30 March 2023
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Human Medicines Division

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/P46/013.1

Note

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

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1. Introduction

On 02 May 2022, the MAH submitted a completed paediatric study for Revestive (teduglutide), 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

The MAH stated that study SHP633-305 is part of a clinical development program.

2.2. Information on the pharmaceutical formulation used in the study

Teduglutide [rDNA origin] is an analog of naturally occurring human glucagon-like peptide-2, a peptide secreted by L-cells of the distal intestine. Teduglutide under the trade name Revestive® first received marketing authorization in the European Union via a 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 investigational product (IP) was teduglutide, which was provided in 3 mL vials containing 5 mg or 1.25 mg teduglutide as a white lyophilized powder that was reconstituted using 0.5 mL sterile water for injection. The formulation also contained L-histidine, mannitol, monobasic sodium phosphate monohydrate, and dibasic sodium phosphate as excipients.

2.3. Clinical aspects

2.3.1. Introduction

The MAH has submitted the results of SHP633-305, a study to evaluate the safety and efficacy of teduglutide in a population of Japanese paediatric subjects with SBS and who were dependent on parenteral support (PS).

SHP633-305 was a Phase 3, prospective, open-label, long-term extension study that was conducted to evaluate the safety and efficacy of teduglutide in a population of Japanese paediatric subjects with SBS who completed Study SHP633-302 (core study).

2.3.2. Clinical study

Clinical study number and title:

SHP633-305

A Phase 3, prospective, open-label, long-term extension study.

Description

Methods

Study participants

Subjects who previously received teduglutide and completed the core study were eligible for this extension study. Eligibility for teduglutide treatment was assessed separately. Subjects could participate in multiple no-teduglutide treatment (NTT) periods and/or multiple 28-week teduglutide treatment cycles depending on the disease course.

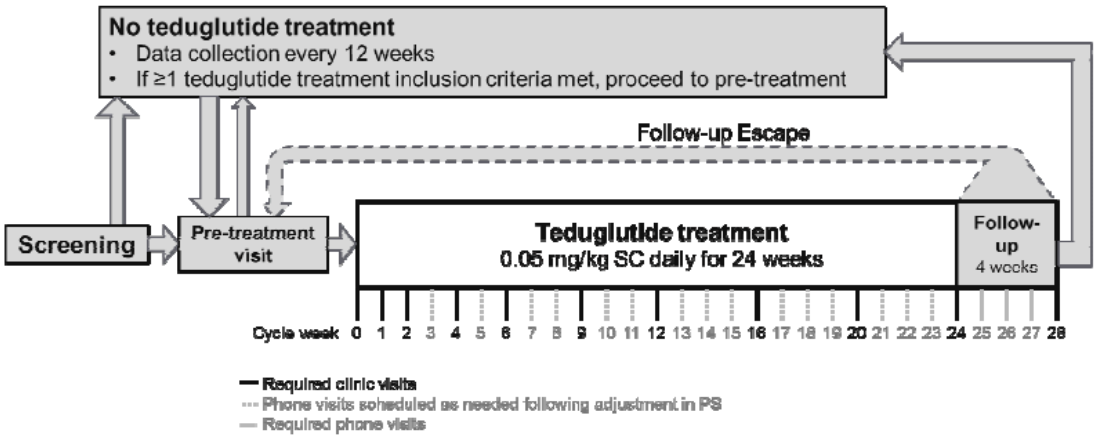
Treatments

The investigational product (IP) was teduglutide, which was provided in 3 mL vials containing 5 mg or 1.25 mg teduglutide as a white lyophilized powder that was reconstituted using 0.5 mL sterile water for injection. The formulation also contained L-histidine, mannitol, monobasic sodium phosphate monohydrate, and dibasic sodium phosphate as excipients.

After screening, subjects who met at least 1 of the teduglutide treatment inclusion criteria and none of the teduglutide treatment exclusion criteria were eligible for teduglutide treatment if the investigator and the subject (and/or parent/guardian) agreed to proceed with teduglutide treatment.

A schematic representation of the study design is presented in **Figure 1.**

Figure 1. SHP633-305 Study Diagram



PS=parenteral support; SC=subcutaneous.

Figure legend: Safety and efficacy data for subjects not receiving teduglutide treatment were captured approximately every 12 weeks, but subjects could proceed to the pretreatment visit at any time in order to assess eligibility for teduglutide therapy. Subjects eligible for teduglutide entered a 28-week cycle. During this cycle, subjects returned to the site for safety and efficacy assessments at Day 1 (Week 0) and Weeks 1, 2, 4, 6, 9, 12, 16, 20, 24, and 28 (**solid black lines**). Phone visits were required approximately 1 week after adjustments in PS during the intervening weeks between Weeks 2 and 24 (**dashed gray lines**). At Week 24, subjects entered a 4-week follow-up period, where teduglutide was not received, with phone visits performed weekly (**solid gray lines**). If at least 1 escape criterion was met during the follow-up period, subjects proceeded directly to another pretreatment visit.

Objective(s)

To evaluate the safety and efficacy of teduglutide in a population of Japanese paediatric subjects with SBS and who were dependent on parenteral support (PS)

Outcomes/endpoints and measurements

The analyses of weekly PS volume were based on 2 data sources: each subject's diary data and the investigator-prescribed data. The diary weekly PS volume was calculated based on the daily diary volumes within 7 days prior to each scheduled visit. Investigator-prescribed data were captured from electronic case report forms.

Treatment-emergent adverse events were defined as any adverse events (AEs) whose onset occurred, severity worsened, or intensity increased after receiving the IP in the core study or this extension study.

The investigator conducted the prespecified examinations, observations, and evaluations at the designated time points shown in **Table 1**, **Table 2**, and **Table 3**.

Subjects who dropped out of the study prior to the final visit had all early termination procedures performed, whenever possible.

Table 1. Schedule of Events Required for All Subjects

Period	Screening	End of Study or Early Termination
Visit Type	**Site**	**Site**
Informed consent/assent[a]	X	
Study eligibility	X	
Demographics, medical history[b], SBS history[c]	X	
Dispense intake and output diaries	X	
Evaluate teduglutide treatment inclusion criteria[d]	X	
Adverse events	X	X
Concomitant medications and procedures	X	X
Physical examination and vital signs, including weight		X
Height and head circumference[e]		X
Review intake and output diaries[f]		X
Record PS prescriptions, and adjust as needed[g]	X	X
Safety laboratory tests[h]		X
Antibodies to teduglutide		X
FOBT[i]		(X)
Colonoscopy/sigmoidoscopy[j]		(X)
Pregnancy test[k]		(X)

Table 1. Schedule of Events Required for All Subjects

Period	Screening	End of Study or Early Termination
Visit Type	**Site**	**Site**

EN=enteral nutrition; EOS=end of study; ET=early termination; FOBT=fecal occult blood test; IP=investigational product; PS=parenteral support; SBS=short bowel syndrome

[a] In general, subjects (and/or parent or guardian, as applicable) signed consent (and informed assent, if applicable) to participate in Study SHP633-305 within 7 days after completion of the core study.

[b] Updates to the medical history were collected, consisting of adverse events that were ongoing at the time of completion of SHP633-302 and events that occurred during the period between completion of SHP633-302 and informed consent/assent to Study SHP-633-305.

[c] If the subject had any changes to the SBS history collected at the baseline of the core study, then the updated SBS history was collected.

[d] If 1 or more teduglutide treatment eligibility criteria were satisfied, the first pretreatment visit assessments could begin immediately and could be combined with the core study Week 28 (EOS) assessments if performed within 7 days of the core study EOS visit.

[e] Head circumference was measured in subjects no more than 36 months of age.

[f] The intake diary was completed daily for a minimum of 2 weeks prior to the EOS/ET visit. The output diary was completed daily over a 48-hour period of PS and EN stability before the EOS/ET visit.

[g] Parenteral support prescription was collected at the screening visit. Parenteral support adjustments were made after review of the intake and output diaries and the safety lab data according to the guidance for nutrition support adjustment provided in Appendix 16.1.1, Protocol Appendix 2 and Appendix 3.

[h] Safety laboratory assessments at site visits consisted of biochemistry, hematology, and urinalysis, with results processed by a central laboratory. Urine specimen collection was attempted as part of the safety lab tests, but lack of urinalysis was not a protocol deviation.

[i] The FOBT was performed on an annual basis, approximately every 48 to 60 weeks at a minimum.

[j] The need for colonoscopy/sigmoidoscopy in response to a positive FOBT result during a no-teduglutide treatment period was at the discretion of the investigator, but all subjects underwent colonoscopy/sigmoidoscopy after they had received the equivalent of 2 treatment cycles (48 weeks of IP exposure).

[k] Pregnancy testing was required for female subjects of childbearing potential at an ET visit if the subject lacked a pregnancy test result 30 days or more after IP discontinuation.

Note: (X) denotes conditional requirement for a given assessment if the subject met certain conditions per protocol.

Table 2. Schedule of Events for Subjects Not Receiving Teduglutide

Visit Number	NTx
Visit Type	**Site**
Visit Frequency	**Every 12 weeks**
Window (days)[a]	±7
Physical examination and vital signs, including weight	X
Height and head circumference[c]	X
Review intake and output diaries[d]	X
Record PS prescriptions, and adjust as needed[e]	X
Safety laboratory tests[f]	X
Antibodies to teduglutide[g]	(X)
FOBT[h]	Annually
Colonoscopy/sigmoidoscopy[i]	(X)
Serum sample[j]	Every 24 weeks

EN=enteral nutrition; FOBT=fecal occult blood test; IP=investigational product; NTx=no teduglutide treatment (x: the cycle number); PS=parenteral support.

[a] Window was relative to the first NTx visit in the current no-teduglutide treatment period.

[b] Subjects who met at least 1 teduglutide treatment inclusion criteria could proceed to the pretreatment visit if the investigator and the subject (and/or parent/guardian, as applicable) agreed to proceed with teduglutide therapy.

[c] Head circumference was measured in subjects no more than 36 months of age.

[d] The intake diary was completed daily for a minimum of 2 weeks prior to each NTx visit. The output diary was completed daily over a 48-hour period of PS and EN stability before each NTx visit.

[e] PS adjustments were made after review of the intake and output diaries and the safety lab data according to the guidance for nutrition support adjustment provided in Appendix 16.1.1, Protocol Appendix 2 and Protocol Appendix 3.

[f] Safety laboratory assessments at site visits consisted of biochemistry, hematology, and urinalysis, with results processed by a central laboratory. Urine specimen collection was attempted as part of the safety lab tests, but lack of urinalysis was not a protocol deviation.

[g] Subjects who were treated previously and tested positive for antibodies specific to teduglutide had follow-up samples collected every 12 weeks until a negative result was obtained or the study ended.

[h] The FOBT was performed on an annual basis, approximately every 48 to 60 weeks at a minimum.

[i] The need for colonoscopy/sigmoidoscopy in response to a positive FOBT result during an NTx period was at the discretion of the investigator, but all subjects underwent colonoscopy/sigmoidoscopy after they had received the equivalent of 2 treatment cycles (48 weeks of IP exposure).

[j] Lack of collection of serum samples was not a protocol deviation. Saved serum samples were omitted for subjects weighing less than 10 kg and whenever local blood volume limitations were exceeded.
Note: (X) denotes conditional requirement for a given assessment if the subject met certain conditions per protocol.

Table 2. Schedule of Events for Subjects Not Receiving Teduglutide

Visit Number	NTx
Visit Type	Site
Visit Frequency	Every 12 weeks
Window (days)[a]	±7
Dispense intake and output diaries	X
Evaluate teduglutide treatment inclusion criteria[b]	X
Adverse events	X
Concomitant medications and procedures	X

Table 3. Schedule of Events for Subjects While Receiving Teduglutide (Teduglutide Treatment Period)

Period	Pre-treatment	Teduglutide Treatment															Follow-Up	
Physical examination and vital signs, including weight	X	X	X	X		X		X		X		X		X		X		X
Height and head circumference[f]	X	X								X						X		
Review intake and output diaries[g]	X	X	X	X		X		X		X		X		X		X	X	X
Record PS Rx, and adjust as needed[h]	X	X	X	X		X		X		X		X		X		X	X	X
Safety laboratory tests[i]	X[i]	X	X	X		X		X		X		X		X		X	(X)	X
Antibodies to teduglutide[j]		X								X						X		X
FOBT	X									X						X		
Colonoscopy/ sigmoidoscopy[k]	(X)									(X)						(X)		
Pregnancy testing[l]	X	X				X			X	X		X		X		X		X
Serum sample[m]	X															X		
Evaluate escape criteria[n]																	X	X

Table 3. Schedule of Events for Subjects While Receiving Teduglutide (Teduglutide Treatment Period)

Period	Pre-treatment	Teduglutide Treatment															Follow-Up	
Visit Number	Px[a]	Cx D1	Cx W1	Cx W2	Phone visit is required approximately 1 week after PS adjustment	Cx W4	Phone visit is required approximately 1 week after PS adjustment	Cx W6	Phone visit is required approximately 1 week after PS adjustment	Cx W9	Phone visit is required approximately 1 week after PS adjustment	Cx W12	Phone visit is required approximately 1 week after PS adjustment	Cx W16	Phone visit is required approximately 1 week after PS adjustment	Cx W20	Phone visit is required approximately 1 week after PS adjustment	Cx W24 (EOT)	Cx W25 Cx W26 Cx W27	Cx W28[c]
Visit Type	Site	Site	Site	Site		Site		Site		Site		Site		Site		Site		Site	Phone[b]	Site
Cycle Day	-21 to 0	1	8	15		29		43		64		85		113		141		169	176 183 190	197
Window (days)[d]			±2	±2		±2		±2		±4		±4		±4		±4		±4	±2	±2
Evaluate teduglutide eligibility (inclusion and exclusion) criteria	X	X[e]																		
Dispense intake and output diaries	X	X	X	X		X		X		X		X		X		X		X		X
Adverse events	X	X	X	X		X		X		X		X		X		X		X	X	X
Concomitant medications and procedures	X	X	X	X		X		X		X		X		X		X		X	X	X

Table 3. Schedule of Events for Subjects While Receiving Teduglutide (Teduglutide Treatment Period)

Period	Pre-treatment	Teduglutide Treatment																Follow-Up	
Review IP administration diary[e]			X	X		X		X		X		X		X		X			
Dispense IP and IP administration diary		X	X	X		X		X		X		X		X					
Confirm administration proficiency		X[p]																	

AE=adverse event; CSR=clinical study report; Cx=Cycle x; D1=Day 1 of teduglutide treatment cycle; eCRF=electronic case report form; EN=enteral nutrition; EOS=end of study; EOT=end of treatment; ET=early termination; FOBT=fecal occult blood test; GI=gastrointestinal; INR= international normalized ratio IP=investigational product; PS=parenteral support; ; Rx=prescription; Px=pretreatment; W=week.

[a] The first pretreatment visit was combined with the screening visit and core study EOS visit (Week 28) if the pretreatment visit assessments occurred within 7 days of the core study EOS assessments. If subjects proceeded directly from screening to the pretreatment visit, the first pretreatment visit occurred within 12 weeks of screening.

[b] Phone visits were required approximately 1 week after an adjustment in PS. The assessments performed at phone visits were the same as those described for CxW25 to 27 (except for evaluation of escape criteria).

[c] Whenever possible, subjects who withdrew early from the study during a teduglutide treatment cycle completed the EOT visit and 4-week follow-up period (CxW25 to 27) and then proceeded to the ET visit in protocol Table 1. The ET visit took place in lieu of the CxW28 visit. The investigator could combine the CxW28 visit with the pretreatment visit if at least one escape criterion was met at the CxW28 visit.

[d] Visit windows were relative to the CxD1 visit.

[e] Eligibility needed to be reconfirmed prior to the first dose in the cycle. A negative urine pregnancy test result was required prior to the first dose of teduglutide, but results of other lab tests obtained at the CxD1 visit were not required to determine teduglutide treatment eligibility.

[f] Head circumference was measured in subjects no more than 36 months of age.

[g] The intake diary was completed daily for a minimum of 2 weeks immediately prior to each clinic visit (except at pretreatment visit), for 1 week after PS adjustment, and daily during the 4-week follow-up period. The output diary was completed daily over a 48-hour period of PS and EN stability before each clinic or phone visit and within 1 week of implementing a change in the PS prescription.

[h] Parenteral support adjustments were made after review of the intake and output diaries and the safety lab data according to the nutritional support adjustment guidelines and weaning algorithms provided in CSR SHP633-305, Appendix 16.1.1, Protocol Appendix 2 and Protocol Appendix 3.

Assessor´s comments

The MAH has submitted the results of SHP633-305, a study to evaluate the safety and efficacy of teduglutide in a population of Japanese paediatric subjects with SBS and who were dependent on parenteral support (PS). SHP633-305 was a Phase 3, prospective, open-label, long-term extension study that was conducted to evaluate the safety and efficacy of teduglutide in a population of Japanese paediatric subjects with SBS who completed Study SHP633-302 (core study).

Subjects who previously received teduglutide and completed the core study were eligible for this extension study. Eligibility for teduglutide treatment was assessed separately. Subjects could participate in multiple no-teduglutide treatment (NTT) periods and/or multiple 28-week teduglutide treatment cycles depending on the disease course.

The investigational product (IP) was teduglutide, which was provided in 3 mL vials containing 5 mg or 1.25 mg teduglutide.

The MAH is asked to clarify the age-limits selected and the number of patients in each age-group included in study SHP633-005 (extension). Furthermore, as only Japanese paediatric subjects were included the present study, the MAH should discuss the contribution of data from the Japanese paediatric population with respect to extrapolation to the general paediatric population e.g. in by integrating covariate information on race in the Pop PK model previously presented **(OC)**.

Results

Participant flow

Recruitment

Baseline data

Demographics and Baseline Characteristics:

The disposition of the subjects in the Safety population is summarized in **Table 4**. One subject received teduglutide in the core study and is counted in the Safety Population, despite the subject not receiving teduglutide in this extension study. This subject had achieved enteral autonomy at Week 12 of the core study and has maintained it; this subject was monitored in the NTT periods of the study to provide safety data. Of the 7 total children who received IP treatment, 1 discontinued treatment due to a treatment-emergent adverse event (TEAE), but all children completed the study. Both infants were treated with IP; 1 discontinued the study due to a TEAE.

The mean (± standard deviation) age of the total children was 6.70 (±3.754) years at the beginning of the core study, and males accounted for 85.7% (6 of 7 subjects).

Table 4. Subject Disposition (Safety Population)

	Total Children (N=7) n (%)	Total Infants (N=2) n (%)
Treated with teduglutide	6 (85.7)	2 (100.0)
Discontinued IP or study due to TEAE	1 (14.3)	1 (50.0)
Completed study	7 (100.0)	1 (50.0)

CSR=clinical study report; IP=investigational product; N=number of subjects in a group; n=number of subjects meeting specified criteria; TEAE=treatment-emergent adverse event

Table 8. Demographic and Other Baseline Characteristics (Safety Population)

Parameters	Statistics	Total Children (N=7)	Total Infants (N=2)
Age of children at core study informed consent (years)	Mean (SD)	6.70 (3.754)	-
Age of infants at core study informed consent (months)			
Chronological age	Mean (SD)	-	10.80 (1.838)
Corrected gestational age	Mean (SD)	-	9.95 (1.202)
Sex			
Male	n (%)	6 (85.7)	1 (50.0)
Female	n (%)	1 (14.3)	1 (50.0)
Race			
Asian (Japanese)	n (%)	7 (100.0)	2 (100.0)
Height/length for age Z-score at baseline	Mean (SD)	-1.965 (1.3906)	-3.652 (1.1428)
Height/length for age percentile at baseline (%)	Mean (SD)	13.95 (26.340)	0.11 (0.157)
Weight for age Z-score at baseline	Mean (SD)	-1.886 (1.4859)	-2.916 (2.6705)
Weight for age percentile at baseline (%)	Mean (SD)	14.35 (17.692)	7.60 (10.751)
BMI for age Z-score at baseline (children only)	Mean (SE)	-0.962 (0.6059)	-
BMI for age percentile at baseline (children only) (%)	Mean (SE)	30.64 (13.692)	-
Weight for length Z-score at baseline (infants only)	Mean (SE)	-	-1.349 (3.4688)
Weight for length percentile at baseline (%) (infants only)	Mean (SE)	-	49.15 (49.148)
Head circumference[a] for age Z-score at baseline	Mean (SE)	2.633 (-)	0.040 (1.9902)
Head circumference[a] for age percentile at baseline (%)	Mean (SE)	99.58 (-)	50.22 (47.663)

BMI=body mass index; N=number of subjects in a group; n=number of subjects meeting specified criteria; SD=standard deviation; SE=standard error.

Note: Demographic and baseline data are from baseline in the core study.

[a] Head circumference was calculated for children up to 36 months of age.

The mean corrected gestational age of the total infant cohort enrolled at the beginning of the core study was 9.95 ±1.202 months, with 1 infant of each sex.

Table 9. Short Bowel Syndrome History (Safety Population)

Parameter	Total Children (N=7)	Total Infants (N=2)
Duration of SBS at baseline for children (years), mean (SD)	6.66 (3.737)	-
Duration of SBS at baseline for infants (months), mean (SD)	-	10.66 (1.928)
Primary reason for diagnosis of SBS:		
Midgut volvulus, n (%)	6 (85.7)	1 (50.0)
Intestinal atresia, n (%)	1 (14.3)	0 (0.0)
Other, n (%)	0 (0.0)	1 (50.0)
Is there a secondary reason for the diagnosis of SBS?		
Yes, n (%)	1 (14.3)	1 (50.0)
No, n (%)	6 (85.7)	1 (50.0)
If yes, secondary reason:		
Necrotizing enterocolitis, n (%)	1 (100.0)	0 (0.0)
Intestinal atresia, n (%)	0 (0.0)	1 (100.0)
Subjects with a stoma, n	0	0
Subjects with remaining colon, n (%)	7 (100.0)	2 (100.0)
Estimated percentage of colon remaining (%):		
Mean (SD)	90.00 (26.458)	75.00 (35.355)
Min, max	30, 100	50, 100
Colon in continuity[a], n (%)	7 (100.0)	2 (100.0)
Colonoscopy within 12 months of core study screening?		
Yes, n (%)	0 (0.0)	0 (0.0)
No, n (%)	7 (100.0)	2 (100.0)
Estimated remaining small intestinal length (cm):		
n	6	2
Mean (SD)	22.00 (17.056)	6.00 (5.657)
Distal/terminal ileum present?		
Yes, n (%)	5 (71.4)	1 (50.0)
No, n (%)	2 (28.6)	1 (50.0)
If yes, is the ileocecal valve present?[b]		
Yes, n (%)	4 (80.0)	1 (100.0)
No, n (%)	1 (20.0)	0 (0.0)

In total children, the mean duration of SBS was 6.66 ±3.737 years. The main underlying cause of SBS was midgut volvulus (6 subjects [85.7%]). The mean remaining small intestine length was 22.00 ±17.056 cm. The children had at least 30% of their colon remaining, with a mean of 90.00 ±26.458%, and none had a stoma. Five of the 7 total children (71.4%) had a distal or terminal ileum and 4 (80.0%) retained an ileocecal valve. In the 2 infants, the mean duration of SBS was 10.66 ±1.928 months (approximately since birth).

The main underlying cause of SBS was midgut volvulus for 1 infant and congenital absence of the midgut for the other. Neither infant had a stoma. The mean remaining small intestine length was 6.00 ±5.657 cm. One infant had 50% of the colon remaining, and the other had 100%. One infant had a distal or terminal ileum and retained an ileocecal valve.

Assessor´s comments

The mean (± standard deviation) age of the total children was 6.70 (±3.754) years at the beginning of the core study, and males accounted for 85.7% (6 of 7 subjects).

The MAH is asked to present demographic and baseline data more detailed:

a) The MAH is asked to add individual age specific data on all subjects in the Table 4

b) The MAH is asked to add median and range for all parameters in table 8 and 9

(OC).

Efficacy results

The MAH states that generally, no remarkable discrepancy between the diary and prescribed-based data was found in efficacy endpoints. The diary data were considered a more representative measure of efficacy than the investigator-prescribed data by the MAH; therefore, the efficacy summary focuses on the diary data results. As the tabulated data indicate, the number of subjects participating in each treatment cycle decreased, such that only 3 of the total children cohort had data for Cycle 5, 2 for Cycle 6, and only 1 had data for Cycles 7, 8, and 9.

Change From Core Study Baseline in Parenteral Support

Change in Weekly Parenteral Support Volume from Baseline Based on Subject

Diary Data

The diary data are presented by cycle in Table 5.

Table 5. Mean Percentage Change From Baseline in Parenteral Support Volume To End of Treatment and Week 28 By Cycle - Diary Data (Safety Population)

	Mean CS Baseline (SD) (mL/kg/day)	Mean Percentage Change From Baseline (SD)[a]											
		Cycle 1		Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8	Cycle 9	Last Cycle
		EOT	Wk 28	EOT	Wk 28	EOT	EOT	EOT	EOT	EOT	EOT	EOT	EOT
Total children (N=7)	61.5 (33.57)	n=6 -39.6 (34.86)	n=6 -36.8 (38.06)	n=6 -44.3 (33.11)	n=2 -60.4 (38.24)	n=6 -52.8 (28.54)	n=5 -62.9 (26.18)	n=3 -73.9 (5.30)	n=2 -75.7 (0.54)	n=1 -82.9	n=1 -70.9	n=1 -69.8	n=6 -62.3 (30.57)
Total infants (N=2)	99.7 (5.56)	n=2 -32.5 (18.10)	n=1 -21.0	n=1 -56.6	ND	n=1 -65.6	n=1 -100.0	ND	ND	ND	ND	ND	n=2 -59.8 (56.79)

CS=core study; CSR=clinical study report; EOT=end of treatment; N=number of subjects in a group; n=number of subjects meeting specified criteria; ND=no data; SD=standard deviation; Wk=week

[a] n=The number of subjects who were treated in the specific treatment period.
Note: End of treatment is defined as the last available measurement after the date of first dose during the 24-week treatment period.

In total children (n=7), the mean diary PS volume at core study baseline was 61.5 ±33.57 mL/kg/day. The mean change from baseline at end of treatment (EOT) of Cycle 1 was -21.5 ±11.83 mL/kg/day (median= -25.3 mL/kg/day) or -39.6 ±34.86%. The Week 28 mean percentage change from baseline for Cycle 1 of -36.8% suggests that clinically meaningful reduction was mostly maintained during the 4-week untreated follow-up period from EOT to Week 28.

In infants (n=2), the mean diary PS volume at core study baseline was 99.7 ±5.56 mL/kg/day.

The mean change from baseline at EOT of Cycle 1 was -31.9 ±16.24 mL/kg/day or -32.5 ±18.10%, which is similar to that for total children in Cycle 1.

The data for subsequent treatment cycles indicate a trend towards increasing IP efficacy, as reflected by increasing percentage decreases from baseline in mean diary PS volumes. This trend was evident for both total children and infants. The descriptive analysis of PS volume diary data is shown by cycle and visit for the safety population in SHP633-305 CSR.

At Least 20% Reduction From Baseline in Parenteral Support Volume

The results of the number and percentage of subjects who achieved at least a 20% reduction in weight-normalized PS volume at Cycle 1 time points based on diary and prescribed data are shown in **Table 6.**

Table 6. Subjects With At Least a 20% Reduction in Parenteral Support Volume During Cycle 1 By Visit - Diary and Prescribed Data (Safety Population)

Parameter	Total Children (N=7)[a]		Total Infants (N=2)[a]	
	Diary n (%)	Prescribed n (%)	Diary n (%)	Prescribed n (%)
Week 16	n=6 3 (50.0)	n=6 3 (50.0)	2 (100)	1 (50.0)
Week 20	n=6 3 (50.0)	n=6 5 (83.3)	2 (100)	2 (100)
Week 24	n=6 4 (66.7)	n=6 5 (83.3)	1 (50.0)	1 (50.0)
EOT	n=6 4 (66.7)	n=6 5 (83.3)	1 (50.0)	1 (50.0)
Week 25 (follow-up)	n=6 4 (66.7)	n=6 5 (83.3)	2 (100)	1 (50.0)
Week 26 (follow-up)	n=6 4 (66.7)	n=6 5 (83.3)	n=1 1 (100)	n=1 0 (0.0)
Week 27 (follow-up)	n=6 4 (66.7)	n=6 5 (83.3)	n=1 1 (100)	n=1 0 (0.0)
Week 28	n=6 4 (66.7)	n=6 5 (83.3)	n=1 1 (100)	n=1 0 (0.0)

CSR=clinical study report; EOT=end of treatment; N=number of subjects in a group; n=number of subjects who had at least a 20% reduction in parenteral support volume

[a] n=The number of subjects who were treated in the specific treatment period.
Note: Percentages are based on the number of subjects who had diary/prescribed data relevant to the visit.
Note: Percentage (%) reduction was calculated as (change from baseline of the core study at the scheduled visit/core study baseline value) × 100, using average daily value normalized by weight.

In total children, 2 subjects (33.3%) were recorded at Day 1 (initiation of this study) in the diary and prescribed data who achieved at least a 20% reduction in weight-normalized PS volume compared to baseline in the core study, and this increased to 4 subjects (66.7%) in diary data and 5 subjects (83.3%) in prescribed data as the visits progressed to the EOT in Cycle 1. These subjects maintained their status during the 4-week untreated follow-up period.

Both infant subjects (100%) achieved at least a 20% reduction in weight-normalized PS volume at Day 1 (initiation of this study) in diary data and 1 subject (50%) in prescribed data.

For NTT periods, reduction in PS volume by visit based on diary/prescribed data is summarized in SHP633-305 CSR.

Achievement of Enteral Autonomy

There were 2 subjects in the total children cohort that achieved enteral autonomy—1 subject sustained from the core study and the second subject achieved enteral autonomy during the extension study. The SBS characteristics at baseline and the changes in PS volume at EOT by subject are summarized in Table 7. The number of subjects achieving enteral autonomy by cycle and visit are presented in SHP633-305 CSR and for diary data in SHP633-305 CSR.

One child achieved enteral autonomy at Cycle 1 Week 4, which was sustained through Cycle 2 Week 12. This subject had SBS due to intestinal atresia. The residual small bowel length was estimated at 48 cm, with no distal or terminal ileum, no ileocecal valve, but 100% of colon remaining.

The other child achieved enteral autonomy at Week 12 in the core study, did not receive teduglutide in this extension study, and maintained enteral autonomy during NTT periods. This subject had SBS due to midgut volvulus. The residual small bowel length was estimated at 25 cm, with distal or terminal ileum and ileocecal valve present and 100% of colon remaining.

While both infants achieved the 20% milestone reduction in PS volume based on diary data, only 1 achieved enteral autonomy. One subject achieved enteral autonomy at Cycle 4 Week 4, which was sustained for 28 days to the end of study participation. This subject had SBS due to midgut volvulus. The residual small bowel length was estimated at 10 cm, with distal or terminal ileum and ileocecal valve present and 100% of colon remaining.

Table 1. Physical Details and Efficacy Results By Subject - Diary Data (Safety Population)

Cohort	Race/Sex	Primary Reason for the Diagnosis of SBS	Estimated Remaining Small Intestinal Length (cm)	Presence of the Distal/ Terminal Ileum?	Ileocecal Valve Present?	Remaining Colon?	Estimated Percentage of Colon Remaining	Cycle/Week Enteral Autonomy Achieved[b]	Change of PS at EOT mg/kg/d	Percent Change of PS at EOT	Change in Days Per Week of PS at EOT
Infant	Asian/ Female	Other: Congenital absence of midgut	2	No	No	Yes	50%	Never	-20.4	-19.7%	0
Infant	Asian/Male	Midgut volvulus	10	Yes	Yes	Yes	100%	Cycle 4/ Week 4	-95.8	-100%	-7
Children	Asian/Male	Midgut volvulus	1.5	Yes	Yes	Yes	100%	Never	-23.9	-23.3%	0
Children	Asian/Male	Midgut volvulus	Unknown	Yes	Yes	Yes	100%	Never	-12.8	-27%	0
Children[c]	Asian/Male	Midgut volvulus	25	Yes	Yes	Yes	100%	NTT1	-27.5	-100%	-7
Children[d]	Asian/Male	Midgut volvulus	6.5	No	No	Yes	100%	Never	-79.1	-69.8%	0
Children	Asian/Male	Midgut volvulus	19	Yes	No	Yes	30%	Never	-41.4	-75.3%	0

Table 1. Physical Details and Efficacy Results By Subject - Diary Data (Safety Population)

Cohort	Race/Sex	Primary Reason for the Diagnosis of SBS	Estimated Remaining Small Intestinal Length (cm)	Presence of the Distal/ Terminal Ileum?	Ileocecal Valve Present?	Remaining Colon?	Estimated Percentage of Colon Remaining	Cycle/Week Enteral Autonomy Achieved[b]	Change of PS at EOT mg/kg/d	Percent Change of PS at EOT	Change in Days Per Week of PS at EOT
Children	Asian/Male	Midgut volvulus	32	Yes	Yes	Yes	100%	Never	-41.6	-78.3%	0
Children	Asian/ Female	Intestinal atresia	48	No	No	Yes	100%	Cycle 1/ Week 4	-31.2	-100%	-7

CSR=clinical study report; d=day; EOT=end of treatment; PS=parenteral support; SBS=short bowel syndrome

[a] Age is shown as years for total children and for infants as age in months/corrected gestational age in months.

[b] A subject was considered to have achieved enteral autonomy when the investigator prescribed no PS and there was no use of PS recorded in the diary during the 7 days prior to the visit, and sustained throughout the treatment period.

[c] Achieved enteral autonomy in the core study at Week 12; sustained in this study.

[d] Subject was enrolled preamendment 3 in the core study and preamendment 2 in this extension study, but approximately 80% of total enrolled days were postamendment.

Note: End of treatment was defined as the last available measurement during the 24-week treatment period.

Decrease of Number of Days Per Week in Parenteral Support Usage

At core study baseline, all subjects had 7 days per week of PS usage. There were 2 total children who achieved enteral autonomy (Section 5.2.1.3). The mean results for change in days per week of PS usage for total children and infants are presented in **Table 8**.

In total children, the mean change from baseline at EOT of each cycle based on diary data was -1.2 ±2.86 days/week for Cycles 1, 2, and 3; -1.4 ±3.13 days/week for Cycle 4; and 0.0 days/week for Cycles 5, 6, 7, and 8. The Week 28 mean change from baseline for Cycle 1 of -1.2 days/week suggests that the reduction was maintained during the 4-week untreated follow-up period from EOT to Week 28.

In infants, the number of days per week in PS usage were not reduced until Cycle 4, when 1 infant achieved enteral autonomy. The other infant required PS 7 days/week both at baseline and throughout the study.

Table 8. Mean Change From Baseline in Days Per Week of Parenteral Support To End of Treatment and Week 28 By Cycle - Diary Data (Safety Population)

		Change From Baseline (SD) in Days Per Week of PS											
	Mean Core Study Baseline (SD) (days/week)	Cycle 1		Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8	Cycle 9	Last Cycle
		EOT	Wk 28	EOT	Wk 28	EOT	EOT	EOT	EOT	EOT	EOT	EOT	EOT
Total children (N=7)	7.0 (0.00)	n=6 -1.2 (2.86)	n=6 -1.2 (2.86)	n=6 -1.2 (2.86)	n=2 -3.0 (4.24)	n=6 -1.2 (2.86)	n=5 -1.4 (3.13)	n=3 0.0 (0.00)	n=2 0.0 (0.00)	n=1 0.0	n=1 0.0	n=1 0.0	n=6 -1.2 (2.86)
Total infants (N=2)	7.0 (0.00)	n=2 0.0 (0.0)	n=1 0.0	n=1 0.0	ND	n=1 0.0	n=1 -7.0	ND	ND	ND	ND	ND	n=2 -3.5 (4.95)

CSR=clinical study report; EOT=end of treatment; N=number of subjects in a group; n=number of subjects meeting specified criteria; ND=no data; PS=parenteral support; SD=standard deviation; Wk=week.
Note: End of treatment is defined as the last available measurement after the date of first dose during the 24-week treatment period.

Assessor´s comments

The MAH states that generally, no remarkable discrepancy between the diary and prescribed-based data was found in efficacy endpoints. The diary data were considered a more representative measure of efficacy than the investigator-prescribed data by the MAH; therefore, the efficacy summary focuses on the diary data results. As the tabulated data indicate, the number of subjects participating in each treatment cycle decreased, such that only 3 of the total children cohort had data for Cycle 5, 2 for Cycle 6, and only 1 had data for Cycles 7, 8, and 9.

Change From Core Study Baseline in Parenteral Support

Change in Weekly Parenteral Support Volume from Baseline Based on Subject

Diary Data

In total children (n=7), the mean diary PS volume at core study baseline was 61.5 ±33.57 mL/kg/day. The mean change from baseline at end of treatment (EOT) of Cycle 1 was -21.5 ±11.83 mL/kg/day (median= -25.3 mL/kg/day) or -39.6 ±34.86%. The Week 28 mean percentage change from baseline for Cycle 1 of -36.8% suggests that clinically meaningful reduction was mostly maintained during the 4-week untreated follow-up period from EOT to Week 28.

In infants (n=2), the mean diary PS volume at core study baseline was 99.7 ±5.56 mL/kg/day.

The mean change from baseline at EOT of Cycle 1 was -31.9 ±16.24 mL/kg/day or -32.5 ±18.10%, which is similar to that for total children in Cycle 1.

At Least 20% Reduction From Baseline in Parenteral Support Volume

In total children, 2 subjects (33.3%) were recorded at Day 1 (initiation of this study) in the diary and prescribed data who achieved at least a 20% reduction in weight-normalized PS volume compared to baseline in the core study, and this increased to 4 subjects (66.7%) in diary data and 5 subjects (83.3%) in prescribed data as the visits progressed to the EOT in Cycle 1. These subjects maintained their status during the 4-week untreated follow-up period.

Both infant subjects (100%) achieved at least a 20% reduction in weight-normalized PS volume at Day 1 (initiation of this study) in diary data and 1 subject (50%) in prescribed data.

Achievement of Enteral Autonomy

There were 2 subjects in the total children cohort that achieved enteral autonomy—1 subject sustained from the core study and the second subject achieved enteral autonomy during the extension study.

One infant achieved enteral autonomy. The subject chieved enteral autonomy at Cycle 4 Week 4, which was sustained for 28 days to the end of study participation. This subject had SBS due to midgut volvulus. The residual small bowel length was estimated at 10 cm, with distal or terminal ileum and ileocecal valve present and 100% of colon remaining.

Decrease of Number of Days Per Week in Parenteral Support Usage

In total children, the mean change from baseline at EOT of each cycle based on diary data was -1.2 ±2.86 days/week for Cycles 1, 2, and 3; -1.4 ±3.13 days/week for Cycle 4; and 0.0 days/week for Cycles 5, 6, 7, and 8. The Week 28 mean change from baseline for Cycle 1 of -1.2 days/week suggests that the reduction was maintained during the 4-week untreated follow-up period from EOT to Week 28.

In infants, the number of days per week in PS usage were not reduced until Cycle 4, when 1 infant achieved enteral autonomy. The other infant required PS 7 days/week both at baseline and throughout the study.

In SHP633-302, administration of teduglutide appeared to reduce PS in Japanese children and infants with SBS in line with previously submitted data. The MAH is asked to discuss whether the results presented add any new age-specific knowledge in treatment of infants and/or children with SBS, whether or not intended for inclusion in the SmPC and/or Risk Management Plan **(OC)**.

Safety results

Exposure

The summary of exposure to teduglutide is shown in Table 9. In total, the mean duration of overall exposure to teduglutide, including core study exposure, was 123.16 ±60.582 weeks (range: 24.0 to 223.0 weeks). All 7 subjects in the total children cohort had at least 24 weeks of treatment. One subject achieved enteral autonomy at Week 12 in the core study, did not receive teduglutide in this extension study, and maintained enteral autonomy during NTT periods. In infants, the mean duration of overall exposure to teduglutide was 70.14 ±45.861 weeks;1 infant received teduglutide treatment for 37.7 weeks and the other for 102.6 weeks.

Table 9. Extent of Exposure (Safety Population)

Parameter	Statistics	Total Children (N=7)	Total Infants (N=2)
Overall extent of exposure (weeks)	Mean (SD)	123.16 (60.582)	70.14 (45.861)
	Median	120.57	70.14
	Min, Max	24.0, 223.0	37.7, 102.6
Any exposure	n (%)	7 (100.0)	2 (100.0)
0 to less than 12 weeks	n (%)	0 (0.0)	0 (0.0)
12 to less than 24 weeks	n (%)	0 (0.0)	0 (0.0)
24 to less than 48 weeks	n (%)	1 (14.3)	1 (50.0)
48 to less than 72 weeks	n (%)	0 (0.0)	0 (0.0)
72 to less than 96 weeks	n (%)	0 (0.0)	0 (0.0)
96 to less than 120 weeks	n (%)	2 (28.6)	1 (50.0)
120 to less than 144 weeks	n (%)	2 (28.6)	0 (0.0)
144 to less than 168 weeks	n (%)	1 (14.3)	0 (0.0)
At least 168 weeks	n (%)	1 (14.3)	0 (0.0)

CSR=clinical study report; Max=maximum; Min=minimum; N=number of subjects in a group; n=number of subjects meeting specified criteria; SD=standard deviation
Note: Overall extent of exposure in weeks is calculated as [the exposure in days in the SHP633-302 study (date of last dose - date of first dose + 1) + the sum of extent of exposure across all cycles in the SHP633-305 extension study] / 7

Adverse Events

Treatment Emergent Adverse Events

Treatment-emergent adverse events were defined as any adverse events (AEs) whose onset occurred, severity worsened, or intensity increased after receiving the IP in the core study or this extension study. Adverse events recorded in the core study are not summarized in this report. An overview of TEAEs reported from all subjects in the safety population is presented in **Table 10.**

In total children, 164 TEAEs were reported in 7 subjects (100%). Of those, 5 TEAEs were related to teduglutide treatment in 4 subjects (57.1%). All TEAEs were mild or moderate in severity. A total of 34 treatment-emergent serious adverse events (TESAEs) were noted in 7 subjects (100.0%); none were

teduglutide related. No subject experienced a TEAE leading to study discontinuation. No deaths or TEAEs of special interest were reported.

A total of 34 TEAEs were reported in both infants, of which 9 were TESAEs. Most TEAEs experienced in infants were mild or moderate in severity. There were 2 severe TESAEs.

One subject had a severe TESAE of pancreatitis acute, and the IP was withdrawn.

Another subject had a severe TESAE of central catheter infection. There were no teduglutide-related TEAEs, deaths, or TEAEs of special interest.

Two TEAEs led to IP discontinuation; 1 was the pancreatitis TESAE with permanent IP discontinuation, and the other was an interruption of IP dosing for 2 days due to catheter issues.

Table 10. Treatment-emergent Adverse Events (Safety Population)

Description	Total Children (N=7), n (%)	Total Infants (N=2), n (%)
Number of TEAEs	164	34
Number of subjects with:		
At least 1 TEAE	7 (100.0)	2 (100.0)
At least 1 treatment-related TEAE	4 (57.1)	0
At least 1 TESAE	7 (100.0)	2 (100.0)
At least 1 treatment-related TESAE	0	0

Table 10. Treatment-emergent Adverse Events (Safety Population)

Description	Total Children (N=7), n (%)	Total Infants (N=2), n (%)
TEAE severity (number of events):		
Mild	136	28
Moderate	28	4
Severe	0	2
TEAE worst severity (number of subjects [%]):		
Mild	2 (28.6)	0
Moderate	5 (71.4)	0
Severe	0	2 (100.0)
TESAE severity (number of events):		
Mild	15	4
Moderate	19	3
Severe	0	2
TEAEs leading to IP discontinuation	0	1
TEAEs leading to death	0	0
TEAEs of special interest[a]	0	0

CSR=clinical study report; IP=investigational product; N=number of subjects in a group; n=number of subjects meeting specified criteria; TEAE=treatment-emergent adverse event; TESAE=treatment-emergent serious adverse event.

[a] TEAEs of special interest were defined as polyps of the colon or neoplasia.

Display of Adverse Events

The incidence of TEAEs by system organ class (SOC) and preferred term (PT) is summarized in **Table 11**. For readability, the table has been sorted by decreasing incidence in the total children group.

As stated above, there were 164 TEAEs in 7 total children (100.0%) and 34 TEAEs in 2 infants (100.0%).

In children, the SOCs with the highest percentage of subjects reporting TEAEs were Gastrointestinal disorders (100.0%), Infections and infestations (85.7%), Skin and subcutaneous tissue disorders (85.7%), Product issues (71.4%), and Injury, poisoning and procedural complications (71.4%).

The most frequently reported TEAEs by PT were viral upper respiratory tract infection (25 events in 4 subjects [57.1%]), device breakage (8 events in 3 subjects [42.9%]), device related infection (6 events in 4 subjects [57.1%]), enteritis (6 events in 2 subjects [28.6%]), dehydration (6 events in 2 subjects [28.6%]), and metabolic acidosis (6 events in 1 subject [14.3%]). All of the device-related TEAEs were complications of central venous catheters used to prepare and administer PS, not the device used to prepare or administer teduglutide.

In infants, the only SOCs reported in both subjects were Infections and infestations and Investigations. All TEAEs by PT were experienced by 1 infant.

Table 11. Treatment-emergent Adverse Events By System Organ Class and Preferred Term (Safety Population)

SOC	Total Children (N=7)		Total Infants (N=2)	
PT	n (%)	Events	n (%)	Events
Any TEAEs	7 (100.0)	164	2 (100.0)	34
Infections and infestations	6 (85.7)	49	2 (100.0)	18
Viral upper respiratory tract infection	4 (57.1)	25	1 (50.0)	6
Device related infection	4 (57.1)	6	1 (50.0)	1
Medical device site infection	1 (14.3)	4	1 (50.0)	1
Influenza	2 (28.6)	2	0	0
Periodontitis	1 (14.3)	2	0	0
Conjunctivitis	1 (14.3)	1	1 (50.0)	3
Adenoviral conjunctivitis	1 (14.3)	1	0	0
Arthritis bacterial	1 (14.3)	1	0	0
Beta hemolytic streptococcal infection	1 (14.3)	1	0	0
Epididymitis	1 (14.3)	1	0	0
Gastroenteritis	1 (14.3)	1	0	0
Streptococcal infection	1 (14.3)	1	0	0
Viral pharyngitis	1 (14.3)	1	0	0
Hand-foot-and-mouth disease	1 (14.3)	1	0	0
Infected bite	1 (14.3)	1	0	0
Upper respiratory tract infection	0	0	1 (50.0)	3
Gastroenteritis adenovirus	0	0	1 (50.0)	1
Oral candidiasis	0	0	1 (50.0)	1
Otitis media	0	0	1 (50.0)	1

Table 11. Treatment-emergent Adverse Events By System Organ Class and Preferred Term (Safety Population)

SOC	Total Children (N=7)		Total Infants (N=2)	
PT	n (%)	Events	n (%)	Events
Viral infection	0	0	1 (50.0)	1
Gastrointestinal disorders	7 (100.0)	28	1 (50.0)	1
Enteritis	2 (28.6)	6	0	0
Enterocolitis	2 (28.6)	3	0	0
Constipation	2 (28.6)	2	0	0
Dental caries	2 (28.6)	2	0	0
Stomatitis	2 (28.6)	2	0	0
Abdominal distension	1 (14.3)	2	0	0
Cheilitis	1 (14.3)	2	0	0
Ileus	1 (14.3)	2	0	0
Abdominal pain	1 (14.3)	1	0	0
Colonic haematoma	1 (14.3)	1	0	0
Gastric disorder	1 (14.3)	1	0	0
Lip dry	1 (14.3)	1	0	0
Nausea	1 (14.3)	1	0	0
Rectal prolapse	1 (14.3)	1	0	0
Vomiting	1 (14.3)	1	0	0
Pancreatitis acute	0	0	1 (50.0)	1
Skin and subcutaneous tissue disorders	6 (85.7)	20	1 (50.0)	2
Rash	3 (42.9)	4	0	0
Urticaria	2 (28.6)	3	0	0
Dry skin	2 (28.6)	2	0	0
Haemorrhage subcutaneous	2 (28.6)	2	0	0
Miliaria	2 (28.6)	2	0	0
Eczema	1 (14.3)	2	0	0
Acne	1 (14.3)	1	0	0
Drug eruption	1 (14.3)	1	0	0
Skin erosion	1 (14.3)	1	0	0
Skin induration	1 (14.3)	1	0	0
Dermatitis allergic	1 (14.3)	1	0	0

Table 11. Treatment-emergent Adverse Events By System Organ Class and Preferred Term (Safety Population)

SOC	Total Children (N=7)		Total Infants (N=2)	
PT	n (%)	Events	n (%)	Events
Dermatitis	0	0	1 (50.0)	1
Dermatitis diaper	0	0	1 (50.0)	1
Metabolism and nutrition disorders	3 (42.9)	14	1 (50.0)	1
Dehydration	2 (28.6)	6	1 (50.0)	1
Metabolic acidosis	1 (14.3)	6	0	0
Hypozincaemia	1 (14.3)	1	0	0
Hypomagnesaemia	1 (14.3)	1	0	0
Product issues	5 (71.4)	12	1 (50.0)	2
Device breakage	3 (42.9)	8	1 (50.0)	2
Device damage	3 (42.9)	3	0	0
Device occlusion	1 (14.3)	1	0	0
Injury, poisoning and procedural complications	5 (71.4)	10	1 (50.0)	2
Wound complication	2 (28.6)	2	0	0
Epiphyseal injury	1 (14.3)	1	0	0
Fall	1 (14.3)	1	0	0
Gastrostomy tube site complication	1 (14.3)	1	0	0
Heat stroke	1 (14.3)	1	0	0
Ligament injury	1 (14.3)	1	0	0
Procedural pain	1 (14.3)	1	0	0
Fracture	1 (14.3)	1	0	0
Injury corneal	1 (14.3)	1	0	0
Auricular haematoma	0	0	1 (50.0)	1
Contusion	0	0	1 (50.0)	1
General disorders and administration site conditions	4 (57.1)	6	1 (50.0)	1
Pyrexia	4 (57.1)	5	0	0
Injection site pain	1 (14.3)	1	0	0
Injection site reaction	0	0	1 (50.0)	1
Respiratory, thoracic and mediastinal disorders	4 (57.1)	6	1 (50.0)	1
Cough	2 (28.6)	2	0	0
Asthma	1 (14.3)	1	0	0

Table 11. Treatment-emergent Adverse Events By System Organ Class and Preferred Term (Safety Population)

SOC	Total Children (N=7)		Total Infants (N=2)	
PT	n (%)	Events	n (%)	Events
Epistaxis	1 (14.3)	1	0	0
Rhinorrhoea	1 (14.3)	1	0	0
Upper respiratory tract inflammation	1 (14.3)	1	0	0
Rhinitis allergic	0	0	1 (50.0)	1
Immune system disorders	2 (28.6)	5	0	0
Food allergy	1 (14.3)	4	0	0
Seasonal allergy	1 (14.3)	1	0	0
Eye disorders	3 (42.9)	4	0	0
Conjunctivitis allergic	1 (14.3)	2	0	0
Eye discharge	1 (14.3)	1	0	0
Strabismus	1 (14.3)	1	0	0
Investigations	3 (42.9)	3	2 (100.0)	5
Lipase increased	1 (14.3)	1	0	0
Transaminases increased	1 (14.3)	1	0	0
Amylase increased	1 (14.3)	1	0	0
Alanine aminotransferase increased	0	0	1 (50.0)	2
Aspartate aminotransferase increased	0	0	1 (50.0)	1
Blood alkaline phosphatase increased	0	0	1 (50.0)	1
Eosinophil count increased	0	0	1 (50.0)	1
Musculoskeletal and connective tissue disorders	2 (28.6)	2	0	0
Joint swelling	1 (14.3)	1	0	0
Myalgia	1 (14.3)	1	0	0
Blood and lymphatic system disorders	1 (14.3)	1	0	0
Anaemia	1 (14.3)	1	0	0
Hepatobiliary disorders	1 (14.3)	1	0	0
Drug-induced liver injury	1 (14.3)	1	0	0
Neoplasms benign, malignant and unspecified	1 (14.3)	1	0	0
Neoplasm	1 (14.3)	1	0	0
Nervous system disorders	0	0	1 (50.0)	1
Seizure	0	0	1 (50.0)	1

Table 11. Treatment-emergent Adverse Events By System Organ Class and Preferred Term (Safety Population)

SOC	Total Children (N=7)		Total Infants (N=2)	
PT	n (%)	Events	n (%)	Events
Psychiatric disorders	1 (14.3)	1	0	0
Head banging	1 (14.3)	1	0	0
Surgical and medical procedures	1 (14.3)	1	0	0
Central venous catheter removal	1 (14.3)	1	0	0

CSR=clinical study report; IP=investigational product; MedDRA=Medical Dictionary for Regulatory Activities; N=number of subjects in a group; n=number of subjects meeting specified criteria; PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event
Note: Treatment-emergent adverse events were defined as any adverse events whose onset occurred, severity worsened, or intensity increased during or after receiving the first IP dose in the core study. Only TEAEs recorded in the current study are summarized.
Note: Subjects were counted no more than once for incidence but counted multiple times for the number of events.
Note: SOCs and PTs were coded using MedDRA 20.0.

Adverse Events by Relationship

The incidence of TEAEs by relationship based on SOC and PT is shown in **Table 12**. In total children, 5 treatment-related TEAEs were reported by 4 subjects (57.1%). These TEAEs were gastric disorder, injection site pain, lipase increased, skin induration, and eczema. No TEAEs related to teduglutide were reported in either infant.

Table 12. Treatment-related Treatment-emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

SOC	Total Children (N=7)		Total Infants (N=2)	
PT	n (%)	Events	n (%)	Events
Any TEAEs related to treatment	4 (57.1)	5	0	0
Skin and subcutaneous tissue disorders	2 (28.6)	2	0	0
Skin induration	1 (14.3)	1	0	0
Eczema	1 (14.3)	1	0	0
Gastrointestinal disorders	1 (14.3)	1	0	0
Gastric disorder	1 (14.3)	1	0	0

Table 12. Treatment-related Treatment-emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

SOC	Total Children (N=7)		Total Infants (N=2)	
PT	n (%)	Events	n (%)	Events
General disorders and administration site conditions	1 (14.3)	1	0	0
Injection site pain	1 (14.3)	1	0	0
Investigations	1 (14.3)	1	0	0
Lipase increased	1 (14.3)	1	0	0

CSR=clinical study report; MedDRA=Medical Dictionary for Regulatory Activities; N=number of subjects in a group; n=number of subjects meeting specified criteria; PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event
Note: Relationship to study treatment was based upon investigator assessment.
Note: SOCs and PTs were coded using MedDRA 20.0.

Adverse Events by Severity

All TEAEs were mild or moderate in severity for all subjects, except for 2 severe TESAEs. One subject had a severe TESAE of pancreatitis acute, and the IP was withdrawn. Another subject had a severe TESAE of central catheter infection. Neither TESAE was treatment related.

Deaths

There were no deaths during the study.

Other Serious Adverse Events

The incidence of TESAEs by SOC and PT is shown in Table 13. In total children, 34 TESAEs were reported in 7 subjects (100.0%). The TESAEs noted in at least 2 subjects by PT were device related infection (6 events in 4 subjects [57.1%]), device breakage (8 events in 3 subjects [42.9%]), and device damage (2 events in 2 subjects [28.6%]). All of the device-related TEAEs were considered as complications of central venous catheters used to prepare and administer PS, not the device used to prepare or administer teduglutide. No TESAEs were treatment related.

All TESAEs were experienced by only 1 infant. A TESAE of acute pancreatitis was reported; IP treatment was interrupted, and study participation was subsequently discontinued). Other TESAEs reported by an infant subject included device related infection, gastroenteritis adenovirus, otitis media, upper respiratory tract infection, viral upper respiratory tract infection, device breakage, and seizure. No TESAEs in infants were treatment related.

Table 13. Treatment-emergent Serious Adverse Events By System Organ Class and Preferred Term (Safety Population)

SOC	Total Children (N=7)		Total Infants (N=2)	
PT	n (%)	Events	n (%)	Events
Any TESAEs	7 (100.0)	34	2 (100.0)	9
Infections and infestations	5 (71.4)	13	1 (50.0)	5
Device related infection	4 (57.1)	6	1 (50.0)	1
Medical device site infection	1 (14.3)	3	0	0
Arthritis bacterial	1 (14.3)	1	0	0
Beta hemolytic streptococcal infection	1 (14.3)	1	0	0
Streptococcal infection	1 (14.3)	1	0	0
Viral pharyngitis	1 (14.3)	1	0	0
Gastroenteritis adenovirus	0	0	1 (50.0)	1
Otitis media	0	0	1 (50.0)	1
Upper respiratory tract infection	0	0	1 (50.0)	1
Viral upper respiratory tract infection	0	0	1 (50.0)	1
Product issues	4 (57.1)	11	1 (50.0)	2
Device breakage	3 (42.9)	8	1 (50.0)	2
Device damage	2 (28.6)	2	0	0
Device occlusion	1 (14.3)	1	0	0
Gastrointestinal disorders	4 (57.1)	7	1 (50.0)	1
Enterocolitis	1 (14.3)	2	0	0
Ileus	1 (14.3)	2	0	0

Table 13. Treatment-emergent Serious Adverse Events By System Organ Class and Preferred Term (Safety Population)

SOC	Total Children (N=7)		Total Infants (N=2)	
PT	n (%)	Events	n (%)	Events
Colonic haematoma	1 (14.3)	1	0	0
Enteritis	1 (14.3)	1	0	0
Vomiting	1 (14.3)	1	0	0
Pancreatitis acute	0	0	1 (50.0)	1
General disorders and administration site conditions	1 (14.3)	1	0	0
Pyrexia	1 (14.3)	1	0	0
Metabolism and nutrition disorders	1 (14.3)	1	0	0
Metabolic acidosis	1 (14.3)	1	0	0
Nervous system disorders	0	0	1 (50.0)	1
Seizure	0	0	1 (50.0)	1
Surgical and medical procedures	1 (14.3)	1	0	0
Central venous catheter removal	1 (14.3)	1	0	0

CSR=clinical study report; MedDRA=Medical Dictionary for Regulatory Activities; N=number of subjects in a group; n=number of subjects meeting specified criteria; PT=preferred term; SOC=system organ class; TESAEs=treatment-emergent serious adverse events
Note: Subjects were counted no more than once for incidence, but counted multiple times for the number of events.
Note: SOCs and PTs were coded using MedDRA 20.0.

Discontinuations Resulting From Adverse Events

A female infant experienced a severe TESAE of acute pancreatitis in 2019, 306 days after initiating IP treatment. Investigational product treatment was interrupted and the subject subsequently discontinued from the study due to severe acute pancreatitis. The TESAE was not treatment related.

Clinical Laboratory Evaluations

Chemistry

Out-of-range high or low chemistry values were observed for most subjects for various chemistry tests at various visits. These results were not remarkable, except as discussed below.

One subject experienced a treatment-related TEAE of blood lipase increased of moderate severity (Common Terminology Criteria for Adverse Events Grade 4), which was ongoing at the end of the study).

One subject had high amylase values for most of Cycles 1 through 9 and high aspartate aminotransferase and gamma glutamyl transferase values during Cycles 1 through 4.

One subject had high alkaline phosphatase and amylase values for most of Cycles 1 through 6.

One subject had high alanine aminotransferase and gamma glutamyl transferase values for most of Cycles 1 through 5.

One subject had high alanine aminotransferase values for most of Cycles 1 through 4 and high triglycerides during Cycles 1, 2, and 4.

One infant subject had alanine aminotransferase, alkaline phosphatase, gamma glutamyl transferase, and lipase levels greater than 3 × the upper limit of normal (ULN) at most visits of Cycle 1, alanine aminotransferase levels of 2 to 3 × ULN at most visits of the study, and intermittent elevations of aspartate aminotransferase, amylase, and triglycerides.

One TEAE of ALP increased, 1 of ALT increase, 1 of AST increased, and 1 of transaminases increased were reported as TEAEs.

Hematology

Out-of-range high or low hematology values were observed for most subjects for various hematology tests at various visits. These results were not remarkable during either period in any cycle except for one subject, who had an abnormally low platelet value of 62 ×109/L (normal range 140 to 450 ×109/L) at Cycle 2, Week 16 (Day 692).

Coagulation

Pretreatment coagulation testing included prothrombin international normalized ratio (INR) and prothrombin time. One subject had INR and prothrombin time values that were abnormally high at Cycles 1 through 9.

Urinalysis

Some subjects had tests that were out of range: one subject had high leukocytes at Cycle 1 EOT; one subject had high erythrocytes at baseline; and one subject had high leukocytes at baseline, Cycle 1 Week 12, Cycle 1 Week 20, Cycle 2 Week 1, Cycle 3 Week 9, Cycle 3 Week 16, and Cycle 4 Week 4. These results were not remarkable.

Pregnancy Testing

There were no females of childbearing potential; pregnancy tests were not performed.

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

Vital Signs

Overall, no clinically meaningful vital sign changes in pulse rate, blood pressure, or body temperature were reported in the study.

Physical Examination Findings

For all subjects, there were no new findings from physical examinations in the study.

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

In children 1 to 15 years of age, no clinically meaningful changes in growth parameters, such as weight, height, BMI, or head circumference z-scores were reported, indicating that the reductions in PS due to teduglutide treatment were appropriately titrated to match the subjects' nutritional needs. In the infants, weight gains were observed, indicating that improvements in nutrient absorption by the small intestine were not entirely captured by the reduction in PS calories.

Antibodies to Teduglutide

In Cycle 1 on Day 1, 1 child (16.7%) and 1 infant (50%) had ADAs detected prior to teduglutide dosing, which increased to up to 3 children and both infants at Week 12. However, at Week 28, the number had decreased to that of Day 1 again.

In subsequent cycles, the rates of positivity continued to trend in a similar fashion. On average, subjects who tested positive for ADAs, including the subjects with neutralizing ADAs, had sustained reduction from baseline in PS, and there was no association between ADAs and lack of efficacy.

The 2 infants only completed Cycle 1, and 1 infant completed through Cycle 4.

There were no reports of teduglutide-related hypersensitivity reaction in the subjects who tested ADA positive. No association between ADA status and hypersensitivity was noted.

Assessor´s comments

In total children, the mean duration of overall exposure to teduglutide, including core study exposure, was 123.16 ±60.582 weeks (range: 24.0 to 223.0 weeks).

In total children 164 TEAEs were reported in 7 subjects (100%). Of those, 5 TEAEs were related to teduglutide treatment in 4 subjects (57.1%). All TEAEs were mild or moderate in severity. A total of 34 treatment-emergent serious adverse events (TESAEs) were noted in 7 subjects (100.0%); none were teduglutide related. No subject experienced a TEAE leading to study discontinuation. No deaths or TEAEs of special interest were reported.

A total of 34 TEAEs were reported in both infants, of which 9 were TESAEs. Most TEAEs experienced in infants were mild or moderate in severity. There were 2 severe TESAEs.

One subject had a severe TESAE of pancreatitis acute, and the IP was withdrawn.

One subject had a severe TESAE of central catheter infection. There were no teduglutide-related TEAEs, deaths, or TEAEs of special interest. Two TEAEs led to IP discontinuation.

In children, the SOCs with the highest percentage of subjects reporting TEAEs were Gastrointestinal disorders (100.0%), Infections and infestations (85.7%), Skin and subcutaneous tissue disorders (85.7%), Product issues (71.4%), and Injury, poisoning and procedural complications (71.4%).

In infants, the only SOCs reported in both infants were Infections and infestations and Investigations. All TEAEs by PT were experienced by 1 infant.

5 children and 1 infant experienced abnormally high value for enzymes, including alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transferase, amylase, and lipase over multiple treatment cycles.

On average, subjects who tested positive for antidrug antibodies (ADAs), including the subjects with neutralizing ADAs, had sustained reduction from baseline in PS, and there was no association between ADAs and lack of efficacy. There were no reports of teduglutide-related hypersensitivity reaction in the subjects who tested ADA positive.

The MAH states that children 1 to 15 years of age, no clinically meaningful changes in growth parameters.

The MAH states that TEAEs reported in this study were generally consistent with the underlying disease and those reported in the core study and in previous studies of pediatric patients with SBS. However, the MAH is asked to describe the 1 case of pancreatitis TESAE in narratives **(OC)**.

2.4. Discussion on clinical aspects

The MAH has submitted the results of SHP633-305, a study to evaluate the safety and efficacy of teduglutide in a population of Japanese paediatric subjects with SBS and who were dependent on parenteral support (PS). SHP633-305 was a Phase 3, prospective, open-label, long-term extension study that was conducted to evaluate the safety and efficacy of teduglutide in a population of Japanese paediatric subjects with SBS who completed Study SHP633-302 (core study).

Subjects who previously received teduglutide and completed the core study were eligible for this extension study. Eligibility for teduglutide treatment was assessed separately. Subjects could participate in multiple no-teduglutide treatment (NTT) periods and/or multiple 28-week teduglutide treatment cycles depending on the disease course.

The investigational product (IP) was teduglutide, which was provided in 3 mL vials containing 5 mg or 1.25 mg teduglutide.

The MAH is asked to clarify the age-limits selected and the number of patients in each age-group included in both study SHP633-002 (core) and -005 (extension). Furthermore, as only Japanese paediatric subjects were included the present study, the MAH should discuss the selection and use of data from this paediatric population with respect to the modelling and extrapolation exercise in the ongoing variation II-54 **(OC)**.

The mean (± standard deviation) age of the total children was 6.70 (±3.754) years at the beginning of the core study, and males accounted for 85.7% (6 of 7 subjects). The MAH is asked to present demographic and baseline data more detailed **(OC)**.

In SHP633-302, administration of teduglutide appeared to reduce PS in Japanese children and infants with SBS in line with previously submitted data. The MAH is asked to discuss whether the results presented add any new age-specific knowledge in treatment of infants and/or children with SBS, whether or not intended for inclusion in the SmPC and/or Risk Management Plan **(OC)**.

The MAH states that TEAEs reported in this study were generally consistent with the underlying disease and those reported in the core study and in previous studies of pediatric patients with SBS. However, the MAH is asked to describe the 1 case of pancreatitis TESAE in narratives **(OC)**.

3. Rapporteur's overall conclusion and recommendation

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. In the present application, the MAH has submitted the results of SHP633-305, a study to evaluate the safety and efficacy of teduglutide in a population of Japanese paediatric subjects with SBS and who were dependent on parenteral support (PS). The MAH claims that the benefit-risk profile for teduglutide remains favorable and unchanged and that there are no regulatory consequences identified by the marketing authorization holder as consequence of study. However, before final approval, four other concerns have to be solved, please refer to RSI in section 4.

☒ Not fulfilled:

Based on the data submitted, the MAH should provide response to the additional clarifications requested per study as part of this procedure. (see section "Request for supplementary information")

4. Request for supplementary information

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

Other concerns:

1. The MAH is asked to clarify the age-limits selected and the number of patients in each age-group included in study SHP633-005 (extension). Furthermore, as only Japanese paediatric subjects were included the present study, the MAH should discuss the contribution of data from the Japanese pediatric population with respect to extrapolation to the general pediatric population e.g. in by integrating covariate information on race in the Pop PK model previously presented (OC)."

2. The mean (± standard deviation) age of the total children was 6.70 (±3.754) years at the beginning of the core study, and males accounted for 85.7% (6 of 7 subjects).

   The MAH is asked to present demographic and baseline data more detailed:

   a) The MAH is asked to add individual age specific data on all subjects in the Table 4

   b) The MAH is asked to add median and range for all parameters in table 8 and 9

3. The MAH is asked to discuss whether the results presented add any new age-specific knowledge in treatment of infants and/or children with SBS, whether or not intended for inclusion in the SmPC and/or Risk Management Plan

4. The MAH is asked to describe the 1 case of pancreatitis TESAE in narratives.

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

5. Assessment of MAH responses to Request for supplementary information

Other Concerns

Question 1

The MAH is asked to clarify the age-limits selected and the number of patients in each age-group included in study SHP633-305 (extension). Furthermore, as only Japanese paediatric subjects were included in the present study, the MAH should discuss the contribution of data from the Japanese paediatric population with respect to extrapolation to the general paediatric population e.g. by integrating covariate information on race in the Pop PK model previously presented.

MAH`s Response

All subjects in Study SHP633-305 were rolled over from Study SHP633-302. The results of Study SHP633-302 were evaluated by the European Medicines Agency (EMA) through the procedure number EMA/H/C/002345/P46/10, approved on 28 January 2021 and were also part of the support documentation for the grouped Type II variation requesting the extension of indication to patients from 4 months of corrected gestational age, submitted to the EMA via procedure number EMEA/H/C/002345/II/0054/G and which is currently ongoing. Procedure number EMEA/H/C/002345/II/0054/G also included the interim results of Study SHP633-305. The subjects from Study SHP633-302 were included in the pharmacokinetic (PK) datasets for the formal population PK analyses (PPK), submitted with procedure EMEA/H/C/002345/II/0053 and EMEA/H/C/002345/II/0054/G. As such, there were no predetermined age limits or number of subjects in each age group for this extension study (SHP633-305). The core study (SHP633-302) plan was to enroll a minimum of 5 subjects aged 1 through 15 years and a minimum of 2 subjects of 4 through less than 12 months of age. The actual enrollment in this core study included 8 Japanese pediatric subjects aged 1 through 15 years and 2 infants aged 4 through less than 12 months. Additionally, no PK samples were collected in Study SHP633-305 in the subjects rolled over from Study SHP633-302. As such, no subjects from Study SHP633-305 were included in the PPK. The corresponding PPK reports, submitted also with sequence 0144, procedure EMEA/H/C/002345/II/0053, are linked for your reference in this response (SHIR-CSC-129-PKglobal; SHIR-CSC-129-Japanese). Age distributions at baseline for subjects in Study SHP633-302 were provided in Appendix 11.6 of the PPK report (SHIR-CSC-129-PKglobal). Further, the MAH has formally evaluated the potential effect of race on PK between Japanese and global pediatrics in the PPK. The results confirmed a lack of race differences in PK of teduglutide between the populations (SHIR-CSC-129-Japanese).

REFERENCES:

Population PK/PD and Exposure-Response Analyses to Support Dosing of Teduglutide in Japanese Patients with Short Bowel Syndrome Who Are Dependent on Parenteral Support. (SHIR-CSC-129-Japanese).

Population PK Analysis of Teduglutide in Patients with Short Bowel Syndrome Who Are Dependent on Parenteral Support (4 Months and Older).(SHIR-CSC-129-PKglobal)

Assessment of the Applicant's Response

The MAH states that all subjects in Study SHP633-305 were rolled over from Study SHP633-302. The subjects from Study SHP633-302 were included in the pharmacokinetic (PK) datasets for the formal population PK analyses (PPK). There were no predetermined age limits or number of subjects in each age group for the extension study (SHP633-305). The core study (SHP633-302) plan was to enroll a minimum of 5 subjects aged 1 through 15 years and a minimum of 2 subjects of 4 through less than 12 months of age. The actual enrollment in this core study included 8 Japanese paediatric subjects aged 1 through 15 years and 2 infants aged 4 through less than 12 months. Additionally, no PK samples were collected in Study SHP633-305 in the subjects rolled over from Study SHP633-302. As such, no subjects from Study SHP633-305 were included in the PPK. Furthermore, the MAH states previous submitted PK analysis revealed no race differences in PK of teduglutide between the populations (SHIR-CSC-129-Japanese). This is accepted.

Conclusion

The issue has not been solved but will not be further pursued.

Question 2

The mean (± standard deviation) age of the total children was 6.70 (±3.754) years at the beginning of the core study, and males accounted for 85.7% (6 of 7 subjects).

The MAH is asked to present demographic and baseline data more detailed:

a) The MAH is asked to add individual age specific data on all subjects in Table 4.

b) The MAH is asked to add median and range for all parameters in Tables 8 and 9.

MAH`s Response

a) Table 4 of the clinical study report (CSR; provided below) provides individual age-specific enrollment and disposition data for subjects receiving teduglutide.

b) The requested data for Table 8 and Table 9 were provided in SHP633-305 CSR, but are also provided below (red font) for convenience for the parameters where median and range are applicable (exceptions are sex, race, reason for diagnosis, answers to questions). Note that since there were only 2 infants, the mean and median values are the same and the age range corresponds to the age of each infant.

Table 4. Subject Enrollment and Disposition (Safety Population)

	Total Children (N=7) n (%)	Total Infants (N=2) n (%)
Subject and Sex		
Female Infant [a]		CA=12.1; CGA=10.8
Male Infant		CA=9.5; CGA=9.1
Male Child	CA=2.7	
Male Child [a]	CA=5.7	
Male Child [b]	CA=12	

Male Child	CA=4.1	
Male Child	CA=11.9	
Male Child	CA=6.1	
Female Child	CA=4.4	
Treated with teduglutide	6 (85.7)	2 (100.0)
Discontinued IP or study due to TEAE	1 (14.3)	1 (50.0)
Completed study	7 (100.0)	1 (50.0)

CA=chronological age; CGA=corrected gestational age; CSR-clinical study report; IP=investigational product; N=number of subjects in a group; n=number of subjects meeting specified criteria; TEAE=treatment-emergent adverse event; TESAE=treatment-emergent serious adverse event

[a] Two TEAEs led to IP discontinuation; 1 was a pancreatitis TESAE with permanent IP discontinuation, and the other was an interruption of IP dosing for 2 days due to catheter breakage.

[b] This subject received teduglutide in the core study, and was counted in the Safety Population despite the subject not receiving teduglutide in this extension study. He had achieved enteral autonomy at Week 12 of the core study and maintained it; he was monitored in the NTT periods of the study to provide safety data.

Table 8. Demographic and Other Baseline Characteristics (Safety Population)

Parameters	Statistics	Total Children (N=7)	Total Infants (N=2)
Age of children at core study informed consent (years)	Mean (SD)	6.70 (3.754)	-
	Median	5.70	
	Min, Max	2.7, 12.0	
Age of infants at core study informed consent (months)			
Chronological age	Mean (SD)	-	10.80 (1.838)
Corrected gestational age	Mean (SD)	-	9.95 (1.202)
Sex			
Male	n (%)	6 (85.7)	1 (50.0)
Female	n (%)	1 (14.3)	1 (50.0)
Race			
Asian (Japanese)	n (%)	7 (100.0)	2 (100.0)
Height/length for age z-score at baseline	Mean (SD)	-1.965 (1.3906)	-3.652 (1.1428)
	Median	-2.454	-3.652
	Min, Max	-3.29, 0.53	-4.46, -2.84
Height/length for age percentile at baseline (%)	Mean (SD)	13.95 (26.340)	0.11 (0.157)
	Median	0.71	0.11
	Min, Max	0.1, 70.2	0.0, 0.2
Weight for age Z-score at baseline	Mean (SD)	-1.886 (1.4859)	-2.916 (2.6705)
	Median	-1.633	-2.916
	Min, Max	-3.81, -0.24	-4.80, -1.03
Weight for age percentile at baseline (%)	Mean (SD)	14.35 (17.692)	7.60 (10.751)
	Median	5.12	7.60
	Min, Max	0.0, 40.6	0.0, 15.2
BMI for age Z-score at baseline (children only)	Mean (SE)	-0.962 (1.6031)	-
	Median	-0.997	
	Min, Max	-3.57, 1.21	
BMI for age percentile at baseline (children only) (%)	Mean (SE)	30.64 (36.226)	-
	Median	15.94	
	Min, Max	0.0, 88.7	

Table 8. Demographic and Other Baseline Characteristics (Safety Population)

Parameters	Statistics	Total Children (N=7)	Total Infants (N=2)
Weight for length Z-score at baseline (infants only)	Mean (SE)	-	-1.349 (3.4688)
	Median		-1.349
	Min, Max		-4.82, 2.12
Weight for length percentile at baseline (%) (infants only)	Mean (SE)	-	49.15 (49.148)
	Median		49.15
	Min, Max		0.0, 98.3
Head circumference[a] for age Z-score at baseline	n	1	2
	Mean (SE)	2.633 (-)	0.040 (1.9902)
	Median	2.633	0.040
	Min, Max	2.63, 2.63	-1.95, 2.03
Head circumference[a] for age percentile at baseline (%)	n	1	2
	Mean (SE)	99.58 (-)	50.22 (47.663)
	Median	99.58	50.22
	Min, Max	99.6, 99.6	2.6, 97.9

SD=standard deviation; SE=standard error.
Note: Demographic and baseline data are from baseline in the core study.
[a] Head circumference was calculated for children up to 36 months of age.

Assessment of the Applicant's Response

The MAH has provided individual age-specific data for subjects receiving teduglutide in Table 4, and medians and ranges for all applicable parameters in Table 8 and 9. This is endorsed.

Conclusion

Issue solved

Question 3

The MAH is asked to discuss whether the results presented add any new age-specific knowledge in treatment of infants and/or children with SBS, whether or not intended for inclusion in the SmPC and/or Risk Management Plan.

MAH`s Response

On 27 July 2021, the MAH submitted a grouped Type II variation to request the extension of indication to patients from 4 months by corrected gestational age. The variation included as support documentation the study results from 2 core studies (SHP633-301, SHP633-302) and 2 extension long-term safety and efficacy studies (SHP633-304, SHP633-305).

Study SHP633-305 was still ongoing at the time of submission. The Type II variation is still under evaluation with the EMA via procedure number EMEA/H/C/002345/II/0054/G. The data showed sustained efficacy of teduglutide in infants and children from the core through the extension studies. In addition, these data are consistent with the data from the adult population. The nature and frequency of the adverse events reported in this study were similar in nature to those observed in the core study and in previous pediatric studies of teduglutide.

Furthermore, Study 305 showed that teduglutide was generally safe and well tolerated in children with SBS who were treated for a mean of 123.16 weeks and infants with SBS who were treated for a mean of 70.14 weeks in the core study and in this extension study. Based on the results of long-term Studies SHP633-305 and other studies, the MAH plans to propose removal of the "Missing Information: Long-term safety in the paediatric population" from the European Union Risk Management Plan (EU-RMP) at the next opportunity.

Assessment of the Applicant's Response

The MAH states that the data showed sustained efficacy of teduglutide in infants and children from the core through the extension studies. In addition, that the nature and frequency of the adverse events reported in this study were similar in nature to those observed in the core study and in previous pediatric studies of teduglutide.

Based on the results of long-term Studies SHP633-305 and other studies, the MAH plans to propose removal of the "Missing Information: Long-term safety in the paediatric population" from the European Union Risk Management Plan (EU-RMP) at the next opportunity. Thus, the MAH has no proposals for changes in the SmPC or the Risk Management Plan at present.

Conclusion

Issue solved

Question 4

The MAH is asked to describe the 1 case of pancreatitis TESAE in narratives.

MAH`s Response

Narratives for each subject who reported a treatment-emergent serious adverse event (TESAE) in SHP633-305 are provided in the CSR. The narrative for the subject is provided below for ease of review.

Subject **Dose: teduglutide:** 0.05 mg/kg/day			
Reason for Narrative: Serious adverse event			
Sex/Race/Ethnicity: female/Asian **Date of first dose of investigational product:** 2019			
Preferred Term/ Reported Term	**Start Date / Stop Date**	**Serious AE/ Severity/ Relationship**	**Action Taken/ Other Action Taken/ Outcome**
	2019 2020	Yes/ Moderate/ Not Related	Not changed / Drug treatment given Recovered/Resolved with sequelae
Pancreatitis acute/ Acute pancreatitis	2019 2020	Yes/ Severe/ Not Related	Withdrawal/ Drug treatment given Recovered/Resolved

The subject is a girl with SBS. She completed the preceding Study SHP633-302 and started treatment with 0.05 mg/kg/day of teduglutide on 2019 in Study SHP633-305.

Pancreatitis Acute

In 2019, the subject had an episode. She was admitted to the hospital for vomiting that resulted from certain condition, which was her concomitant disease. Adjustment of her therapy was initiated.

In 2019, her lipase level began to rise significantly to a high of 2328 IU/L (started 50 IU/L or below, 353 IU/L the next day, and 173 IU/L the day after) associated with tachypnoea. Abdominal echocardiography and computed tomography (CT) were performed. Severe acute pancreatitis of second degree was considered.

The subject was transferred to an intensive care unit for systemic management. Teduglutide dosing was suspended. A large volume of fluid replacement, and respiratory management with ventilator were started for deteriorated circulatory dynamics and acidosis. In addition, deep sedation with a muscle relaxant was performed for her unstable condition with muscle tightness and poor oxygenation. Treatment with an enzyme inhibitor was started for acute pancreatitis.

On 2020 (day 0), the lipase level improved to 212 U/L and amylase dropped to 39 U/L.

On day 1, treatment with the muscle relaxant was stopped and a drug was started.

On day 5, the respiratory management with ventilator was stopped as her general condition improved. She received nasal high flow oxygen.

On day 8, the therapy was changed to nasal oxygen with favorable oxygenation, then the therapy was stopped. Oxygen therapy was performed as appropriate depending on the oxygenation maintenance status. In addition, the enzyme inhibitor was discontinued due to drip leakage from the periphery.

On day 10, the subject was transferred to the general pediatric ward as her general condition had stabilized.

On day 17, her symptoms had stabilized and relieved after the transfer to the general pediatric ward.

On day 19, her lipase and amylase levels were elevated again to 589 U/L and 81 U/L, respectively. However, abdominal ultrasound showed no findings suggestive of aggravation of pancreatitis.

On day 20, her lipase level was remarkably increased to 1231 U/L, while abdominal CT showed no findings of pancreatitis.

On day 21, her lipase and amylase levels were increased to 2440 U/L and 164 U/L, respectively.

On day 28, her lipase and amylase levels were slightly decreased to 901 U/L and 60 U/L, respectively.

On day 44, the enzyme inhibitor was resumed as the lipase level increased again to 2705 U/L. Abdominal echocardiography showed slight pancreatic enlargement with no findings of pancreatitis.

On day 52, the treatment with the enzyme inhibitor was stopped as there had been no flare up of the pancreatitis.

On day 76, the 2019 episode was considered to be resolved with sequelae.

On day 82, abdominal CT showed that pancreatic enlargement remained, but it was improved with no flare up of pancreatitis.

On day 121, her lipase level had remained within reference range with no flare up of pancreatitis since day 97. Her general condition was also stable. Thus, the subject recovered from the event and was eventually discharged from the hospital.

The outcome of pancreatitis acute was reported as recovered/resolved with the severity as severe, and the dosing of teduglutide was withdrawn. On causality, the investigator judged the event as not related to teduglutide based on the below findings:

The subject was diagnosed with acute pancreatitis in 2019 with lipase level of 3000 U/L when a drug was administered; in the intensive care unit, the treatment of the drug and teduglutide were stopped, and lipase level improved immediately. However, the prior lipase value was increasing slightly without teduglutide, and the subject was being treated with the drug again. Therefore, the investigator considered that pancreatitis might be related to the other drug and not related to teduglutide.

The company pharmacovigilance physician also assessed the events and acute pancreatitis as not related to teduglutide, in agreement with the investigator. The alternative explanation for the acute pancreatitis was worsening of the patient's concomitant disease and underlying SBS. The acute pancreatitis occurred 10 days after the onset of worsening condition. Prolonged condition activity may increase intraduodenal pressure leading to the reflux of the duodenal contents into the pancreatic duct, altered metabolism of oxygen-derived free radicals, and hypoxia/ischemia resulting in pancreatic acinar cell injury. The concomitant medications alfacalcidol, famotidine, and other drugs might have been confounding factors.

Assessment of the Applicant's Response

The MAH has described the 1 case of pancreatitis TESAE in infant subject, in narratives as requested. The subject is a girl with SBS. She completed the preceding Study SHP633-302 and started treatment with 0.05 mg/kg/day of teduglutide on 2019 in Study SHP633-305. On 2019, her lipase level began to rise significantly in 2019 to a high of 2328 IU/L (started on 50 IU/L or below, 353 IU/L on the next day, and 173 IU/L the day after) associated with tachypnoea. Abdominal echocardiography and computed tomography (CT) showed severe acute pancreatitis of second. The MAH suggest that the incident of acute pancreatitis was not related to teduglutide treatment but to prolonged event, leading to reflux of the duodenal contents into the pancreatic duct. This is questioned since acute pancreatitis is specified as a common adverse drug effects in the SmPC and due to the questionable temporal coincidences. The MAH is asked to address a possible risk of acute pancreatitis in the pediatric population adequately in the SmPC.

Conclusion

Not solved (OC)

6. Rapporteur's updated overall conclusion and recommendation

The MAH has submitted the results of SHP633-305 to evaluate the safety and efficacy of teduglutide in a population of Japanese paediatric subjects with SBS and who were dependent on parenteral support (PS). One other concern remains to be addressed, see section 7.

☒ Not fulfilled:

Based on the data submitted, the MAH should provide response to the additional clarifications requested as part of this procedure. (see section "Request for supplementary information")

7. Request for 2. supplementary information

Other concerns:

1. The MAH is asked to address a possible risk of acute pancreatitis in the pediatric population adequately in the SmPC.

8. Assessment of MAH responses to 2. Request for supplementary information

Question

1. The MAH is asked to address a possible risk of acute pancreatitis in the pediatric population adequately in the SmPC.

MAH's Response

Upon further review of the circumstances for the 1 treatment-emergent serious adverse event of pancreatitis in one subject and considering that pancreatitis is already a common adverse drug reaction of teduglutide, the MAH has reassessed the causality of acute pancreatitis as possibly related to the study medication and updated the safety database accordingly. However, an alternative explanation is the use of a medication, because following reintroduction of this medication, the level of lipase increased again (ie, positive rechallenge).

Section 4.4 "Special warnings and precautions for use" of the SmPC already provides a cautionary statement about pancreatic diseases in both adults and pediatric populations for both the 1.25 mg and 5 mg strengths of REVESTIVE. The analysis of the global safety database did not reveal any increased incidence of pancreatic events in the pediatric population. In particular, the analysis of available data in Study TED-R13-002, a prospective, multicenter registry for patients with SBS, as of the latest cutoff date of 30 Jun 2022 and comparing teduglutide "ever treated" and "never treated" cohorts, did not reveal any increase in the incidence of acute pancreatitis in children.

Based on the above, the MAH considers that no further updates are needed to the REVESTIVE product information, as acute pancreatitis is sufficiently and adequately described in both Section 4.4 and Section 4.8 of the SmPC, for both adults and pediatric population and for both 1.25 mg and 5 mg strengths.

Assessment of the Applicant's Response

The MAH states that upon further review of the circumstances for the 1 treatment-emergent serious adverse event of pancreatitis in one subject and considering that pancreatitis is already a common adverse drug reaction of teduglutide, the MAH has reassessed the causality of acute pancreatitis as possibly related to the study medication and updated the safety database accordingly. Furthermore, the MAH states that Section 4.4 "Special warnings and precautions for use" of the SmPC already provides a cautionary statement about pancreatic diseases in both adults and pediatric populations for both the 1.25 mg and 5 mg strengths of REVESTIVE. The analysis of the global safety database did not reveal any increased incidence of pancreatic events in the pediatric population. The MAH therefore proposes that no further updates are needed to the REVESTIVE product information. This is accepted.

Conclusion

Issue solved.

9. Rapporteur's updated overall conclusion and recommendation

The MAH has submitted the results of SHP633-305 to evaluate the safety and efficacy of teduglutide in a population of Japanese paediatric subjects with SBS and who were dependent on parenteral support (PS). In the assessment report based on the results of SHP633-305 submitted by the MAH, the benefit-risk profile for teduglutide remains positive.

☒ Fulfilled:

No regulatory action required.