0%) subjects with alanine aminotransferase (ALT) levels greater than 8 × the upper limit of normal (ULN), 4 (8.0%) subjects with amylase levels greater than 3 × ULN, 1 (2.0%) subject with aspartate aminotransferase levels greater than 8 × ULN, 1 (2.0%) subject with direct bilirubin greater than 34.208 µmol/L, 1 (2.0%) subject with total bilirubin greater than 3 × ULN, 2 subjects (4.0%) with blood urea nitrogen greater than 12.495 mmol/L, 3 subjects with C reactive protein at least 100 mg/L, 1 subject with calcium greater than 3 mmol/L, 1 subject with glucose less than 2.22 mmol/L, and 3 subjects with phosphate greater than 2.254 mmol/L.

For the 11 subjects in the TED/TED group with 25 events of ALT greater than 8 × ULN, values ranged from 162 to 680 U/L (reference range 5-20 U/L). In most cases, the increased values were reported in the first 2 cycles; 2 subjects had elevated values at Day 1 of the first cycle. In the NTT/NTT group, 4 of the 6 subjects had high ALT levels over most visits, with 33 cases ranging from 24 to 158 U/L. However, all but 1 of the 11 TED/TED subjects with elevated ALT values had bilirubin levels within the reference range. This indicates that although the ALT and other liver enzymes were increased, the clinical picture and liver function was acceptable for this population.

During the no-teduglutide treatment periods (NTT/NTT group), 1 subject each had markedly abnormal laboratory values for magnesium (greater than 1.2342 mmol/L) and for phosphate (greater than 2.254 mmol/L).

CHMP's comment

Elevated hepatobiliary and pancreatic enzymes were frequent. This is not unexpected. Of note, all but 1 of the 11 TED/TED subjects with elevated ALT values had bilirubin levels within the reference range. It is acknowledged that this indicates that although the ALT and other liver enzymes were increased, the clinical picture and liver function was acceptable for this population.

Hematology

Few subjects in the TED/TED group had hematology values outside the normal range: 1 subject (2.0%) had a hematocrit of less than 0.21, 1 subject had hemoglobin less than 70 g/L, 2 subjects had leukocytes less than 2×10^9 per liter, 1 subject had leukocytes greater than 30×10^9 per liter, 3 subjects had neutrophils less than 0.5×10^9 per liter, 1 subject had platelets less than 75×10^9 per liter, and 1 subject had platelets greater than 700×10^9 per liter. In the NTT/NTT group, no markedly abnormal hematology values were reported.

Vital Signs and Other Observations Related to Safety

Vital Signs

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

Other Observations Related to Safety

No clinically meaningful changes in stool output, stool consistency, or urine output were observed during the study, despite the reductions in parenteral support in the TED/TED group, indicating that the adjustments in parenteral were appropriately titrated to match the changes in intestinal absorptive capacity.

No clinically meaningful changes in weight, height, BMI, or Z-scores were noted in the TED/TED and NTT/NTT groups indicating that the reductions in PS in the TED/TED group were appropriately titrated to match the subjects' nutritional needs.

The response of anti-teduglutide antibody formation in SHP633-304 was similar to the response of antibody formation in adult studies with teduglutide. Forty-two of 49 subjects in the TED/TED group tested negative for anti-teduglutide antibodies at Cycle 1 Day 1; 6 subjects were positive with no neutralizing antibodies present, and 1 subject was positive with neutralizing antibodies (SHP633-304 CSR, Section 12.5).

The GI-specific testing included colonoscopy, sigmoidoscopy, and fecal occult blood test. In the TED/TED group, 7 subjects were reported as having clinically significant findings: 3 subjects had ulceration of a jejunocolic anastomosis; 1 subject each had a positive fecal occult blood test at screening (colonoscopy revealed candida infection), stomal stenosis, jejunitis, and cecal polyp (which was originally recorded from colonoscopy but could not be confirmed subsequently). There were no clinically significant abnormal findings in the NTT/NTT group.

In this extension study, the safety profile of teduglutide was consistent with the prior pediatric studies in children/infants with SBS and previous experience in adult subjects with SBS.

CHMP's comment

It is agreed that in this extension study, the safety profile of teduglutide was consistent with the prior pediatric studies in children/infants with SBS and previous experience in adult subjects with SBS.

2.3.3. Discussion on clinical aspects

Study design and patient population

SHP633-304 was a Phase 3, prospective, open-label, long-term extension study to evaluate the safety and efficacy of teduglutide in pediatric subjects, including infants, with SBS who completed their core study, TED-C14-006 or SHP633-301, and who were dependent on PS.

The number of subjects in this study was not based on statistical power considerations. The maximum number of subjects was determined by the enrollment in TED-C14-006 and SHP633-301.

A total of 61 subjects were screened and enrolled. These 61 subjects constituted the safety population. All analyses were based on the safety population.

The numbers of enrollment in each of the core studies, the numbers of subjects eligible and ineligible, respectively, for the extension study at the end of the core studies, and the reasons for eligibility and ineligibility, respectively, should be provided. **OC.**

Comparisons of results observed in this extension study are made against the core study baseline, i.e. the baseline data in the TED-C14-006 and SHP633-301 studies, respectively.

The core study 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 had LPLV 18 August 2017 and a variation was submitted 16 March 2018 (CTD sequence 0112). The results of study TED-C14-006 were implemented in the SmPC in 2018.

The core study SHP633-301, a study to evaluate the safety, efficacy/pharmacodynamics (PD), and pharmacokinetics (PK) of teduglutide in infants 4 to 12 months corrected gestational age (a premature baby's chronological age minus the number of weeks or months he/she was born early) with SBS and who are dependent on parenteral support (PIP Study 8) had LPLV 24 September 2020 and the results submitted 24 March 2021(CTD sequence 0144) and are currently under regulatory review.

The present extension study included 6 infants 4 to 12 months corrected gestational age out of 10 initially included in the core study SHP633-301. The Applicant states that there were no new efficacy or safety findings from the subset analysis of these subjects. However, since the core study SHP633-301 is currently under regulatory review, no separate assessment of results compared to the core study SHP633-301 baseline in these 6 infants can be made in the extension study at this time.

As no subgroup analysis was performed this assessment concerns the results provided for the overall study population only.

As stated by the Applicant, descriptive statistics were used with a goal of summarizing the sample. As such, no claims of significance were made for any of the data. This is accepted.

A total of 8 subjects who did not receive teduglutide in the extension study: 7 subjects in the NTT/NTT group and 1 subject in the TED/NTT group. The applicant should discuss the reason for why teduglutide apparently was not needed in the 8 subjects in the NTT/NTT and TED/NTT groups. **OC.**

The efficacy summary focuses on the subject diary data. The applicant states the diary data was considered a more representative measure of efficacy than the investigator prescribed data. This is accepted.

Furthermore, as stated in the CSR, it was decided that the focus of discussion in the CSR text would compare data from approximately 2 years of subject participation in the TED/TED vs NTT/NTT groups. Therefore, the summary of teduglutide treatment efficacy focuses on the end of teduglutide treatment in Cycle 4 for the TED/TED group compared with the end of Visit NT 8 for the NTT/NTT group.

However, this time period seems arbitrary and the rationale for this decision needs further discussion. **OC.**

Efficacy

Efficacy was defined as a secondary objective of the study.

Efficacy endpoints were analyzed at the end of each teduglutide treatment period (Week 24 or end of treatment [EOT]), and at each study visit, relative to the baseline of the core study and/or first exposure to teduglutide. The following efficacy endpoints were analyzed:

- Reduction in PS volume of at least 20%, 50% and 75% at the end of each teduglutide treatment period
- Change and percentage change in PS volume and intake calories
- Enteral autonomy (complete weaning off PS)
- Change in hours per day and days per week of PS
- Quality of Life measures

While the changes in PS volume are measured against the respective core studies' baselines, the proportion of subjects achieving at least 20%, 50% and 75% reduction in PS, respectively, are calculated on the basis of the number of patients being seen at the visits Cycle 1 Day 1 (n=50) / NT1 (n=6) and Cycle 4 EOT (n=27) / NT8 (n=5), respectively.

However, these proportions do not consider the changes in PS, if any, from the core studies' baselines in the subjects not being seen at the respective visits. Therefore, the change in proportions achieving at least 20%, 50% and 75% reduction in PS, respectively, as described cannot be considered conclusive evidence of efficacy.

Furthermore, the difference between the TED/TED and the NTT/NTT groups with respect to the change in proportions achieving at least 20%, 50% and 75% reduction in PS, respectively, is difficult to interpret because the apparent smaller change in proportions in the NTT/NTT group compared to the TED/TED group may be confounded by the fact that teduglutide apparently was not needed in the 8 subjects in the NTT/NTT and TED/NTT groups.

With respect to the mean change in diary PS volume, PS calories, PS infusion time and Quality of Life measures, the means estimated at the core studies' baselines, at Cycle 1 Day 1 /NT1 and at Cycle 4 EOT / NT8, respectively, were estimated on the basis of different numbers of subjects, who were seen at these respective visits. These means do not consider the mean changes in PS volume, PS calories, PS infusion time and Quality of Life measures, if any, in the subjects not seen at these visits. Therefore, the change in means of PS volume, PS calories, PS infusion time and Quality of Life measures as described cannot be considered conclusive evidence of efficacy.

Furthermore, the difference between the TED/TED and the NTT/NTT groups with respect to the mean changes in PS volume, PS calories, PS infusion time and Quality of Life measures is difficult to interpret because the apparent smaller change (in some instances in the opposite direction) in these means in the NTT/NTT group compared to the TED/TED group may be confounded by the fact that teduglutide apparently was not needed in the 8 subjects in the NTT/NTT and TED/NTT groups.

Achievement of sustained enteral autonomy in a number of subjects is a more straightforward endpoint because both core studies required per design that all subjects were dependent on parenteral support to be eligible to enroll in the core studies. On this background this outcome is readily interpretable as a beneficial effect, although other factors than the teduglutide treatment may have contributed since the extension study is not a randomized controlled study.

Of note, since a number of patients in the core study TED-C14-006 achieved enteral autonomy during the core study, it should be clarified if all subjects enrolled in the extension study were dependent on parenteral support. **OC.**

It is noted that there are no regulatory consequences identified by the MAH as a result of this study. The extension study was primarily designed for long-term safety assessment, whereas the efficacy assessment is only a secondary objective. As the above-mentioned efficacy endpoints are presented they are considered descriptive and supportive for the existing data on efficacy only.

Safety

Safety was defined as the primary objective of the study.

The long-term exposure of 3.5±1.61 cycles or 103.19±42.047 weeks (range = 28.3 to 165.3 weeks). for the 50 subjects in the TED/TED group and similar for the ANY TED group is adequate for safety evaluation.

TEAE was reported in 100% of patients receiving teduglutide and 85.7% of patients not receiving teduglutide. TESAE was reported in 81.5% of patients receiving any teduglutide and 57.1% of patients not receiving teduglutide. This reflects the general health condition of this patient population, as only a smaller proportion of TEAEs overall was considered related to teduglutide, e.g. 31 treatment-related TEAEs in 16 subjects (32.0%) and 5 TESAEs in 4 subjects (8.0%) in the TED/TED group. Only few TEAEs led to treatment discontinuation. The most frequent TEAEs were vomiting, pyrexia, abdominal pain, upper respiratory tract infection and cough. These are all known frequent adverse events described in the SmPC.

Two deaths occurred in the study. This is not unexpected in this patient population. Both deaths were considered related to the underlying health condition and not to teduglutide. This is accepted.

It is agreed that in this study, the deaths, TESAEs, discontinuations due to TEAEs, and AESIs were consistent with the prior pediatric studies of teduglutide and previous experience with teduglutide in adult subjects with SBS.

Of note, no AESIs, meaning no Adverse events of special interest, which were defined as growth of pre-existing polyps of the colon, benign neoplasia of the GI tract including the hepatobiliary system, and tumor promoting ability (e.g., benign and/or malignant neoplasia of any kind, not limited to those of the GI or hepatobiliary system) were identified during the study.

Elevated hepatobiliary and pancreatic enzymes were frequent. This is not unexpected. Of note, all but 1 of the 11 TED/TED subjects with elevated ALT values had bilirubin levels within the reference range. It is acknowledged that this indicates that although the ALT and other liver enzymes were increased, the clinical picture and liver function was acceptable for this population.

It is agreed that in this extension study, the safety profile of teduglutide was consistent with the prior pediatric studies in children/infants with SBS and previous experience in adult subjects with SBS.

3. CHMP overall conclusion and recommendation

A number of questions are raised concerning the clarity of the data presented including details of the patient populations rolling over from the core studies to the extension study, the reason for why teduglutide apparently was not needed in the 8 subjects in the NTT/NTT and TED/NTT groups, the arbitrarily selected time period of 2 years for efficacy assessment. Overall, the efficacy data presented as change in proportions of subjects achieving 20% reduction in PS and change in means of PS volume, PS calories, PS infusion time and Quality of Life measures as described cannot be considered conclusive evidence of efficacy. Furthermore, the difference between the TED/TED and the NTT/NTT groups with respect to these efficacy endpoints is difficult to interpret because the apparent smaller change (in some instances in the opposite direction) in these proportions and means in the NTT/NTT group compared to the TED/TED group may be confounded by the fact that teduglutide apparently was not needed in the 8 subjects in the NTT/NTT and TED/NTT groups. An exception is the achievement of sustained enteral autonomy in a number of subjects. This is a more straightforward endpoint readily interpretable as a beneficial effect, although other factors than the teduglutide treatment may have contributed since the extension study is not a randomized controlled study. It is noted that there are no regulatory consequences identified by the MAH as a result of this study. The extension study was primarily designed for long-term safety assessment, whereas the efficacy assessment is only a secondary objective. As the above-mentioned efficacy endpoints are presented they are considered descriptive and supportive for the existing data on efficacy only.

With respect to safety, which is the primary objective of the study, the exposure is adequate for long-term safety evaluation. It is agreed that in this extension study, the safety profile of teduglutide was consistent with the prior pediatric studies in children/infants with SBS and previous experience in adult subjects with SBS.

☐ **Fulfilled**

☒ **Not fulfilled:**

Based on the data submitted, the MAH should provide clarifications of the data presented in the extension study report as part of this procedure (see section "Additional clarification requested")

4. Additional clarification requested

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1. SHP633-304 was a Phase 3, prospective, open-label, long-term extension study to evaluate the safety and efficacy of teduglutide in pediatric subjects, including infants, with SBS who completed their core study, TED-C14-006 or SHP633-301, and who were dependent on PS. A total of 61 subjects were screened and enrolled. These 61 subjects constituted the safety population. All analyses were based on the safety population. The numbers of enrollment in each of the core studies, the numbers of subjects eligible and ineligible, respectively, for the extension study at the end of the core studies, and the reasons for eligibility and ineligibility, respectively, should be provided.
2. Since a number of patients in the core study TED-C14-006 achieved enteral autonomy during the core study, it should be clarified if all subjects enrolled in the extension study were dependent on parenteral support.

3. A total of 8 subjects who did not receive teduglutide in the extension study: 7 subjects in the NTT/NTT group and 1 subject in the TED/NTT group. The applicant should discuss the reason for why teduglutide apparently was not needed in the 8 subjects in the NTT/NTT and TED/NTT groups.
4. As stated in the CSR, it was decided that the focus of discussion in the CSR text would compare data from approximately 2 years of subject participation in the TED/TED vs NTT/NTT groups. Therefore, the summary of teduglutide treatment efficacy focuses on the end of teduglutide treatment in Cycle 4 for the TED/TED group compared with the end of Visit NT 8 for the NTT/NTT group. However, this time period seems arbitrary and the rationale for this decision needs further discussion.

The timetable is a 30 day response timetable with clock stop.

5. MAH responses to Request for supplementary information

Question 1

SHP633-304 was a Phase 3, prospective, open-label, long-term extension study to evaluate the safety and efficacy of teduglutide in pediatric subjects, including infants, with SBS who completed their core study, TED-C14-006 or SHP633-301, and who were dependent on PS. A total of 61 subjects were screened and enrolled. These 61 subjects constituted the safety population. All analyses were based on the safety population. The numbers of enrollment in each of the core studies, the numbers of subjects eligible and ineligible, respectively, for the extension study at the end of the core studies, and the reasons for eligibility and ineligibility, respectively, should be provided.

MAH's response

A total of 59 subjects were enrolled in Study TED-C14-006 and all completed. The eligibility and ineligibility criteria for enrollment into the extension study are described in Section 9.3 of the SHP633-304 clinical study report (CSR). Of the 59 subjects, 55 subjects chose to enroll into Study SHP633-304 and were considered eligible. The remaining 4 subjects who did not screen for the extension study are listed in Table 1. If a subject chose not to enroll and was not screened, no assessments for eligibility were performed. The case report forms did not capture the reason for subject non-participation.

Table 1 Subjects in Study TED-C14-006 Who Did Not Enroll in Study SHP633-304

Subject ID	Reason For Not Continuing to the SHP633-304 304 Extension Study
[redacted]	The subject was not screened for the -304 study.
	The subject was not screened for the -304 study.
	The subject was not screened for the -304 study.
	The subject was not screened for the -304 study.

A total of 10 subjects were enrolled in Study SHP633-301; 8 subjects completed and 2 subjects discontinued early from the study. The eligibility and ineligibility criteria for enrollment into the extension study are described in Section 9.3 of the SHP633-304 CSR. Of the 8 subjects, 4 did not continue to Study SHP633-304. The reasons for the 4 subjects that did not participate are listed in Table 2.

Table 2 Subjects in Study SHP633-301 Who Did Not Enroll in Study SHP633-304

Subject ID	Reason For Non-participation in the SHP633-304 Extension Study
[redacted]	The subject was terminated early from study -301 due to withdrawal by parents, and did not transfer to -304
	The subject did not transfer because the -304 study was closing. The subject eventually transitioned to the post-approval interim access (PAIA) program.
	The subject did not transfer because the -304 study was closing. The subject was eventually transitioned to the PAIA program.
	The subject did not transfer because the -304 study was closing and because of a request for enrollment into the PAIA program.

Assessment of the MAH's response

The Applicant has provided the numbers of patients enrolled and followed in the two core studies TED-C14-006 and SHP633-301 and the extension study SHP633-304, respectively.

From study TED-C14-006 55/59 patients continued in the extension study, whereas 4 patients chose not to participate with no reason given and no assessment of potential eligibility (or ineligibility) done.

From study SHP633-301 4/10 patients continued in the extension study, whereas 2 patients discontinued the core study early and 4/8 patients, who completed the core study, did not continue to the extension study. The reasons for those 4 not continuing is provided in table 2, but, confusingly, in one of the patients it is stated that this subject was terminated early from study -301. It seems contradictory that this patient is among the 8 completers, but was terminated early from the study. The three others opted not to continue the extension study because it was closing and transitioned to the post-approval interim access program instead.

For the 4 subjects in study TED-C14-006, who competed the core study, but did not continue in the extension study, their reasons for not continuing and, more importantly, their patient characteristics with respect to the eligibility and ineligibility criteria were not captured. This is unfortunate, but since the objective of the extension study is primarily a safety study, and the impact of this data gap on the interpretation of the extension study is probably limited, it will not be pursued further.

The seemingly contradictory reason for one of the four patients, who completed study SHP633-301 but did not continue in the extension study because of early withdrawal is difficult to interpret, but the impact on the interpretation of the safety extension study, overall, is probably limited and it will not be pursued further.

Conclusion

Issue not to be pursued further.

Question 2

Since a number of patients in the core study TED-C14-006 achieved enteral autonomy during the core study, it should be clarified if all subjects enrolled in the extension study were dependent on parenteral support.

MAH's response

A total of 61 subjects were screened and enrolled in the SHP633-304 extension study. Of these, 50 received teduglutide in both their core study and the extension study (TED/TED group) and 3 subjects in the NTT/TED group had not received teduglutide in their core study but did receive teduglutide in the extension study. These 53 subjects were all dependent on PS at enrollment. To receive teduglutide treatment in the extension study required dependence upon parenteral nutrition.

Of the remaining 8 subjects, 7 in the NTT/NTT group had never received teduglutide and did not qualify for teduglutide treatment according to the treatment inclusion/exclusion criteria, and 1 subject (TED/NTT group) received teduglutide in the core study but did not receive teduglutide in this extension study (TED/NTT), again according to the treatment inclusion/exclusion criteria. These 8 subjects who did not meet all the treatment eligibility criteria for the extension study entered multiple non-teduglutide treatment periods (NTT) and were seen approximately every 12 weeks.

Treatment eligibility criteria are provided by subject in the CSR for Study SHP633-304, Appendix 16.2.1, Listing 16.2.1.3.

Assessment of the MAH's response

The Applicant has clarified that 53/61 patients enrolled in the extension study were dependent on PS at enrolment. This dependency of PS was required to meet the criteria for receiving treatment with teduglutide and it is stated that these 53 patients all received teduglutide in the extension study.

Furthermore, it is stated that 8/61 did not receive treatment with teduglutide in the extension study. It is noted that there is a long list of exclusion criteria for teduglutide treatment, which means that non-dependency of PS is the only possible reason for not receiving teduglutide. However, although not stated directly and explicitly, it may be interpreted in the context that the reason why these 8 patients were not receiving teduglutide was because they were not dependent on PS.

While the question is only partly answered and, hence, leaving a part for interpretation, the impact of this uncertainty on the overall interpretation of the safety extension study is probably limited. Not to be pursued further.

Conclusion

Issue not to be pursued further.

Question 3

A total of 8 subjects who did not receive teduglutide in the extension study: 7 subjects in the NTT/NTT group and 1 subject in the TED/NTT group. The applicant should discuss the reason for why teduglutide apparently was not needed in the 8 subjects in the NTT/NTT and TED/NTT groups.

MAH's response

The MAH would like to highlight that the SHP633-304 extension study had 2 sets of eligibility criteria - one for study eligibility and the other for treatment eligibility. While the 7 subjects in the NTT/NTT group and 1 subject in the TED/NTT group did meet the study eligibility criteria, they did not meet the teduglutide treatment eligibility criteria as indicated in the CSR for Study SHP633-304, Section 9.3.2. Subjects who did not receive teduglutide treatment (i.e., in a NTT period) were followed up every 12 weeks for safety, parenteral support requirements, and quality of life.

Assessment of the MAH's response

This question is not about the eligibility criteria, which are all described in the scientific discussion above. The Applicant's response by referring to the eligibility criteria does not answer the question.

The question is, as stated, why teduglutide apparently was not needed in the extension study in the 8 subjects in the NTT/NTT and TED/NTT groups.

However, as already discussed in the assessment of the Applicant's response to Question 2 above, although not stated directly and explicitly, it may be interpreted in the context that the reason why these 8 patients were not receiving teduglutide was because they were not dependent on PS.

While the question is only partly answered and, hence, leaving a part for interpretation, the impact of this uncertainty on the overall interpretation of the safety extension study is probably limited. Not to be pursued further.

Conclusion:

Issue not to be pursued further.

Question 4

As stated in the CSR, it was decided that the focus of discussion in the CSR text would compare data from approximately 2 years of subject participation in the TED/TED vs NTT/NTT groups. Therefore, the summary of teduglutide treatment efficacy focuses on the end of teduglutide treatment in Cycle 4 for the TED/TED group compared with the end of Visit NT 8 for the NTT/NTT group. However, this time period seems arbitrary and the rationale for this decision needs further discussion.

MAH's response

A total of 61 subjects were enrolled in this study with 50 subjects classified in the TED/TED group. Of these, all 50 subjects entered teduglutide treatment in Cycle 1, 41 subjects entered Cycle 2, 33 subjects entered Cycle 3, 27 subjects entered Cycle 4, 20 entered Cycle 5, and 3 subjects entered Cycle 6 (CSR for Study SHP633-304, Table 14.1.6.1). Of the 7 subjects in the NTT/NTT group, 5 provided data at the NT1 through NT3 visits, 4 at NT4 and NT5, 5 at NT6 through NT9, and 1 at NT10 through NT14 (CSR for Study SHP633-304, Table 14.2.2.3).

Due to the decrease in the number of subjects entering sequential treatment cycles and NTT periods, there was a corresponding decrease in the number of observations over time. Since the study intent was to present data covering as long a time as possible, while still having a large enough subject population to adequately represent the results, it was decided that the final study report should focus on data from approximately 2 years of subject participation in the TED/TED vs NTT/NTT groups. One cycle of teduglutide treatment was 24 weeks and 1 cycle in an NTT period was 12 weeks. Thus, 4 cycles of teduglutide treatment and 8 cycles of NTT each corresponded to approximately 2 years of time, giving a valid comparison in terms of length of study participation.

This summary of teduglutide treatment efficacy through the end of teduglutide treatment in Cycle 4 for the TED/TED group compared with the end of Visit NT8 in the NTT/NTT group is reflective of the durability of efficacy in the target population over the 2-year period and provides meaningful insights for clinical practice.

Assessment of the MAH's response

The explanation provided in the Applicant's response on why the summary of teduglutide treatment efficacy focuses on the end of teduglutide treatment in Cycle 4 for the TED/TED group compared with the end of Visit NT 8 for the NTT/NTT group is accepted. This was a compromise between on the one hand the desire to apply as long follow-up time as possible, and on the other hand to ensure sufficient number of patients still undergoing the treatment cycles (or equivalent non-treatment observational cycles). Furthermore, the duration of one treatment cycle of 24 weeks corresponds to two non-treatment cycles of 12 weeks. This explains that 4 treatment cycles and 8 non-treatment cycles corresponding to a period of approximately 2 years was chosen as the basis for the efficacy evaluation.

This is accepted.

On a separate note should be remembered that as the efficacy endpoints in the extension study are presented in the dossier they will be considered descriptive and supportive for the existing data on efficacy only. The extension study was primarily designed for long-term safety assessment, whereas the efficacy assessment is only a secondary objective.

Conclusion

Issue resolved.

6. CHMP Updated overall conclusion and recommendation

A number of questions that were raised during the initial assessment concerning the clarity of the data presented including details of the patient populations rolling over from the core studies to the extension study, the reason for why teduglutide was not needed in the 8 subjects in the NTT/NTT and TED/NTT groups have been at least partly clarified and will not be pursued further. The selected time period of 2 years for efficacy assessment has been adequately justified.

Overall, the efficacy data presented as change in proportions of subjects achieving 20% reduction in PS and change in means of PS volume, PS calories, PS infusion time and Quality of Life measures as described cannot be considered conclusive evidence of efficacy. Furthermore, the difference between the TED/TED and the NTT/NTT groups with respect to these efficacy endpoints is difficult to interpret because the apparent smaller change (in some instances in the opposite direction) in these proportions and means in the NTT/NTT group compared to the TED/TED group may be confounded by the fact that teduglutide was not needed in the 8 subjects in the NTT/NTT and TED/NTT groups. An exception is the achievement of sustained enteral autonomy in a number of subjects. This is a more straightforward endpoint readily interpretable as a beneficial effect, although other factors than the teduglutide treatment may have contributed since the extension study is not a randomized controlled study. It is noted that there are no regulatory consequences identified by the MAH as a result of this study. The extension study was primarily designed for long-term safety assessment, whereas the efficacy assessment is only a secondary objective. As the above-mentioned efficacy endpoints are presented they are considered descriptive and supportive for the existing data on efficacy only.

With respect to safety, which is the primary objective of the study, the exposure is adequate for long-term safety evaluation. It is agreed that in this extension study, the safety profile of teduglutide was consistent with the prior pediatric studies in children/infants with SBS and previous experience in adult subjects with SBS.

☒ Fulfilled:

No regulatory action required.