26 May 2016
EMA/531666/2016
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

Invented name: Revestive

International non-proprietary name: teduglutide

Procedure No. EMEA/H/C/002345/II/0020

Marketing authorisation holder (MAH): NPS Pharma Holdings Limited

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

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List of abbreviations

ALAG	Absorption lag time
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
AUCss	Area under the curve at steady state
BLQ	Below limit of quantification
BSV	Between subject variability (also known as inter-individual variability)
CI	Confidence interval
CL/F	Apparent clearance of teduglutide
C_{max}	Maximum plasma concentration
$C_{max,ss}$	Concentration maximum at steady state
C_{min}	Minimum plasma concentration
$C_{min, ss}$	Concentration minimum at steady state
CRCL	Creatinine clearance
CV	Coefficient of variation
CWRES	Conditional weighted residuals
DV	Dependent variable (i.e., Observed plasma concentration)
ECG	Electrocardiogram
EMA	European Medicine Agency
EN	Enteral nutrition
EOT	End of treatment
ETA	Random effect
FDA	Food and drug administration
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
HPN	Home parenteral nutrition
IPRED	Individual predicted plasma concentration
ITT	Intention-to-treat
IV	Intravenous

Ka	First-order rate constant of absorption
LOESS	Locally weighted scatter plot smoothing
Max	Maximum
Min	Minimum
MOF	Minimum objective function
N/A	Not applicable
NEC	Necrotising enterocolotis
PD	Pharmacodynamics
PD	Pharmacodynamic
PIP	Paediatric Investigational Plan
PK	Pharmacokinetic
PN	Parenteral nutrition
PN/IV	Parenteral nutrition and intravenous fluid
Pop-PK	Population PK
PRED	Population predicted plasma concentration
QA	Quality assurance
QC	Quality control
RSE	Relative standard error
SAP	Statistical analysis plan
SBS	Short bowel syndrome
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, NPS Pharma Holdings Limited submitted to the European Medicines Agency on 7 July 2015 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include the treatment of patients aged 1 year and above with short bowel syndrome who are stable following a period of intestinal adaptation. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet has been updated accordingly.

The Risk Management Plan was also updated to reflect the study completion and results and the MAH took the opportunity to update due dates of the International Short Bowel Syndrome Registry reflected in Annex II.

Furthermore, the PI is brought in line with the latest QRD template.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

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

The new indication, which is the subject of this application, falls within the above mentioned orphan designation.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) PIP EU/3/01/077 on the agreement of a paediatric investigation plan (PIP) and the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

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

Protocol assistance

The applicant did not seek Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Sinan B. Sarac

Timetable	Dates
Submission date	7 July 2015
Start of procedure:	22 August 2015
CHMP Co-Rapporteur Assessment Report	13 October 2015
CHMP Rapporteur Assessment Report	13 October 2015
PRAC Rapporteur Assessment Report	23 October 2015
PRAC members comments	28 October 2015
Updated PRAC Rapporteur Assessment Report	30 October 2015
PRAC Outcome	6 November 2015
CHMP members comments	N/A
Updated CHMP Rapporteur(s) (Joint) Assessment Report	13 November 2015
Request for supplementary information (RSI)	19 November 2015
CHMP Rapporteur Assessment Report	2 March 2016
PRAC Rapporteur Assessment Report	2 March 2016
PRAC members comments	N/A
Updated PRAC Rapporteur Assessment Report	22 March2016
Request for supplementary information (RSI)	01 April2016
Joint Assessment Report	11 May2016
PRAC Outcome	13 May2016
CHMP members comments	18 May 2016
Updated CHMP Rapporteur Assessment Report	19 May 2016
CHMP opinion:	26 May 2016

2. Scientific discussion

2.1. Introduction

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

The product has been licensed for the indication “Short Bowel Syndrome in adults” in the year 2012.

With this variation, the applicant is intending to extend the indication, or rather to extend the population to be treated, to the paediatric population aged 1 year and older. The patient population intended to be included additionally is essentially a similar population to the adult population, in the sense that it is a population in which phases of PN-treatment and current standard of care have already been performed for a considerable time, and the so-called “adaptation phase” has already taken place.

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

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

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

2.2. Non-clinical aspects

No new non-clinical data was submitted. This was considered acceptable by the CHMP.

In the course of the procedure the applicant referred to non-clinical data submitted within the initial marketing authorisation application in order to support the applicability data derived from adults to the

paediatric setting. This approach is addressed alongside clinical safety and efficacy data further below in the report.

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, teduglutide is not expected to pose a risk to the environment.

2.2.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table 1: Listing of Individual SBS Efficacy and Safety Studies

Study ID Number of Centers Locations	Study Start and Stop, Dates Subjects Randomized or Enrolled/ Planned	Study Design Type of Control	Study Objective	Test Product(s); Control Dose, Route and Regimen	No. of subjects by arm entered / compl.	Total Duration of Treatment	Diagnosis Inclusion Criteria	Endpoint(s)
TED-C13-003 17 centers 16 US, 1 UK	Study initiation date: 14 NOV 2013 Study completion date: 09 JAN 2015 42/ 24-36	Phase 3, multicenter, open-label, cohort study 3 active cohorts, 1 observational standard-of-care cohort	To evaluate the pharmacokinetic profile, safety and tolerability and pharmacodynamic effects of teduglutide compared with standard of care in paediatric subjects (aged 1-17 years) with PN/IV-dependent SBS	A: teduglutide 0.0125 mg/kg/day SC B: teduglutide 0.025 mg/kg/day SC C: teduglutide 0.05 mg/kg/day SC D: Standard of care Teduglutide administered once daily into 1 of the 4 quadrants of the abdomen (in subjects without a stoma) or either the thigh or arm.	A: 8/7 B: 14/14 C: 15/14 D: 5/5	12 weeks	Male and female children and adolescents, aged 1-17 years, with SBS and PN/IV requirement of at least 30% of caloric and/or fluid/ electrolyte needs	The pharmacodynamic endpoints included: - >20% reduction from baseline in PN/IV volume- ≥ 10% reduction in PN/IV; - Increase in enteral nutritional tolerance; -Decrease in parenteral support; -Change in hours per day or days per week of PN/IV ; -Complete weaning off PN/IV support

compl. = completed; No. = number; PN/IV= parenteral nutrition/intravenous fluids; SBS = short bowel syndrome; SC = subcutaneous; TED = teduglutide; UK = United Kingdom; US = United States

2.2.2. Pharmacokinetics

Population PK modelling was used to describe the PK data from the subjects receiving active treatment in Study TED-C13-003: A 12-Week Pharmacokinetic, Safety, and Pharmacodynamic Study of Teduglutide in Paediatric Subjects Aged 1 Year through 17 Years, with Short Bowel Syndrome who are Dependent on Parenteral Support.

The model incorporated the paediatric PK data with the previously developed adult population PK model based on data collected in five Phase 1 studies and three Phase 2/3 studies in the clinical development of teduglutide.

Six blood samples were drawn during the 12 weeks study in paediatric patients, for the analysis of teduglutide PK. The aim of the PK simulation was to compare the systemic exposure of teduglutide at

three different dose levels (0.025, 0.05, and 1.0 mg/kg s.c once daily for 14 days) in adults and paediatric SBS patients at different ages.

Table 11-12 Summary of Pharmacokinetic Results

Dose	Statistic	Vc/F (L)	CL/F (L/h)	Ka (1/h)	$t_{1/2}$ (h)	C_{max} (ng/mL)	$AUC_{0-\tau}$ (ng.h/mL)	$C_{min,ss}$ (ng/mL)	$C_{max,ss}$ (ng/mL)	$T_{max,ss}$ (h)	$AUC_{0-\tau,ss}$ (ng.h/mL)
	N	9	9	9	9	9	9	9	9	9	9
	Mean	3.35	6.59	0.442	0.273	10.2	32.9	0.00240	10.2	0.934	32.9
	SD	5.11	2.01	0.0599	0.299	2.21	11.4	0.00639	2.21	0.555	11.4
0.0125 mg/kg	Min	0.742	4.71	0.305	0.0891	8.11	22.5	0.000105	8.11	0.565	22.5
	Median	1.02	5.77	0.441	0.127	9.29	27.4	0.000325	9.29	0.670	27.4
	Max	16.4	11.3	0.516	1.01	14.2	53.1	0.0194	14.2	2.29	53.2
	CV%	152.7	30.5	13.5	109.4	21.7	34.7	266.3	21.7	59.4	34.7
	N	13	13	13	13	13	13	13	13	13	13
	Mean	3.56	7.16	0.383	0.301	17.9	65.7	0.0113	17.9	1.09	65.7
	SD	3.81	1.98	0.0958	0.214	5.05	13.5	0.0159	5.04	0.441	13.5
0.025 mg/kg	Min	0.961	4.23	0.276	0.140	12.3	46.3	0.000109	12.3	0.687	46.3
	Median	2.61	7.37	0.346	0.245	15.8	62.6	0.00563	15.8	1.03	62.6
	Max	15.2	11.4	0.529	0.922	25.7	96.3	0.0563	25.7	2.27	96.4
	CV%	106.9	27.6	25.0	71.1	28.2	20.5	140.0	28.1	40.6	20.6
	N	15	15	15	15	15	15	15	15	15	15
	Mean	2.42	7.28	0.363	0.218	31.7	114	0.0177	31.7	0.913	114
	SD	2.37	1.85	0.0905	0.140	11.8	30.5	0.0197	11.8	0.293	30.4
0.05 mg/kg	Min	0.829	4.49	0.247	0.0998	18.8	79.2	0.0000673	18.8	0.638	79.3
	Median	1.86	7.21	0.339	0.180	30.7	106	0.0108	30.8	0.833	106
	Max	10.7	11.2	0.594	0.664	58.8	170	0.0642	58.8	1.85	170
	CV%	97.8	25.4	25.0	64.2	37.4	26.7	111.5	37.3	32.1	26.6

CV% = percent coefficient of variation; Max = maximum; Min = minimum; N = number of subjects; SD = standard deviation
Source: PopPK Study NPS-NCS-105, Table 8

A one-compartment disposition with first-order absorption and lag time and allometric exponents for parameters Ka, CL/F and Vc/F adequately described the profile of observed plasma concentrations of teduglutide over time throughout the studies and across populations of subjects. Due to low number of samples PK parameters were presented by descriptive statistics.

Absorption

Simulations were performed to compare teduglutide exposure in adult subjects and paediatric SBS subjects at unit doses of 0.025, 0.05, and 0.10 mg/kg administered subcutaneously every 24 hours for 14 days. Simulated Cmax and Cmin increased with increasing doses as shown in Table 11-13.

An age-dependent decrease in AUCss was observed in younger children. For example, the simulated AUCss following dosing of 0.05 mg/kg resulted in a mean of 308 ng.h/mL in adults and 95.0 ng.h/mL in children between 1 and 2 years of age.

Table 11-13 Simulated Steady State Exposure Parameters of Teduglutide Following Repeated Daily Subcutaneous Administration of 0.025 mg/kg, 0.05 mg/kg, and 0.10 mg/kg in Adults and Pediatric SBS Subjects

Age category	Mean (SD) Median [90% CI]								
	0.025 mg/kg			0.05 mg/kg			0.10 mg/kg		
	AUC_{ss} (ng.h/mL)	$C_{min,ss}$ (ng/mL)	$C_{max,ss}$ (ng/mL)	AUC_{ss} (ng.h/mL)	$C_{min,ss}$ (ng/mL)	$C_{max,ss}$ (ng/mL)	AUC_{ss} (ng.h/mL)	$C_{inx,ss}$ (ng/mL)	$C_{max,ss}$ (ng/mL)
Adults	NA	NA	NA	308 (106) 293 [169 - 505]	2.70 (1.87) 2.22 [1.08 – 5.96]	35.7 (12.5) 33.7 [19.8 - 59.8]	626 (213) 591 [345 - 1020]	4.11 (4.11) 2.81 [1.10 - 11.8]	72.4 (25.3) 68.3 [39.8 - 119]
12-18 years	114 (35.7) 108 [66.8 - 182]	1.77 (0.64) 1.62 [1.05 – 2.93]	19.1 (7.12) 18.0 [10.1 – 31.9]	232 (72.0) 220 [135 - 367]	2.32 (1.12) 2.08 [1.06 - 4.54]	38.8 (13.6) 37.2 [21.3 – 65.5]	464 (147) 438 [268 - 748]	2.75 (1.63) 2.29 [1.06 – 6.18]	76.3 (28.8) 72.5 [38.3 - 129]
8-12 years	86.6 (28.4) 82.7 [48.2 - 142]	1.83 (0.66) 1.72 [1.05 - 3.11]	19.4 (7.73) 18.1 [9.22 – 33.6]	174 (56.5) 167 [98.7 - 274]	2.28 (0.99) 2.11 [1.08 - 4.13]	39.2 (15.9) 36.0 [19.2 – 69.3]	348 (114) 335 [196 - 553]	2.63 (1.40) 2.29 [1.09 - 5.38]	77.8 (32.0) 72.3 [37.8 - 136]
6-8 years	78.4 (25.8) 74.4 [43.2 - 125]	1.81 (0.63) 1.69 [1.06 – 2.99]	19.8 (7.91) 18.4 [9.22 - 35.3]	159 (54.4) 152 [85.0 - 251]	2.22 (0.97) 2.02 [1.08 – 4.08]	40.2 (16.9) 38.2 [18.6 – 71.1]	312 (104) 295 [181 - 509]	2.51 (1.28) 2.21 [1.06 – 5.02]	78.6 (33.7) 71.9 [37.0 - 142]
4-6 years	65.0 (21.0) 63.2 [36.3 – 102]	1.80 (0.63) 1.69 [1.08 - 2.93]	19.0 (8.64) 17.2 [8.51 – 35.1]	134 (44.0) 128 [76.4 - 217]	2.11 (0.84) 1.98 [1.09 - 3.69]	38.2 (15.8) 34.9 [18.2 – 68.7]	263 (85.7) 252 [146 - 429]	2.36 (1.14) 2.04 [1.06 - 4.66]	76.1 (32.9) 71.0 [34.5 - 139]
2-4 years	57.0 (18.3) 54.3 [30.8 – 92.9]	1.76 (0.62) 1.61 [1.05 - 2.89]	18.6 (8.01) 17.1 [8.38 - 34.3]	111 (38.5) 104 [59.1 - 182]	1.93 (0.76) 1.77 [1.05 - 3.29]	36.6 (16.4) 33.9 [15.6 - 65.3]	225 (79.7) 214 [125 - 373]	2.34 (1.14) 2.09 [1.08 - 4.4]	73.9 (33.8) 67.0 [33.6 - 141]
1-2 years	46.5 (15.6) 43.8 [26.0 – 74.4]	1.66 (0.55) 1.54 [1.04 - 2.76]	17.2 (8.29) 15.8 [7.21 – 32.8]	95.0 (33.5) 89.3 [50.7 - 159]	1.93 (0.74) 1.80 [1.06 - 3.30]	35.2 (16.8) 31.6 [14.6 - 67.4]	184 (61.7) 178 [102 - 303]	2.25 (0.94) 2.05 [1.07 – 3.96]	70.2 (34.9) 63.0 [30.3 – 132]

AUCss = Area under the concentration-time curve under steadystate; CI = confidence interval; Cmax,ss = maximum (peak) concentration at steady state; Cmin,ss = minimum (trough) concentration at steady state; NA = not applicable; SD = standard deviation.
Source: PopPK Study NPS-NCS-105, Tables 4.4.1 and 4.4.2

Distribution

Following subcutaneous administration, teduglutide has an apparent volume of distribution of 26 litres in patients with SBS.

In the paediatric study TED-C13-003, mean values of Vc/F from 2.42 to 3.56 litres, dependent on the dose administered, were observed with large standard deviations and large CV%. Large variabilities in the distribution of teduglutide were seen, however, this is expected due to the low number and heterogeneity of the patients.

Elimination

The mean clearance of teduglutide is approximately equivalent to the Glomerular Filtration Rate (GFR), which indicated that teduglutide is mainly cleared by the kidneys. Data from the PopPK analysis showed that Creatinine clearance (Cl_{cr}) depended on renal function. The half-life is short in both adults (2 hours) and in children (0.22 – 0.30 hours), the drug is therefore cleared before the next dose in both populations. The renal clearance of teduglutide was confirmed by study CL0600-018 in renally impaired volunteers as assessed within the initial marketing authorisation application. Teduglutide was eliminated with a t½ of 1.6 and 1.7 hours, respectively, in subjects with moderate and severe renal impairment, and 2.2 hours in subjects with end stage renal disease (ESRD) compared with 1.4 to 1.6 hours in healthy matched-control subjects.

Dose proportionality and time dependencies

No formal dose-proportionality analysis was performed, but both AUC, C_{min}, and C_{max} increased with increasing doses in all age groups.

Table 1 Typical PK Parameters of Teduglutide – Seven Levels of Age Group

Age Group	Median Weight (kg)	Dose (mg/ kg)	Total Dose (µg)	CL/F (L/h)	Vc/F (L)	Ka (1/h)	AUC = (Total Dose)/ (CL/F) (ng.h/mL)
≥ 1 year and < 2 years	10.5	0.05	525	5.70	0.81	0.44	92.11
≥ 2 years and < 4 years	12.7	0.05	635	6.14	1.17	0.42	103.48
≥ 4 years and < 6 years	16.5	0.05	825	6.79	1.96	0.40	121.46
≥ 6 years and < 8 years	22.3	0.05	1115	7.63	3.55	0.37	146.04
≥ 8 years and < 12 years	26.9	0.05	1345	8.21	5.14	0.36	163.81
≥ 12 years and < 18 years	44.3	0.05	2215	9.96	13.72	0.32	222.29
Adults (≥ 18 years)	70.9	0.05	3545	11.96	34.66	0.29	296.43

AUC = Area under the concentration-time curve at steady state; CL/F = apparent clearance; Ka = first-order rate of absorption; Vc/F = apparent central volume of distribution

Table 2 Typical PK Parameters of Teduglutide – Three Levels of Age Group

Age Group	Median Weight (kg)	Dose (mg/kg)	Total Dose (µg)	CL/F (L/h)	Vc/F (L)	Ka (1/h)	AUC Total Dose / (CL/F) (ng.h/mL)
≥ 1 year and < 4 years	12.05	0.05	602.5	6.01	1.06	0.42	100.20
≥ 4 years and < 18 years	18.7	0.05	935	7.13	2.51	0.39	131.13
Adults (≥ 18 years)	70.9	0.05	3545	11.96	34.66	0.29	296.43

AUC = Area under the concentration-time curve at steady state; CL/F = apparent clearance; Ka = first-order rate of absorption; Vc/F = apparent central volume of distribution

Special populations

This application is a line extension for a paediatric indication. 37 children aged 1 – 17 years were included in the study. No further special populations were addressed which was considered acceptable by the CHMP.

Pharmacokinetic interaction studies

No new interaction studies were performed which was considered acceptable by the CHMP.

2.2.3. Pharmacodynamics

In study TED-C13-003, the PD effects of teduglutide in terms of PN/IV support changes were evaluated. These PD effects will be discussed in the Efficacy section. Plasma citrulline and teduglutide antibodies were assessed as well.

Mechanism of action

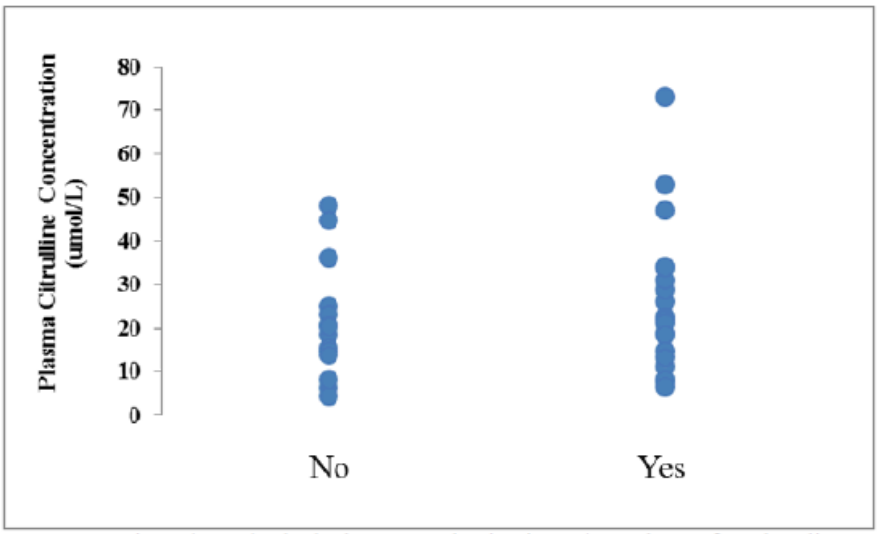
The naturally occurring human glucagon-like peptide-2 (GLP-2) is a peptide secreted by L cells of the intestine which is known to increase intestinal and portal blood flow, inhibit gastric acid secretion, and decrease intestinal motility. Teduglutide is an analogue of GLP-2. In several nonclinical studies,

teduglutide has been shown to preserve mucosal integrity by promoting repair and normal growth of the intestine through an increase of villus height and crypt depth.

Primary and secondary pharmacology

In study TED-C13-003, plasma citrulline was measured as an assessment of enterocyte mass. At Week 12 and EOT, citrulline levels were increased from baseline in a dose-related manner, with the greatest increase in the 0.05 mg/kg/day cohort. Further the Applicant explored the relationship between reduction in the clinical relevant endpoint "reduction in PN/IV – yes/no" and plasma levels of citrulline in the paediatric study and no apparent link could be observed.

Figure 1 Plasma Citrulline Concentrations (µmol/L) vs 20% PN/IV Reduction from Baseline at Week 12 Post-Treatment with Teduglutide (TED-C13-003)



Yes: SBS patients (N=19) who had ≥ 20% reduction in PN/IV volumes from baseline; and No: SBS patients (N=14) who did not at Week 12 post-treatment with teduglutide across 3 dose levels

Teduglutide antibodies were assessed at baseline, week 12 and 16. Based on the results of the immunogenicity test in study TED-C13-003, only one subject had a positive result for the presence of teduglutide specific antibodies. Post-hoc and exposure PK parameters derived from the final model for subjects taking 0.025 mg/kg (same dose level as Subject in study TED-C13-003 are presented in Table 4.5.1. PK and exposure parameters for this subject were within the range of those observed for subjects with negative immunogenicity test. The presence of antibodies did not affect teduglutide PK parameters of this patient.

Table 4.5.1 Posthoc and Exposure Parameters of Teduglutide Following Repeated Daily Subcutaneous Administration of 0.025 mg/kg in Pediatric SBS Patients

Subject ID	Antibody	Age (years)	Sex	CL/F (L/h)	Vc/F (L)	Ka (h^{-1})	$t_{1/2}$ (h)	$C_{min,ss}$ (ng/mL)	$C_{max,ss}$ (ng/mL)	$T_{max,ss}$ (h)	$AUC_{0-\tau,ss}$ (ng.h/mL)
[redacted]	Negative	8.97	Female	8.48	6.36	0.302	0.520	0.0220	15.5	1.61	79.1
	Positive	**5.12**	**Male**	**7.94**	**3.17**	**0.356**	**0.277**	**0.00509**	**16.1**	**1.08**	**62.6**
	Negative	6.39	Female	9.22	4.34	0.280	0.327	0.0232	12.3	1.27	59.7
	Negative	4.61	Male	7.27	3.02	0.297	0.288	0.0173	14.0	1.16	63.3
	Negative	2.46	Male	5.10	1.07	0.529	0.145	0.000109	24.2	0.687	60.2
	Negative	3.89	Male	5.40	1.10	0.464	0.142	0.000344	16.8	0.701	46.3
	Negative	14.4	Male	11.4	15.2	0.276	0.922	0.0563	14.9	2.27	96.4
	Negative	5.43	Male	7.40	2.61	0.317	0.245	0.0108	14.6	1.04	60.8
	Negative	1.93	Female	4.23	0.961	0.500	0.157	0.000227	25.1	0.727	66.2
	Negative	7.64	Male	7.37	3.31	0.505	0.311	0.000277	25.7	1.03	78.7
	Negative	2.07	Male	4.73	1.54	0.474	0.225	0.000477	24.9	0.888	74.0
	Negative	4.02	Male	7.61	1.54	0.334	0.140	0.00566	13.2	0.753	47.9
	Negative	5.46	Male	6.92	2.09	0.346	0.209	0.00563	15.8	0.930	59.5

$AUC_{0-\tau,ss}$ = Area under the concentration-time curve from Time 0 to 24 hours at steady-state; CL/F = apparent clearance; $C_{max,ss}$ = maximum (peak) concentration at steady-state; $C_{min,ss}$ = minimum concentration at steady-state; Ka = first-order rate of absorption; $t_{1/2}$ = terminal (or disposition) half-life; $T_{max,ss}$ = time of maximum concentration at steady-state; Vc/F = apparent central volume of distribution

2.2.4. PK/PD modelling

Please refer to the above sections.

2.2.5. Discussion on clinical pharmacology

With the use of the sparse PK sampling in the paediatric study TED-C13-003, together with PK samples from adult studies, a population PK modelling and simulation analysis was performed to support the dosing rationale of teduglutide in paediatric patients with short bowel syndrome. Simulations were performed to compare teduglutide exposure in adult subjects and paediatric subjects at unit doses of 0.025, 0.05, and 0.10 mg/kg administered subcutaneously every 24 hours for 14 days. Simulation results indicated that paediatric subjects (1-17 years) are expected to display similar steady state Cmin and Cmax values of teduglutide as adults. Conversely, simulated AUCs values were highly age-dependent and gradually decreased from adults to children.

Also T½ decreases with age – presumably as a result of higher clearance in the paediatric population. However, the half-life is short in both adults (2 hours) and in children (0.22 – 0.30 hours) and the drug is cleared before the next dose in both populations therefore and impact on the efficacy of the drug is not expected.
It is recognized that there are PK differences between adults and children showing a lower exposure (AUC) and shorter half-life in paediatric patients 1 to 17 years of age, as compared with adults. However, Cmax was found to be independent of age and there was a suggestion of dose proportionality for AUCss, Cmax and Cmin. Furthermore the demonstrated efficacy in the paediatric clinical trial TED-C13-003 supports the proposed dosing, and the primary relevance of Cmax (peak concentrations), rather than exposure (Cmin or AUC). Therefore it was considered that there was sufficient evidence to support the recommendation for a dose of 0.05 mg/kg body weight once daily in both children and adults.

Teduglutide is eliminated primarily through the kidneys through a mechanism involving both glomerular filtration and tubular catabolism. A physiological difference in clearance (and following lower AUC and shorter half-life) between children and adults is possible related to the renal elimination of the drug.

Based on the pharmacokinetic properties of teduglutide children with renal impairment are expected to be exposed to higher concentrations and thus a dose reduction of 50% is reasonable in children with moderate and severe renal impairment and ESRD as included in 4.2 of the SmPC. Furthermore the limited data from children with moderate to severe renal impairment and ESRD is mentioned in 5.2 if the SmPC which is considered acceptable by the CHMP.

In study TED-C13-003, the PD effects of teduglutide were assessed by PN/IV support, plasma citrulline and teduglutide antibodies. PN/IV support will be further discussed in the efficacy section. Plasma citrulline and teduglutide antibodies were measured at baseline and at 12 weeks (end of study). Only one patient was tested antibody positive and there were no impact on the teduglutide PK. Plasma citrulline increased from baseline to 12 weeks, and was supposed to reflect an increased enterocyte mass. However, the Applicant has explored the relationship between reduction in the clinical relevant endpoint "reduction in PN/IV – yes/no" and plasma levels of citrulline in the paediatric study and no apparent link could be observed.

2.2.6. Conclusions on clinical pharmacology

Similar C_{max} of teduglutide across age groups was demonstrated by population pharmacokinetics modelling and there was a suggestion of dose proportionality for AUCss, Cmax and Cmin. Cmax was more predictive of the effect based on study TEDC13-003 (see also efficacy part of this assessment report) and it is considered that there is sufficient evidence to support the recommendation for a dose of 0.05 mg/kg body weight once daily in both children and adults.

Nevertheless the pharmacokinetic profile of teduglutide in this paediatric population, as evaluated by clearance and volume of distribution was different from that observed in adults after correcting for body weights. Specifically, clearance decreases with increasing age from 1 year old to adults and this is appropriately reflected in the SmPC.

Based on the pharmacokinetic properties of teduglutide children with renal impairment are expected to be exposed to higher concentrations and thus a dose reduction of 50% is reasonable in children with moderate and severe renal impairment and ESRD as included in 4.2 of the SmPC. Furthermore the limited data from children with moderate to severe renal impairment and ESRD is mentioned in 5.2 if the SmPC which is considered acceptable by the CHMP.

2.3. Clinical efficacy

2.3.1. Dose response study

Please refer to the main study described below.

2.3.2. Main study

Title of Study

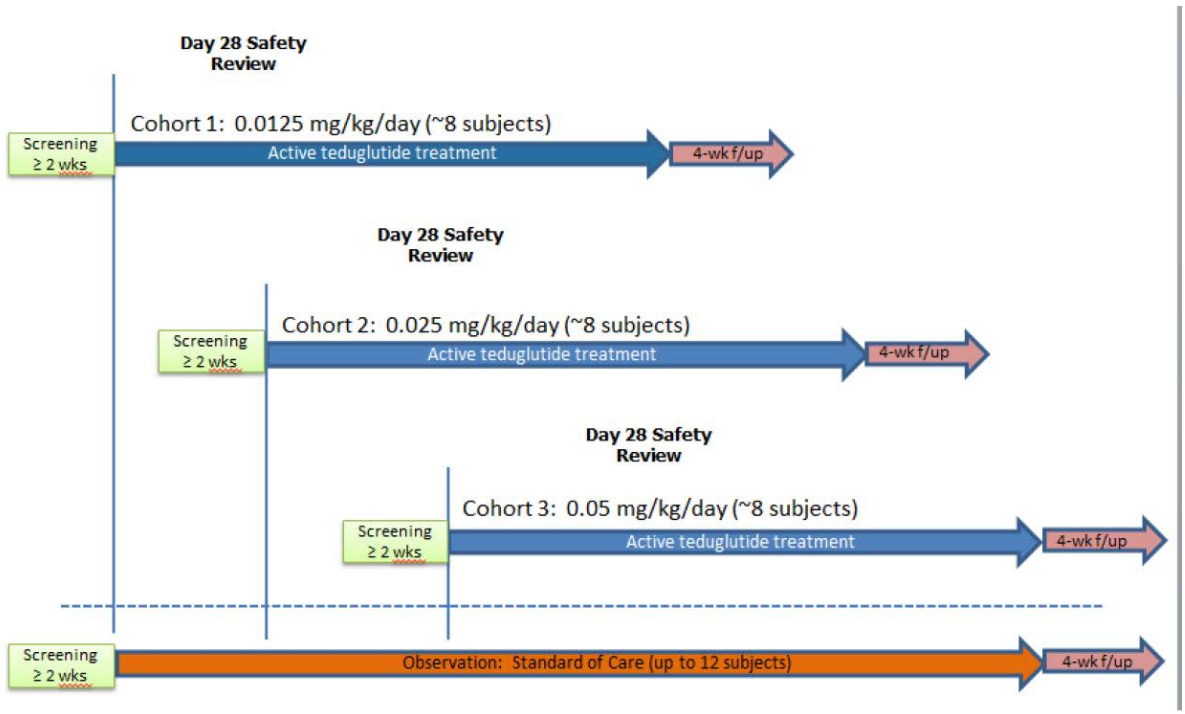
A 12-Week Pharmacokinetic, Safety, and Pharmacodynamic Study of Teduglutide in Pediatric Subjects Aged 1 through 17 Years, with Short Bowel Syndrome who are Dependent on Parenteral Support

Methods

The pivotal study TED-C13-003, was an open-label, 4-cohort study in which approximately 8 subjects in each of the 3 active cohorts were to receive subcutaneous (SC) injections of teduglutide. An attempt was

made to enroll up to 12 subjects into an observational cohort who would receive standard of care treatment. Three doses of teduglutide, 0.0125 mg/kg/day, 0.025 mg/kg/day, and 0.05 mg/kg/day, were investigated for 12 weeks in a staggered sequential approach starting with the lowest dose. All subjects were screened for a minimum of 2 weeks prior to SOT to verify the requirements for nutritional support for each subject and to ensure adherence to eligibility parameters. Subjects were to be enrolled in the study for 16 weeks.

Figure 9-1 Study Diagram



Study participants

Inclusion criteria

Male and female children and adolescents, aged 1 year through 17 years, who met the following inclusion criteria, were enrolled in the study:

1. Informed consent by a parent or guardian or emancipated minor prior to any study-related procedures
2. When applicable, an informed assent by the subject prior to any study-related procedures (as deemed appropriate by the IEC/ IRB
3. Current history of SBS as a result of major intestinal resection, (e.g., due to necrotizing enterocolitis, midgut volvulus, intestinal atresia, or gastroschisis) for at least 12 months prior to screening
4. Short bowel syndrome that requires PN/IV support that provides at least 30% of caloric and/or fluid/electrolyte needs
5. Stable PN/IV support for at least 3 months (defined as inability to significantly reduce PN/IV support, usually associated with minimal or no advance in enteral feeds [i.e., 10% or less change in PN or advance in feeds]) prior to baseline, based upon the opinion of the investigator
6. Female subjects of childbearing potential must use medically acceptable methods of birth control during and for 30 days after the treatment period.

Exclusion Criteria

Subjects who met any of the following exclusion criteria at baseline were not eligible for enrollment into the study:

1. Serial transverse enteroplasty or any other bowel lengthening procedure performed within 3 months of screening
2. Evidence of clinically significant untreated intestinal obstruction or active stenosis
3. Unstable absorption due to cystic fibrosis, untreated Hirschsprung's disease or known DNA abnormalities (i.e., Familial Adenomatous Polyposis, Fanconi syndrome)
4. Radiographic or manometric evidence of pseudo-obstruction or severe known dysmotility syndrome, including persistent, severe gastroschisis-related motility disorders
5. Evidence of clinically significant obstruction on upper GI series done within 6 months prior to screening
6. Major gastrointestinal surgical intervention within 3 months prior to screening (insertion of feeding tube or endoscopic procedure was allowed)
7. Unstable cardiac disease, congenital heart disease or cyanotic disease, with the exception of subjects who had undergone ventricular or atrial septal defect repair
8. History of cancer or clinically significant lymphoproliferative disease, not including resected cutaneous basal or squamous cell carcinoma, or *in situ* non-aggressive and surgically resected cancer
9. Pregnant or lactating female subjects
10. Participation in a clinical study using an experimental drug within 1 month or an experimental antibody treatment within 3 months prior to screening, or concurrent participation in any clinical study using an experimental drug that would have affected the safety of teduglutide
11. Previous use of native GLP-2 and glucagon-like peptide-1 analog or human growth hormone within 3 months prior to screening.
12. Previous use of oral or IV glutamine, octreotide, or dipeptidyl peptidase IV inhibitors within 3 months prior to screening
13. Previous use of teduglutide
14. Subjects with active Crohn's disease who had been treated with biological therapy (e.g., antitumor necrosis factor or natalizumab) within the 6 months prior to screening
15. Subjects with inflammatory bowel disease (IBD) who required chronic systemic immunosuppressant therapy that had been introduced or changed during the 3 months prior to screening
16. More than 3 SBS-related or PN-related hospital admissions (e.g., catheter sepsis, clots, bowel obstruction, severe water-electrolyte disturbances) within 3 months prior to screening
17. Any unscheduled hospital admission within 1 month prior to screening (24-hour observations or central line replacement/repair, in an otherwise stable subject, were allowed)
18. Body weight < 5 percentile for age or < 10 kg
19. Signs of active severe or unstable, clinically significant hepatic impairment shown by any of the below laboratory test results at screening:
    a. Total bilirubin ≥ 2x upper limit of normal (ULN)
    b. Aspartate aminotransferase (AST) ≥ 5x ULN
    c. Alanine aminotransferase (ALT) ≥ 5x ULN

For subjects with Gilbert's disease:

d. Indirect (unconjugated) bilirubin ≥ 2x ULN

20. Signs of known continuous, active or unstable, clinically significant renal dysfunction shown by any of the below laboratory test results at screening:

    a. Serum creatinine ≥ 2x ULN

    b. Creatinine clearance < 50 mL/min*

*Only applied to subjects with a history of creatinine clearance < 50 mL/min who then were required to have > 50 mL/min to participate in the study.

21. Parent(s) and/or subjects who were not capable of understanding or not willing to adhere to the study visit schedule and other protocol requirements
22. Unstable, clinically significant pancreatic or biliary disease
23. Any condition or circumstance that in the investigator's opinion put the subject at any undue risk, prevented completion of the study, or interfered with analysis of the study results
24. Presence of any of the excluded disease states

Treatments

Daily doses of 0.0125, 0.025, and 0.05 mg/kg/day of teduglutide were administered in the morning to the subjects in Cohorts 1, 2, and 3, respectively. The dose calculation was based on body weight measured at the Baseline Visit (Visit 2). No adjustments to dose were made during the study period. Teduglutide was administered by SC injection once daily into 1 of the 4 quadrants of the abdomen (in subjects without a stoma) or either thigh or arm. Cohort 4 received standard of care (no placebo).

Subject compliance with study drug dosing was monitored by the sponsor or designee by counting and examining used and unused vials. In addition, compliance was to be checked by site personnel at every visit by asking the subject or the subject's parent or guardian if they had administered the study drug according to instructions.

Compliance was considered achieved if the subject had at least 80% of the planned doses administered.

Objectives

The objective of this clinical study was to evaluate the PK profile, safety and tolerability, and pharmacodynamic effects of teduglutide compared with standard of care in paediatric subjects (aged 1 year through 17 years) with SBS who are dependent on parenteral support.

Outcomes/endpoints

A PD endpoint of a 10% or greater reduction in PN/IV support at the end of 12 weeks of treatment compared to baseline was considered to be a valid PD marker of increased intestinal absorptive capacity. In the adult study, CL0600-020, 26 of the 30 subjects (86.9%) who ultimately had a 20% reduction in PN/IV volume already had a 10% reduction after 12 weeks of teduglutide treatment. Looking at the relationship from the other direction, 26 of the 31 subjects (83.8%) who had a 10% reduction in PN/IV volume at 12 weeks went on to have a 20% reduction by 6 months of teduglutide treatment. These data supported a 10% decrease at Week 12 as a predictor of pharmacodynamic effect.

In addition to the PD endpoint of ≥ 10% reduction in PN/IV support, other PD endpoints included:

- ≥ 20% reduction in PN/IV support
- An increase in enteral nutritional tolerance (calories and volume)
- A decrease in parenteral support (calories and volume)

- Ostomy output/stool balance testing (at selected sites)
- Urine output (mL/day)
- Weight gain or stabilization (Z-scores calculated based on individual institutional guidelines/standards including adjusting for gestational age), height (length)
- Changes in plasma citrulline from baseline to Weeks 12 (or EOT)
- Change in PN/IV support 4 weeks after EOT compared to baseline
- If applicable, change in PN/IV support 3 and 6 months after EOT compared to baseline for those who developed antibodies specific to teduglutide
- Change in hours per day or days per week of PN/IV as well as any subjects who were able to completely wean off PN/IV support

Sample size

The small sample size resulting from the small study population required the use of descriptive statistics with a goal of summarizing the sample. Continuous variables, including those assessed on a discrete scale, were summarized using descriptive statistics including number of subjects, mean, median, standard deviation (SD), maximum, and minimum. For categorical variables, statistical summaries included number of subjects and percentages.

Randomisation

This was a non-randomised study. At any time during the 2-week minimum screening period, the subject or subject's parent/guardian/caretaker decided whether to participate in the dosing cohort or the standard of care cohort. The timing of the subject's screening period determined which dosing cohort was available for the subject to enter. At the end of the screening period, the investigator reviewed and confirmed that the subject continued to meet all Inclusion/Exclusion criteria. If the subject qualified, the subject was provided with study drug at the dose level associated with the cohort that was enrolling at the time. Those subjects opting for the standard of care cohort continued in the study, but without clinical supplies. There were no cases of cross-over.

Blinding (masking)

Study medication was administered in an open-label fashion during the study.

Statistical methods

PK/PD Analysis Population

The intent-to-treat (ITT) population consisted of all subjects who enrolled into the trial. The ITT population was the primary analysis population analysed for PK/PD endpoints.

The Per Protocol (PP) population consisted of all subjects in the ITT population who completed the study without meeting any of the following conditions:

1. Missing PK data at both baseline and postbaseline
2. Absence of Week 12 visit
3. Non-compliance to study drug for the treatment group
4. Discrepancies between planned and actual treatment

The PP population was the secondary analysis population analysed for PD endpoints.

Safety Analysis Population

The Safety Population consisted of all subjects in the ITT population who received at least one dose of study medication or standard of care. For reporting purposes, these subjects were included in the

treatment group reflective of the treatment they actually received, regardless of the treatment group they were assigned to. All safety analyses were conducted on this population, unless otherwise specified. For this study, the safety population was identical to the intent-to-treat population.

Analysis of pharmacodynamic variables

All pharmacodynamic analyses were conducted on the ITT and PP population. Analyses of PN/IV support and enteral nutrition support included 2 sets of results based on 2 data sources: subject diary data and the investigator prescribed data.

The actual weekly PN volume, EN volume (by mouth and by tube feeding), ostomy output, and urine output were calculated based on the daily volumes recorded in subjects' diaries within 7 days prior to each scheduled visit. The calculation followed the formula below.

Weekly value = (sum of daily values in the diary/number of days with values) * 7

Missing daily PN or EN volumes were not imputed. If there were more than 2 days of missing diary data within an interval, the interval was classified as missing actual volume information. An exception to this rule was the baseline visit. For this visit, actual volume was based on all diaries prior to the first dose date. Data were summarised at all scheduled visits. An EOT time point was also added.

Results

Participant flow

Table 10-1 Subject Disposition – Intent-to-Treat Population

		Teduglutide (mg/kg/day)				
Category	Standard of Care (N=5) n (%)	0.0125 (N=8) n (%)	0.025 (N=14) n (%)	0.05 (N=15) n (%)	Total Teduglutide (N=37) n (%)	Total (N=42) n (%)
Enrolled	5 (100.0)	8 (100.0)	14 (100.0)	15 (100.0)	37 (100.0)	42 (100.0)
Treated	5 (100.0)	8 (100.0)	14 (100.0)	15 (100.0)	37 (100.0)	42 (100.0)
Completed Treatment [a]	5 (100.0)	7 (87.5)	14 (100.0)	14 (93.3)	35 (94.6)	40 (95.2)
Discontinued Treatment Early	0	1 (12.5)	0	1 (6.7)	2 (5.4)	2 (4.8)
Adverse Event	0	0	0	0	0	0
Withdrawal of consent and assent	0	0	0	1 (6.7)	1 (2.7)	1 (2.4)
Protocol non-compliance	0	1 (12.5)	0	0	1 (2.7)	1 (2.4)
Completed Study [b]	5 (100.0)	7 (87.5)	14 (100.0)	14 (93.3)	35 (94.6)	40 (95.2)

N = total number of subjects in dosing cohort; n = number of subjects in category specified
[a] Completion of treatment is based on whether the subject completed 12 weeks of study medication or standard of care.
[b] Completion of study is based on the End of Study page of the electronic case report form at Visit 15 (Week 16).
Source: Section 14, Table 14.1.2.1; Appendix 16.2, Listing 16.2.1.1

Recruitment

The study had the first subject first visit on 14th November 2013 and the last subject last visit on 09th January 2015.

Conduct of the study

There were no changes to the statistical methodology presented in the protocol. Other amendments to the protocol are summarised in Table 9-4 below.

Table 9-4 History of Protocol TED-C13-003 and Amendments

Document	Key Changes and Rationale	Version Date
Protocol v1.0 (Original Protocol)	Not applicable.	02 July 2013
Protocol v2.0 (Amendment 1)	The following substantial changes were made for implementation for the United Kingdom (UK) only: 1) The observation time after the first SC injection was increased to 4 hours to allow for monitoring of hypersensitivity reactions. 2) The definition of true abstinence was added for females of child bearing potential in order to clarify study requirements.	31 January 2014
Protocol v3.0 (Amendment 2)	The following substantial changes were made for implementation for Sweden only: 1) A rationale for the study design was added to provide risk/benefit information for PN/IV support in relation to the protocol design. 2) Additional safety visits were added after EOT and before End of Study for 3 consecutive weeks to provide follow-up safety monitoring. 3) Post-treatment guidance was added to ensure that subjects were returned to their previous standard of care. 4) The time frame of 5 years was added to Exclusion Criterion 8 for history of cancer or clinically significant lymphoproliferative disease. 5) The duration of record retention was extended to 10 years. (Note: the study was not initiated in Sweden)	26 February 2014
Protocol v4.0 (Amendment 3)	The following substantial changes were made for implementation at all study sites: 1) Inclusion Criterion 5 was clarified to provide further specific definition of stable PN/IV support. 2) Exclusion Criterion 17 was clarified to provide further details regarding prestudy hospital admissions. 3) The details surrounding the storage conditions of the study medication were clarified. 4) Details for dose interruption of individual subjects and study termination were included in the protocol. 5) Changes from local Amendments 1 and 2 were incorporated for all sites.	11 July 2014

Protocol deviation data were collected from monitoring reports. Protocol deviations from these reports were consolidated into a deviation log at the Contract Research Organization, which transferred the log to NPS during the study and after the data base lock. The number and percent of subjects with protocol deviations were presented for each treatment group and all subjects combined. There was no interim analysis performed for this study.

Table 10-2 Site-reported Protocol Deviations – Intent-to-Treat Population

Category	Standard of Care (N=5) n (%)	Teduglutide 0.0125 mg/kg/day (N=8) n (%)	Teduglutide 0.025 mg/kg/day (N=14) n (%)	Teduglutide 0.05 mg/kg/day (N=15) n (%)	Total Teduglutide (N=37) n (%)	Total (N=42) n (%)
Subjects with at Least One Protocol Deviation	5 (100.0)	7 (87.5)	13 (92.9)	15 (100.0)	35 (94.6)	40 (95.2)
Informed Consent	1 (20.0)	2 (25.0)	4 (28.6)	8 (53.3)	14 (37.8)	15 (35.7)
Inclusion/Exclusion Criteria	1 (20.0)	0	1 (7.1)	1 (6.7)	2 (5.4)	3 (7.1)
Study Medication	0	2 (25.0)	9 (64.3)	4 (26.7)	15 (40.5)	15 (35.7)
Study Procedure or Assessment	5 (100.0)	7 (87.5)	11 (78.6)	10 (66.7)	28 (75.7)	33 (78.6)
Subject Visit Completion or Timing	3 (60.0)	5 (62.5)	3 (21.4)	8 (53.3)	16 (43.2)	19 (45.2)
(Serious) Adverse Event Reporting	1 (20.0)	1 (12.5)	4 (28.6)	2 (13.3)	7 (18.9)	8 (19.0)
Other	1 (20.0)	2 (25.0)	3 (21.4)	4 (26.7)	9 (24.3)	10 (23.8)

N = total number of subjects in a dosing cohort; n = number of subjects for category specified
Note: Percentages are based on the Intent-to-Treat population in each treatment arm.
Note: Three additional deviations found subsequent to database lock (ie, minor errors in diary entries) are not included in this table
Source: Section 14, Table 14.1.2.1, Appendix 16.2, Listing 16.2.2.2

Baseline data

Table 11-1 Demographics and Baseline Characteristics – Intent-to-Treat Population

Parameter	Statistic	Standard of Care (N=5)	Teduglutide 0.0125 mg/kg/day (N=8)	Teduglutide 0.025 mg/kg/day (N=14)	Teduglutide 0.05 mg/kg/day (N=15)	Total Teduglutide (N=37)	Total (N=42)
Age at Informed Consent (years)	n	5	8	14	15	37	42
	Mean (SD)	2.2 (0.45)	5.1 (4.55)	4.6 (3.43)	4.5 (3.16)	4.7 (3.50)	4.4 (3.38)
	Median	2.0	3.0	4.0	4.0	4.0	3.0
	Min, Max	2, 3	1, 14	1, 14	1, 14	1, 14	1, 14
Age Category at Informed Consent							
1 to 3 years	n(%)	5 (100.0)	4 (50.0)	6 (42.9)	7 (46.7)	17 (45.9)	22 (52.4)
4 to 12 years	n(%)	0	3 (37.5)	7 (50.0)	7 (46.7)	17 (45.9)	17 (40.5)
13 to 17 years	n(%)	0	1 (12.5)	1 (7.1)	1 (6.7)	3 (8.1)	3 (7.1)
Gender							
Male	n(%)	3 (60.0)	6 (75.0)	11 (78.6)	8 (53.3)	25 (67.6)	28 (66.7)
Female	n(%)	2 (40.0)	2 (25.0)	3 (21.4)	7 (46.7)	12 (32.4)	14 (33.3)
Race							
White	n(%)	3 (60.0)	6 (75.0)	11 (78.6)	13 (86.7)	30 (81.1)	33 (78.6)
Black or African American	n(%)	1 (20.0)	2 (25.0)	1 (7.1)	1 (6.7)	4 (10.8)	5 (11.9)
Asian	n(%)	1 (20.0)	0	0	1 (6.7)	1 (2.7)	2 (4.8)
Native Hawaiian or Other Pacific Islander	n(%)	0	0	0	0	0	0
American Indian or Alaska Native	n(%)	0	0	0	0	0	0
Other	n(%)	0	0	1 (7.1)	0	1 (2.7)	1 (2.4)
Not Applicable	n(%)	0	0	1 (7.1)	0	1 (2.7)	1 (2.4)
Ethnicity							
Hispanic or Latino	n(%)	0	1 (12.5)	6 (42.9)	3 (20.0)	10 (27.0)	10 (23.8)
Not Hispanic or Latino	n(%)	4 (80.0)	7 (87.5)	7 (50.0)	11 (73.3)	25 (67.6)	29 (69.0)
Not Applicable	n(%)	1 (20.0)	0	1 (7.1)	1 (6.7)	2 (5.4)	3 (7.1)

Table 11-1 Demographics and Baseline Characteristics – Intent-to-Treat Population

Parameter	Statistic	Standard of Care (N=5)	Teduglutide 0.0125 mg/kg/day (N=8)	Teduglutide 0.025 mg/kg/day (N=14)	Teduglutide 0.05 mg/kg/day (N=15)	Total Teduglutide (N=37)	Total (N=42)
Height at Informed Consent (cm)	n	5	6	14	15	35	40
	Mean (SD)	88.88 (4.995)	105.57 (29.293)	104.51 (21.794)	101.21 (15.567)	103.28 (20.274)	101.48 (19.600)
	Median	92.00	95.00	99.75	99.30	99.30	96.60
	Min, Max	81.5, 93	80, 157.5	81, 160.5	77.6, 145	77.6, 160.5	77.6, 160.5
Weight at Informed Consent (kg)	n	5	8	14	15	37	42
	Mean (SD)	12.86 (1.626)	19.94 (13.369)	18.75 (9.012)	16.87 (6.600)	18.24 (9.086)	17.60 (8.709)
	Median	12.20	13.00	16.70	16.00	16.00	14.60
	Min, Max	10.9, 14.6	10.3, 48	10.7, 45.1	10.4, 38.7	10.3, 48	10.3, 48
BMI at Informed Consent (kg/m^2)	n	5	6	14	15	35	40
	Mean (SD)	16.290 (1.7131)	15.797 (1.9071)	16.438 (1.2198)	16.031 (1.1969)	16.154 (1.3251)	16.171 (1.3542)
	Median	16.760	15.390	16.155	15.900	16.020	16.030
	Min, Max	14.3, 18.37	13.76, 19.35	14.81, 18.19	14.33, 18.41	13.76, 19.35	13.76, 19.35
Weight Z-Score at Informed Consent	n	5	6	9	13	28	33
	Mean (SD)	0.182 (0.7886)	-0.835 (0.8258)	-0.051 (0.8519)	0.029 (0.7521)	-0.182 (0.8454)	-0.127 (0.8356)
	Median	0.520	-0.795	-0.300	-0.140	-0.235	-0.190
	Min, Max	-0.69, 1.1	-1.9, 0.04	-0.9, 1.76	-1, 1.24	-1.9, 1.76	-1.9, 1.76

BMI = body mass index; Max = maximum; Min = minimum; N = total number of subjects in a dosing cohort; n = number of subjects for category specified; SD = standard deviation
Note: Percentages are based on the Intent-to-Treat population in each treatment arm.
Source: Section 14, Table 14.1.3.1; Appendix 16.2, Listing 16.2.4.1 and Listing 16.2.8.11

Table 11-2 Short Bowel Syndrome History – Intent-to-Treat Population

Parameter	Statistic	Standard of Care (N=5)	Teduglutide 0.0125 mg/kg/day (N=8)	Teduglutide 0.025 mg/kg/day (N=14)	Teduglutide 0.05 mg/kg/day (N=15)	Total Teduglutide (N=37)	Total (N=42)
Reason for Major Intestinal Resection							
Necrotizing Enterocolitis	n (%)	2 (40.0)	1 (12.5%)	2 (14.3)	3 (20.0)	6 (16.2)	8 (19.0)
Midgut Volvulus	n (%)	2 (40.0)	2 (25.0)	4 (28.6)	7 (46.7)	13 (35.1)	15 (35.7)
Intestinal Atresia	n (%)	1 (20.0)	1 (12.5)	4 (28.6)	2 (13.3)	7 (18.9)	8 (19.0)
Gastroschisis	n (%)	0	2 (25.0)	7 (50.0)	3 (20.0)	12 (32.4)	12 (28.6)
Trauma	n (%)	0	0	0	0	0	0
Cancer	n (%)	0	0	0	0	0	0
Crohns Disease	n (%)	0	0	0	0	0	0
Other	n (%)	0	2 (25.0)	0	1 (6.7)	3 (8.1)	3 (7.1)
Does the subject have a stoma?							
Yes	n (%)	0	1 (12.5)	1 (7.1)	1 (6.7)	3 (8.1)	3 (7.1)
No	n (%)	5 (100.0)	7 (87.5)	13 (92.9)	14 (93.3)	34 (91.9)	39 (92.9)
Type of Stoma [a]							
Jejunostomy	n (%)	0	0	0	0	0	0
Ileostomy	n (%)	0	1 (100.0)	1 (100.0)	1 (100.0)	3 (100.0)	3 (100.0)
Colostomy	n (%)	0	0	0	0	0	0
Other	n (%)	0	0	0	0	0	0
Does the subject have any remaining colon?							
Yes	n (%)	5 (100.0)	7 (87.5)	14 (100.0)	14 (93.3)	35 (94.6)	40 (95.2)
No	n (%)	0	1 (12.5)	0	1 (6.7)	2 (5.4)	2 (4.8)
Estimated percent of colon remaining	n	5	6	11	12	29	34
	Mean (SD)	66.6 (31.27)	75.0 (30.17)	67.1 (34.64)	75.4 (29.77)	72.2 (30.91)	71.4 (30.55)
	Median	50.0	85.0	60.0	77.5	75.0	75.0
	Min,Max	33 , 100	30 , 100	10 , 100	8 , 100	8 , 100	8 , 100

Table 11-2 Short Bowel Syndrome History – Intent-to-Treat Population

Parameter	Statistic	Standard of Care (N=5)	Teduglutide 0.0125 mg/kg/day (N=8)	Teduglutide 0.025 mg/kg/day (N=14)	Teduglutide 0.05 mg/kg/day (N=15)	Total Teduglutide (N=37)	Total (N=42)
Is the colon in continuity? [b]							
Yes	n (%)	5 (100.0)	7 (100.0)	12 (85.7)	14 (100.0)	33 (94.3)	38 (95.0)
No	n (%)	0	0	2 (14.3)	0	2 (5.7)	2 (5.0)
Has the subject had a colonoscopy in the last 12 months?							
Yes	n (%)	0	1 (12.5)	2 (14.3)	6 (40.0)	9 (24.3)	9 (21.4)
No	n (%)	0	1 (12.5)	0	0	1 (2.7)	1 (2.4)
Not Applicable	n (%)	5 (100.0)	6 (75.0)	12 (85.7)	9 (60.0)	27 (73.0)	32 (76.2)
Total estimated remaining small intestinal length (cm)	n	5	7	13	13	33	38
	Mean (SD)	37.4 (25.89)	28.1 (25.89)	66.3 (37.19)	32.8 (21.74)	45.0 (33.60)	44.0 (32.49)
	Median	35.0	15.0	68.0	26.0	30.0	32.5
	Min,Max	10 , 75	2 , 75	15 , 145	0 , 68	0 , 145	0 , 145
< 25 cm	n (%)	2 (40.0)	4 (50.0)	1 (7.1)	6 (40.0)	11 (29.7)	13 (31.0)
≥ 25 cm	n (%)	3 (60.0)	3 (37.5)	12 (85.7)	7 (46.7)	22 (59.5)	25 (59.5)
< 40 cm	n (%)	3 (60.0)	5 (62.5)	4 (28.6)	8 (53.3)	17 (45.9)	20 (47.6)
≥ 40 cm	n (%)	2 (40.0)	2 (25.0)	9 (64.3)	5 (33.3)	16 (43.2)	18 (42.9)
< 60 cm	n (%)	4 (80.0)	6 (75.0)	5 (35.7)	11 (73.3)	22 (59.5)	26 (61.9)
≥ 60 cm	n (%)	1 (20.0)	1 (12.5)	8 (57.1)	2 (13.3)	11 (29.7)	12 (28.6)
Distal/terminal Ileum present							
Yes	n (%)	1 (20.0)	2 (25.0)	1 (7.1)	4 (26.7)	7 (18.9)	8 (19.0)
No	n (%)	4 (80.0)	6 (75.0)	11 (78.6)	11 (73.3)	28 (75.7)	32 (76.2)

Table 11-2 Short Bowel Syndrome History – Intent-to-Treat Population

Parameter	Statistic	Standard of Care (N=5)	Teduglutide 0.0125 mg/kg/day (N=8)	Teduglutide 0.025 mg/kg/day (N=14)	Teduglutide 0.05 mg/kg/day (N=15)	Total Teduglutide (N=37)	Total (N=42)
If Yes, is the ileocecal value present [c]							
Yes	n (%)	1 (100.0)	2 (100.0)	1 (100.0)	4 (100.0)	7 (100.0)	8 (100.0)
No	n (%)	0	0	0	0	0	0
Length of remaining anatomy determined by							
Surgery	n (%)	4 (80.0)	5 (62.5)	7 (50.0)	12 (80.0)	24 (64.9)	28 (66.7)
Radiology	n (%)	0	1 (12.5)	3 (21.4)	1 (6.7)	5 (13.5)	5 (11.9)
Other	n (%)	1 (20.0)	2 (25.0)	4 (28.6)	2 (13.3)	8 (21.6)	9 (21.4)

Max = maximum; Min = minimum; N = total number of subjects in a dosing cohort; n = number of subjects for category specified; SD = standard deviation
Note: Percentages are based on the Intent-to-Treat population in each treatment arm.
Note: A subject may have multiple reasons for major intestinal resection. In that case, the subject will be counted once under each of the reasons.
[a] Percentages are based on subjects with a stoma in each treatment arm.
[b] Percentages are based on subjects with remaining colon in each treatment arm.
[c] Percentages are based on subjects with distal/terminal ileum in each treatment arm.
Source: Section 14, Table 14.1.4.1; Appendix 16.2, Listing 16.2.4.2

Table 11-3 Selected Parenteral and Enteral Nutrition History – Intent-to-Treat Population

			Teduglutide				
Parameter	Statistic	Standard of Care (N=5)	0.0125 mg/kg/day (N=8)	0.025 mg/kg/day (N=14)	0.05 mg/kg/day (N=15)	Total Teduglutide (N=37)	Total (N=42)
Years Since Start of PN Dependency (years)	n	5	8	14	15	37	42
	Mean(SD)	2.43 (0.431)	4.68 (3.744)	4.25 (2.155)	4.36 (2.977)	4.39 (2.806)	4.15 (2.710)
	Median	2.35	3.56	4.21	4.03	4.03	3.65
	Min,Max	2.0 , 3.1	0.9 , 12.2	1.3 , 8.8	0.5 , 12.2	0.5 , 12.2	0.5 , 12.2
Prescribed PN/IV Volume (L/Week)	n	5	8	14	15	37	42
	Mean(SD)	7.422 (2.2720)	7.084 (3.5813)	8.931 (3.4304)	7.164 (3.0627)	7.815 (3.3423)	7.769 (3.2139)
	Median	7.700	5.350	8.050	5.570	6.940	7.320
	Min,Max	4.41 , 9.80	4.20 , 13.87	4.35 , 16.00	4.00 , 13.06	4.00 , 16.00	4.00 , 16.00
Prescribed PN Calorie (kcal/Week)	n	5	8	14	15	37	42
	Mean(SD)	5797.80 (2329.344)	5774.13 (2893.405)	5752.79 (2487.716)	5256.33 (1562.615)	5556.13 (2208.007)	5584.90 (2194.623)
	Median	5399.00	5458.00	5891.50	4767.00	5292.00	5345.50
	Min,Max	3045.0 , 8288.0	1785.0 , 10759.0	2455.0 , 11956.0	3378.2 , 8561.7	1785.0 , 11956.0	1785.0 , 11956.0
Prescribed Number of Days per Week of PN/IV	n	5	8	14	15	37	42
	Mean(SD)	7.0 (0.00)	7.0 (0.00)	6.9 (0.53)	6.7 (0.90)	6.8 (0.66)	6.8 (0.62)
	Median	7.0	7.0	7.0	7.0	7.0	7.0
	Min,Max	7 , 7	7 , 7	5 , 7	4 , 7	4 , 7	4 , 7
Years Since Start of EN Dependency (years)	n	2	4	11	6	21	23
	Mean(SD)	2.42 (0.128)	4.02 (3.972)	5.35 (3.565)	2.33 (1.381)	4.24 (3.313)	4.08 (3.202)
	Median	2.42	3.12	4.37	2.54	3.66	3.32
	Min,Max	2.3 , 2.5	0.5 , 9.4	2.0 , 14.3	0.6 , 3.9	0.5 , 14.3	0.5 , 14.3
Prescribed EN Volume (L/Week)	n	4	4	13	10	27	31
	Mean(SD)	4.340 (2.3371)	8.493 (4.4122)	7.225 (3.6140)	3.696 (1.5643)	6.106 (3.5858)	5.878 (3.4716)
	Median	5.240	9.205	6.000	3.630	5.650	5.390
	Min,Max	0.88 , 6.00	2.86 , 12.70	1.90 , 13.36	1.66 , 6.30	1.66 , 13.36	0.88 , 13.36

Table 11-3 Selected Parenteral and Enteral Nutrition History – Intent-to-Treat Population

			Teduglutide				
Parameter	Statistic	Standard of Care (N=5)	0.0125 mg/kg/day (N=8)	0.025 mg/kg/day (N=14)	0.05 mg/kg/day (N=15)	Total Teduglutide (N=37)	Total (N=42)
Prescribed EN Calorie (kcal/Week)	n	4	4	13	10	27	31
	Mean(SD)	3510.250 (2080.8999)	7738.000 (4072.0263)	6366.448 (3693.9450)	4223.826 (2581.5295)	5776.077 (3494.4351)	5483.713 (3407.6606)
	Median	3982.500	7664.000	5998.000	4261.400	5390.000	4746.000
	Min,Max	700.00 , 5376.00	2856.00 , 12768.00	1890.00 , 12600.00	1.66 , 9240.00	1.66 , 12768.00	1.66 , 12768.00
Prescribed Number of Days per Week of EN	n	4	4	13	10	27	31
	Mean(SD)	7.0 (0.00)	7.0 (0.00)	7.0 (0.00)	7.0 (0.00)	7.0 (0.00)	7.0 (0.00)
	Median	7.0	7.0	7.0	7.0	7.0	7.0
	Min,Max	7 , 7	7 , 7	7 , 7	7 , 7	7 , 7	7 , 7

EN = enteral nutrition; Max = maximum; Min = minimum; N = total number of subjects in a dosing cohort; n = number of subjects for category specified; PN = parenteral nutrition; PN/IV = parenteral nutrition/intravenous fluid; SD = standard deviation
Note: Percentages are based on the Intent-to-Treat population in each treatment arm.
Source: Adapted from Section 14, Table 14.1.6.1, 14.1.7.1; Appendix 16.2, Listing 16.2.4.4, Listing 16.2.4.5

Table 2 Total Estimated Remaining Small Intestinal Length in TED 0.025 mg/kg/daily and TED 0.05 mg/kg/daily dose groups

Statistic	TED 0.025 mg/kg/daily N = 13	TED 0.05 mg/kg/daily N = 13
Mean (SD)	66.3 (37.19) cm	32.8 (21.74) cm
Median	68.0 cm	26.0 cm
Min, Max	15, 145 cm	0, 68 cm

TED-C13-003 Table 11-2

Numbers analysed

The ITT population included all subjects who were enrolled in the study. This was the primary study population used to evaluate pharmacodynamic measures of efficacy. The Safety population was identical to the ITT population. The PP population consisted of all subjects in the ITT population who completed the study without meeting any of the following conditions:

1. Missing PK data at both baseline and post-baseline;

2. Absence of Week 12 visit,

3. Non-compliance to study drug for the treatment group, and

4. Discrepancies between planned and actual treatment.

The PP population was the secondary analysis population analysed for PD endpoints.

Table 14.1.1.2.1
Study Analysis Populations
All Enrolled Subjects

		Teduglutide				
	Standard of Care (N=5) n(%)	0.0125 mg/kg/day (N=8) n(%)	0.025 mg/kg/day (N=14) n(%)	0.05 mg/kg/day (N=15) n(%)	Total Teduglutide (N=37) n(%)	Total (N=42) n(%)
Intention-to-treat	5 (100.0)	8 (100.0)	14 (100.0)	15 (100.0)	37 (100.0)	42 (100.0)
Per-protocol	5 (100.0)	7 (87.5)	13 (92.9)	14 (93.3)	34 (91.9)	39 (92.9)
Safety	5 (100.0)	8 (100.0)	14 (100.0)	15 (100.0)	37 (100.0)	42 (100.0)

Outcomes and estimation

Complete Weaning

Based on physician-prescribed data, a total of 4 of 37 (10.8%) subjects in the ITT population had completely weaned off of PN at the EOT visit. These subjects included 3 of 15 (20.0%) subjects in the 0.05 mg/kg/day cohort and 1 of 14 (7.1%) subjects in the 0.025 mg/kg/day cohort. One subject in the 0.05 mg/kg/day cohort achieved this goal by Week 4.

Reduction in PN volume support

The mean decrease in PN/IV volume from baseline at Week 12 based on physician-prescribed data was -2.78 (± 1.99) and -2.57 (± 3.56) L/week in the 0.025 and 0.05 mg/kg/day cohorts, respectively. These corresponded to a -37.34% (± 26.42) and a -39.11% (± 40.79) mean decrease, respectively, compared with a -9.95% (± 21.63) decrease in the 0.0125 mg/kg/day cohort and a 7.38% (± 12.76) increase in the standard of care cohort. Four weeks following EOT (Week 16), PN/IV volume reductions were still seen in all dosing cohorts, although these were less robust than those at Week 12 in the 0.025 and 0.05 mg/kg/day cohorts, when subjects were still receiving teduglutide. The mean change in PN/IV volume in the standard of care and the 0.0125 mg/kg/day cohorts continued to decline slightly during the 4 post-treatment weeks.

Reduction in total PN caloric intake

Based on physician-prescribed data in the ITT population, reductions from baseline at Week 12 in total PN caloric intake were -35.16% (± 38.78) and -35.11% (± 53.04) in the 0.025 and 0.05 mg/kg/day cohorts, respectively. Changes in the standard of care and teduglutide 0.0125 mg/kg/day cohorts were 4.31% (± 5.36) and -10.04% (± 26.10), respectively. At Week 16, this effect was still evident, with PN/IV calories decreasing further in the 0.05 mg/kg/day (n = 14) and standard of care cohorts (n = 5), increasing slightly in the 0.0125 mg/kg/day cohort (n = 7) and staying at a similar level in the 0.025 mg/kg/day cohort (n = 13).

Reduction in infusion time

Mean decreases from baseline at Week 12 in the number of days/week of PN/IV required, based on physician-prescribed data, were -0.69 (± 1.97) days/week and -1.36 (± 2.37) days/week, corresponding to a percentage decrease of -10.77% (± 29.00) days/week and -24.49% (± 42.46) days/week in the 0.025 and 0.05 mg/kg/day cohorts, respectively. There was no change from baseline in either the 0.0125 mg/kg/day or standard of care cohorts. These decreases translated to a reduction in days on PN/IV support. Based on physician-prescribed data in the ITT population at Week 12, 1 subject in the 0.025 mg/kg/day cohort had a 3-day or more reduction in days on PN/IV. Four subjects in the 0.05 mg/kg/day cohort achieved a 3-day or greater reduction in days on PN/IV. No subjects in the standard of care or 0.0125 mg/kg/day cohorts achieved a reduction of days on PN/IV support. Based on subject diary data at Week 12, subjects in the 0.025 and 0.05 mg/kg/day cohorts had mean decreases from baseline of 3.94 (± 3.75) and 4.18 (± 4.08) hours, respectively, in daily PN usage, corresponding to mean percentage reductions of -27.41% (± 33.52) and -35.55% (± 35.23), respectively. Subjects in the standard of care and 0.0125 mg/kg/day cohorts showed minimal changes in this parameter at the same time point.

Increase in Enteral Volume and Calories

Based on subject diary data, mean enteral volume at Week 12 increased from baseline by 50.93% (± 61.42) in the 0.025 cohort and by 57.96% (± 44.95) in the 0.05 mg/kg/day cohort, compared with 23.50% (± 22.06) in the 0.0125 mg/kg/day cohort and 16.82% (± 14.92) in the standard of care cohort. Four weeks after the end of teduglutide treatment (Week 16), EN intake was maintained in the 0.05 mg/kg/day cohort (n = 9), while dropping slightly in the 0.025 mg/kg/day cohort (n = 11). The standard of care cohort (n = 4) also showed an increase in EN volume at Week 16. There were data for only 1 subject in the 0.0125 mg/kg/day cohort at Week 16. The increases in EN intake in the active treatment cohorts corresponded to increases in EN calories, which were highest in the 0.05 mg/kg/day cohort. At Week 12 in the ITT population, the percentage increase from baseline in prescribed EN calories in the 0.05 mg/kg/day cohort was 58.80% (± 64.20) compared with 53.10% (± 63.76) and 17.09% (± 20.50) in the 0.025 and 0.0125 mg/kg/day cohorts, respectively. The standard of care cohort, in which an increase in PN volume was observed, also had an increase in EN calories (57.02% [± 55.25]), indicating that the key goal in paediatric SBS intestinal rehabilitation is the concept of advancing enteral feeds. At Week 16, intake of EN calories continued to rise, with percentage increases from baseline of 59.63% (± 52.62), 28.37 (± 40.11), 56.13% (± 67.78) and 64.57% (± 57.53) in the standard of care and the teduglutide 0.0125, 0.025 and 0.05 mg/kg/day cohorts, respectively. These changes corresponded to changes from Week 12 to Week 16 of 2.33% (± 4.65), 6.36% (± 12.21), 1.52% (± 4.96) and 7.09% (± 22.43) in the standard of care and 0.0125, 0.025 and 0.05 mg/kg/day cohorts, respectively.

Maintenance of clinical nutritional status

Concurrent with decreases in PN volume, subjects treated with teduglutide maintained their clinical nutritional status, as evidenced by stability of laboratory parameters, weight and height parameters, indicating effective EN absorption of nutrients and fluids.

Changes in Plasma Citrulline

Plasma citrulline levels at all 3 time points measured (Week 12, EOT and Week 16) were increased from baseline in a dose-related manner, with the greatest increase in the teduglutide 0.05 mg/kg/day cohort. Citrulline was not measured in the standard of care cohort. Although the increases were still evident at Week 16, they had decreased from the Week 12 level.

Subjects Who Achieved at Least a 20% PN Volume Reduction

By Week 12 in the ITT population, 10/14 (71.4%) and 8/15 (53.3%) subjects in the 0.025 and 0.05 mg/kg/day cohorts, respectively, had achieved a 20% or greater reduction in PN/IV volume compared with no subjects in the standard of care cohort and 1/8 (12.5%) subjects in the 0.0125 mg/kg/day cohort, based on physician-prescribed data. Eight out of 14 (57.1%) subjects in the 0.025 mg/kg/day cohort and 9/15 subjects (60.0%) in the 0.05 mg/kg/day cohort achieved a 20% or greater calorie reduction. No subjects in the standard of care cohort achieved this milestone and 1/8 (12.5%) subjects achieved a 20% calorie reduction at Week 12 in the 0.0125 cohort.

Comparable results were seen when based on subject diary data and the per-protocol populations as well as for the 10% reduction in PN supplements.

Ancillary analyses

Subgroup analyses of PN volume change from baseline was evaluated in the ITT population by etiology of SBS, remaining length of small intestine, presence of a stoma, and presence of a colon. Due to the small sample size, results of these subset analyses are inconclusive and, at best, only can offer a suggestion of influence.

The majority of subjects in all study cohorts had a colon and did not have a stoma and, therefore, reduction totals at Week 12 in these 2 subsets were similar to the overall totals. There were too few subjects without a colon to be able to assess the impact of this parameter. Similarly, only 1 subject in each of the 3 dosing cohorts had a stoma and no standard of care subject had a stoma. Therefore, no conclusions can be drawn from these.

Overall, the subjects' etiology of SBS was distributed evenly between necrotizing enterocolitis, midgut volvulus, gastroschisis, and "other" causes. Intestinal atresia was the reason for intestinal resection in 3 subjects. As in the colon and stoma subgroups, the PN reductions across the study cohorts were similar to the overall totals.

The subset analyses for remaining length of small intestine evaluated subjects with less than and greater than or equal to 25 cm, 40 cm, and 60 cm. Therefore, the categories of 25 and 40 cm were subsets of the 60-cm group. The mean and median reductions of PN volume at Week 12 in all length categories were similar to that seen overall. Except for subjects in the ≥ 60 cm and < 60 cm category in the standard of care cohort for which data was available for only 2 subjects, within the 2 highest dosing cohorts and the other length categories in the standard of care cohort, subjects with greater remaining length of small intestine showed a slightly higher reduction percentage than subjects with a smaller amount of intestine remaining. In the 0.0125 mg/kg/day dosing cohort, however, the opposite was true.

The change in PN calories by subgroups was also provided for the ITT population based on physician prescribed data for etiology of SBS, remaining intestinal length, presence of stoma, and presence of colon, respectively.

Summary of main study

The following tables summarise the efficacy results from the main study supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 1. Summary of Efficacy for trial TED-C13-003.

Title: A 12-Week Pharmacokinetic, Safety, and Pharmacodynamic Study of Teduglutide in Pediatric Subjects Aged 1 Year through 17 Years, with Short Bowel Syndrome who are Dependent on Parenteral Support		
Study identifier	TED-C13-003	
Design	Open label, 4-cohort study: three treatment groups and a standard of care group as control	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	12 weeks 2 weeks 4 weeks
Hypothesis	Compare teduglutide treatment to standard of care in SBS	

Treatments groups	Standard of care		N=5		
	Teduglutide 0.0125 mg/kg/day		N=8		
	Teduglutide 0.025 mg/kg/day		N=14		
	Tedugutide 0.05 mg/kg/day		N=15		
Endpoints and definitions	Primary endpoint	10% reduction in PN volume at week 12			
	Secondary endpoint	10% reduction in PN calories at week 12			
	Secondary endpoint	20% reduction in PN volume at week 12			
	Secondary endpoint	20% reduction in PN calories at week 12			
	Secondary endpoint	Actual PN volume and absolute and percent change at week 12			
	Secondary endpoint	Actual PN calories and absolute and percent change at week 12			
Database lock	5th February 2015				
Results and Analysis					
Analysis description	**Primary Analysis**				
Analysis population and time point description	Intent to treat 12 weeks				
Descriptive statistics and estimate variability	Treatment group	Standard of care	Teduglutide 0.0125 mg/kg	Teduglutide 0.025 mg/kg	Teduglutide 0.05 mg/kg
	Number of subject	5	8	14	15
	10% reduction in PN volume at week 12 (n/N (%))	0/5	1/8 (12.5%)	10/14 (71%)	8/15 (53%)
	10% reduction in PN calories at week 12 (n/N (%))	0/5	2/8 (25%)	9/14 (64%)	10/15 (67%)
	20% reduction in PN volume at week 12 (n/N (%))	0/5	1/8 (12.5%)	10/14 (71%)	8/15 (53%)

	20% reduction in PN calories at week 12 (n/N (%))	0/5	1/8 (12.5%)	8/14 (57%)	9/15 (60%)
	Absolute change in PN volume (L/week) at 12 weeks (mean (SD))	0.43 (0.746)	-0.50 (0.910)	-2.78 (1.985)	-2.57 (3.564)
	Percent change in PN volume (L/week) at 12 weeks (mean (SD))	7.38 (12.756)	-9.95 (21.625)	-37.34 (26.422)	-39.11 (40.792)
	Absolute change in PN calories (kcal/week) at 12 weeks (mean (SD))	173.20 (209.530)	-253.43 (575.750)	-1852.62 (1952.644)	-1480.28 (2913.704)
	Percent change in PN calories (kcal/week) at 12 weeks (mean (SD))	4.31 (5.362)	-10.04 (26.098)	-35.16 (38.779)	-35.11 (53.042)
	Primary endpoint	Comparison groups	NA		

Extrapolation

Because only a non-randomised, short-term study was been presented to support the indication in children, further justification was provided in the course of the procedure to support that the data observed in adults can be extrapolated to the paediatric population.

The applicant bases their answer on four parts related to the following:

- Similarities in disease characteristics and course of the disease for adults and children
- The pre-clinical pharmacology and toxicology
- The efficacy and safety from clinical trials

Similar disease characteristics:

The applicant made the case that although the cause for surgical resections of the bowel might be different between children and adults (in children: NEC and volvulus, atresia, gastroschisis which do not occur in adults), the resulting disease with diminished absorptive capacity for fluids and nutrients is the same, including the resulting manifestations such as malabsorption, diarrhoea, steatorrhea, abdominal pain, fluid/electrolyte disturbance, dehydration, and weight loss.

A further argument in favour of similarities is the postulate that the occurrence and character, as well as the management of SBS complications is also similar in adults and children. The consequences of insufficient adaptation/compensation are usually treated with IV/PN support, and the resulting complications are – both in children and adults – liver disease, catheter-related infections (including

sepsis), venous thrombosis, and dwindling central venous access. The further stimulation of potential compensation mechanisms by enteral feeding is also considered similar in the two groups.

Differences between adults and children concern the likelihood of being weaned off, which is higher in children, leading to about 60% of the initially PN/IV dependent infants and small children being weaned off by the age of 5. Intestinal transplantation remains an option, especially for children, however, this is considered more challenging and in the end unsuccessful, compared to solid organ transplantation (with about 85% acute resections).

Pre-clinical pharmacology:

The applicant first refers to the fact that Teduglutide treatment has been shown in animal models and adult humans to induce mucosal growth, mainly in the small intestine, through an increase of crypt cell proliferation and a reduction of enterocyte apoptosis.

Further reference was made to the neonatal pig model of SBS, which was chosen to be investigated due to anatomic and physiological similarities between infants and piglets, and is regarded to be an established model of intestinal failure (Study SP10-002-0600).

The data in neonatal piglets demonstrate that teduglutide structural and transiently increases functional measures of intestinal adaptation similar to that observed in adult animals of other species. Teduglutide improved ($p < 0.05$) mucosal surface area (villus height: duodenum, jejunum, ileum; crypt depth: ileum, colon; proliferation: duodenum, jejunum, ileum; colon; apoptosis: jejunum, ileum, colon) and acute nutrient processing capacity (glucose: duodenum, jejunum, ileum; glutamine: duodenum, jejunum)..

The results of a 13-week study with teduglutide conducted in juvenile minipigs indicated that there were no new or unique toxicities in juvenile minipigs as compared to young adult mice, rats and monkeys (Study #66585).

Efficacy from clinical trials:

With regard to efficacy, the applicant refers to the results adult study CL0600-020 (responder rates as per 20% to 100% reduction of PN/IV bolume at weeks 20 and 24 which was 62.8% for active treatment and 30.2% for placebo) and compares this with the results of the children's study TED-C13-003 (where an at least 20% reduction of PN/IV needs was achieved by 71.4% and 53.3% in the 0.025 mg/kg/day and 0.05 mg/kg/day cohorts) as well as other results. A "synoptic table" for these results is presented, which is shown in the following:

Table 1. Mean change from baseline in PN/IV volume (L/week) at Week 12

	≥20% reduction in PN/IV		Absolute change		Percent change	
	Paediatric 003 study	**Adult 020 study**	**Paediatric 003 study**	**Adult 020 study**	**Paediatric 003 study**	**Adult 020 study**
0.05mg/kg daily dose						
Physician prescribed	53.3%	n/a	-2.57 L	-2.72L	-39.11%	-21.39%
Patient diary	46.7%	50.0%	-2.93 L	-2.92L	-39.06%	-21.10%
SOC or placebo						
Physician prescribed	0.0%	n/a	-0.43 L	-1.45 L	7.38%	-11.64%
Patient diary	0.0%	25.6%	0.58 L	-1.50 L	9.58%	-12.96%

Safety in clinical trials:

The applicant postulated that the overall safety profile in the paediatric TED-C13-003 study was consistent with that observed in the adult studies in an SBS patient population. Below a summary of the adverse events reported in the CSR of study TED-C13-003 is described which matches with the current information on adults of Chapter 4.8 of the SmPC:

- The most commonly reported adverse events reported in >3 (>10%) patients in the total teduglutide group were: vomiting, upper respiratory tract infection, catheter-related infection, pyrexia, cough, abdominal pain, blood bicarbonate decreased, fatigue, headache, nausea, central line infection, diarrhea, increased fecal volume. The majority of AEs were mild or moderate in intensity.
- The most commonly reported drug-related adverse events reported in >1 patient in the total teduglutide group were: abdominal pain, abdominal distention, eyes sunken, headache, injection site haemorrhage, nausea, painful defecation and vomiting.
- The most commonly reported serious adverse events reported in >1 patient in the total teduglutide group were: central line infection, pyrexia, catheter-related complication and parainfluenza virus infection. None of the reported SAEs were considered by the investigator to be drug-related.

Other adverse events reported in the pediatric trial but not present in the SmPC usually reflected complications of the indwelling catheter used for TPN (catheter-related infection, central line infection, catheter-related complication), adverse events that may reflect the underlying disease in children (blood bicarbonate decreased, fatigue, diarrhea, increased fecal volume) or adverse events that reflect teduglutide administration route (injection site haemorrhage).

No new or unexpected safety signals were observed in paediatric patients treated with teduglutide for 12 weeks at doses of 0.0125, 0.025, and 0.05 mg/kg/d.

2.3.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The applicant has undertaken a combined PK/PD clinical study in the paediatric population. The population comprised paediatric patients in the age range of 1-17 with SBS requiring PN. The inclusion criteria defined an adequate patient population for which the process of adaptation was likely to have been completed, and a further reduction of PN needs and/or weaning from PN was not expected. The patient population appeared therefore adequate, although an optimisation phase for the PN therapy was not included in the study.

The study was conducted open-label and in non-randomised fashion, with a staggered approach starting with the lowest dose group. The control group was taken from a small group of patients treated with current standard of care. Despite the non-randomised nature of the study, it appears that the baseline characteristics of the included patient population in the different dose groups was sufficiently comparable. Therefore, the results achieved in the study do not suffer from confounding through differential baseline conditions, and can be counted to reflect real clinical effects.

The study recruited 42 patients into the four different treatment groups and used a 12-week treatment period only. The study was conducted with an explorative approach from a statistical point of view only.

A paediatric investigational plan (PIP) was agreed upon in 2013, and modified in 2015 with the acceptance of enrolling 5 patients in the standard of care group. In the PIP, a study duration of 12 weeks with 4 weeks follow-up was agreed upon. The primary endpoint agreed upon in the PIP was the change in percentage of parenteral support in terms of both volume and calories from baseline to the end of the 12-week treatment period, and results were to be reported by descriptive statistics. In the submitted study reduction in PN calories at week 12 was included as secondary endpoint.

Efficacy data and additional analyses

Overall, 12 weeks teduglutide treatment was associated with a reduction in parenteral nutrition PN/IV support in terms of volume and calories in children aged 1-14 years, when compared with the group of children treated with standard of care. Three different dose levels were evaluated: 0.0125, 0.025, and 0.05 mg/kg. The adult dose of 0.05 mg/kg was also chosen for the paediatric population.

The number of patients achieving a 10% and 20% reduction in PN/IV volume and calories use were higher in the 0.025 mg/kg (71%) and 0.05 mg/kg (53%) dose groups compared with the lowest dose of 0.0125 mg/kg (12.5%) and the standard of care group (0%). The absolute and percent changes in PN/IV volume and calories were about 2.7 L/week and 1800 kcal/week, translating into a percent change of about 37% in the two highest dose groups. Days of PN/IV usage was estimated to be reduced by 1.3 days per week in the 0.05 mg/kg dose group and 0.69 days per week in the 0.025 mg/kg group. Four patients were completely weaned off at 12 weeks; however, 2 patients had resumed PN/IV support at week 16. These subjects included 3 of 15 (20.0%) subjects in the 0.05 mg/kg/day cohort and 1 of 14 (7.1%) subjects in the 0.025 mg/kg/day cohort.

To address the CHMP concern that the effect on PN/IV support for the 0.025 mg/kg dose was not distinguishable from the effect of the highest dose further data were provided showing that patients in the 0.025 mg/kg group had a significantly longer residual gut at baseline when compared with patients in the 0.05 mg/kg group. Thus, the absorptive capacity in the 0.025 mg/kg group was higher. This explains the observed efficacy being comparable in both groups.

Further arguments in support of the choice of the 0.05 mg/kg dose where brought forward by the applicant such as a faster clearance in children compared to adults and the association of higher systemic levels of teduglutide in children with increased likelihood of response (20% PN reduction) as well as decreases in weekly PN/IV volume difference from baseline according to PK-PD modelling. Overall, the Applicant has in a satisfactory manner justified the proposed dose of 0.05 mg/kg.

The evaluation of the results of the trial has shown a consistent dose-response relationship in the chosen pharmacodanymic parameters, showing relatively high activity of the compound for the reduction of PN volumes and PN calories in the two high-dose groups. This effect was consistent in the ITT and PP evaluation and for different parameters. The standard of care group, and partly also the low-dose group, did not show consistent effects on these parameters, thus providing some evidence of “assay sensitivity” of the trial, and the validity/appropriateness of the included patient population (which does not improve spontaneously to a relevant extent).

The evaluation of the reduction of infusion times (based on hours or days) as well as the categorical evaluation of the infusion times (at least 1 day, at least 3 days), did confirm the results of the volumetric and calorimetric evaluations, with both high-dose groups showing even effects considered to be relevant from a clinical point of view. These conclusions are also supported by the categorical evaluations of the “at least 10% PN volume reduction” and “at least 20% PN volume reduction” endpoints.

The data on enteral volume and especially calorie increases are less convincing, especially for the calorie intake which showed highly similar results across all treatment groups. The applicant explains this with the principal mechanism of action (enhancement of absorption of nutrients by increased villous height and crypt depth, and hence an improved nutritional intake despite constant caloric count for the given intake) and the potential problem of incomplete recording of the total oral intake, when there was an increase of additional “ad lib” oral non formula food. The applicant has therefore pointed to a potential “confounder” which cannot be accounted for (the improved absorption). Nevertheless the rational was considered acceptable by the CHMP.

The evaluation of the potentially clinically most relevant parameters, the complete weaning from PN need does again show effects indicating clinical efficacy at least for the highest dose of 0.05 mg/kg. This evaluation suffers from the low numbers of patients included and achieving this endpoint (3/15 in the highest dose group) but can be seen in the context of the data generated with adults.

In the adult studies, a 20% reduction in the PN/IV support is considered clinically relevant, and a superior effect of teduglutide was seen already after 8-12 weeks. The effect increased over time with more than 70% of patients reaching a 20% reduction in PN/IV volume at 6 months. Similar results were seen for the

doses 0.025 and 0.05 mg/kg in the paediatric population, supporting that also the paediatric population accordingly benefits in the long term from teduglutide treatment. Furthermore, one day off PN/IV support is also considered relevant for paediatric patients.

Because only a non-randomised, short-term study was been presented to support the indication in children, further argumentation to support the extrapolation of evidence of efficacy from adults was provided in the course of the procedure.

Disease characteristics and course of the disease

The Applicant argued that in children SBS is caused by congenital abnormalities or major surgical resection due to intestinal disease. In older children and adults SBS may be due to IBD, trauma or cancer. The clinical manifestation of the disease are similar and due to diminished absorption, which leads to malabsorption, diarrhea leading to dehydration and malnutrition, abdominal pain, fluid and electrolyte disturbances, etc. It is agreed that the management and complications of SBS are similar between adults and children. The only relevant difference is obviously the chances in being fully weaned from IV/PN, which is relevantly higher for (at least small) children. This could be regarded to be relevant due to the short follow-up of the presented study TED-C13-003.

Preclinical pharmacology and toxicology

The Applicant argued that the effect of teduglutide seen in adults, can be extrapolated also based on preclinical data. The Applicant referred to data from non-clinical studies part of the initial marketing authorisation with neonatal piglets, showing that teduglutide leads to similar structural and transient increases in functional measures of intestinal adaptation as those observed in the adult animals.

Efficacy and safety from clinical trials

The Applicant provided data comparing mean change from baseline in PV/IN volume at week 12 between adults (study 020) and children (study 003). Although, there are limitations to this direct comparison due to the non-randomised nature of the paediatric study, similar effects of teduglutide are observed in both populations.

With regard to safety, the most common AEs in the adult population were abdominal pain, vomiting, nausea, injection site reactions, headache, peripheral oedema, etc. The same AE pattern was observed in the paediatric population. No new or unexpected safety signals were observed in paediatric patients treated with teduglutide for 12 weeks at doses of 0.0125, 0.025, and 0.05 mg/kg/d.

Based on the disease characteristics, course of disease, the preclinical and clinical data from the adult population, there is sufficient data to conclude that the data observed in adults can be used to draw conclusions on efficacy in the paediatric population.

2.3.4. Conclusions on the clinical efficacy

The applicant could show clinical relevant effects of treatment with Revestive within a combined PK/PD and clinical study in children and adolescents over a 12-week treatment period. Based on the disease characteristics, course of disease, the preclinical and clinical data from the adult population, there is sufficient data to conclude that the data observed in adults can be used to draw conclusions on efficacy in the paediatric population.

In particular the number of patients achieving a 10% and 20% reduction in PN/IV volume and calories were higher in the 0.025 mg/kg (71%) and 0.05 mg/kg (53%) dose groups compared with the lowest dose of 0.0125 mg/kg (12.5%) and the standard of care group (0%).

The evaluation of the potentially clinically most relevant parameters, the complete weaning from PN need did again show effects indicating clinical efficacy at least for the highest dose of 0.05 mg/kg. This evaluation suffers from the low numbers of patients included and achieving this endpoint (3/15 in the highest dose group) but can be seen in the context of the data generated with adults.

In the adult studies, a 20% reduction in the PN/IV support is considered clinically relevant, and a superior effect of teduglutide was seen already after 8-12 weeks. The effect increased over time with more than 70% of patients reaching a 20% reduction in PN/IV volume at 6 months. Similar results after 12 weeks were seen for the doses 0.025 and 0.05 mg/kg in the paediatric population, supporting that also the paediatric population accordingly benefits in the long term from teduglutide treatment. Furthermore, one day off PN/IV support is also considered relevant for paediatric patients.

The presented data in paediatric patients shows a comparable clinical activity of the compound to adults, showing a clear dose-response, and producing clinically relevant effects in the dose proposed for marketing. In the context of the adult data clinical efficacy in the applied indication is considered to be demonstrated.

Furthermore the applicant took the opportunity for an editorial change of the indication statement deleting the term “after surgery” (“Patients should be stable following a period of intestinal adaptation ~~after surgery~~) which was considered acceptable by the CHMP since all patient (adults and paediatric patients) undergo surgery.

2.4. Clinical safety

Introduction

The current SmPC summarizes the safety profile of the compound as follows:

Adverse reactions were retrieved from 2 placebo-controlled clinical studies with Revestive in 109 patients with SBS treated with doses of 0.05 mg/kg/day and 0.10 mg/kg/day for up to 24 weeks. Approximately 52% of the patients treated with Revestive experienced adverse reactions (versus 36% of the patients given placebo). The most commonly reported adverse reactions were abdominal pain and distension (49%), respiratory tract infections (28%), nausea (27%), injection site reactions (21%), headache (17%), vomiting (14%) and oedema peripheral (10%). Approximately 38% of the treated patients with a stoma experienced gastrointestinal stoma complications. The majority of these reactions were mild or moderate.

No new safety signals have been identified in patients exposed to 0.05 mg/kg/day of Revestive for up to 30 months in a long-term open-label extension study.

Patient exposure

Table 12-1 Extent of Exposure – Intent-to-Treat Population

Parameter	Statistic	Teduglutide 0.0125 mg/kg/day (N = 8)	Teduglutide 0.025 mg/kg/day (N = 14)	Teduglutide 0.05 mg/kg/day (N = 15)	Total Teduglutide (N = 37)
Extent of Exposure	n	8	14	15	37
(days)	Mean (SD)	77.6 (17.39)	82.8 (3.66)	82.1 (8.26)	81.4 (9.71)
	Median	84.0	84.0	85.0	84.0
	Min, Max	35, 88	74, 90	53, 88	35, 90
Any exposure	n (%)	8 (100.0)	14 (100.0)	15 (100.0)	37 (100.0)
< 1 week	n (%)	0	0	0	0
1 to < 4 weeks	n (%)	0	0	0	0
4 to < 8 weeks	n (%)	1 (12.5)	0	1 (6.7)	2 (5.4)
8 to < 12 weeks	n (%)	2 (25.0)	6 (42.9)	4 (26.7)	12 (32.4)
≥ 12 weeks	n (%)	5 (62.5)	8 (57.1)	10 (66.7)	23 (62.2)

Max = maximum; Min = minimum; N = total number of subjects in dosing cohort; n = number of subjects in category indicated; SD = standard deviation
Note: Percentages were based on the Intent-to-Treat population in each arm.
Note: Extent of exposure was defined as: (last dose date – first dose date + 1) / 7. Interruptions of the study medication are subtracted from the calculations of exposure.
Note: Subjects in the standard of care cohort did not receive study drug.
Source: Section 14, Table 14.3.1.1; Appendix 16.2, Listings 16.2.5.1

Adverse events

TESAE Severity										
Mild	0		1 (12.5)	1	3 (21.4)	4	2 (13.3)	3	6 (16.2)	8
Moderate	2 (40.0)	4	0		1 (7.1)	2	2 (13.3)	3	3 (8.1)	5
Severe	1 (20.0)	2	2 (25.0)	2	4 (28.6)	10	5 (33.3)	9	11 (29.7)	21
TESAE Relationship										
Not Related	3 (60.0)	6	3 (37.5)	3	6 (42.9)	16	8 (53.3)	15	17 (45.9)	34
Related	0		0		0		0		0	
TEAE Leading to Study Drug Discontinuation	0		0		0		0		0	
TEAE Leading to Death	0		0		0		0		0	

N = total number of subjects; n = number of subjects within parameter indicated; TEAE = treatment-emergent adverse events; TESAE = treatment-emergent serious adverse event
Note: Percentages are based on the Safety population in each treatment arm.
Note: TEAEs are defined as any adverse events whose onset occurs, severity worsens or intensity increases after receiving the study medication and within 30 days after discontinuation of study medication.
Note: Relationship to study treatment is based upon investigator assessment.
Note: Subjects are counted no more than once for incidence, but can be counted multiple times for the number of events.
Source: Study TED-C13-003 CSR, Table 12-2

Table 2 **Treatment-emergent Adverse Events by System Organ Class and Preferred Term Occurring in ≥ 5% of Subjects in the Total Teduglutide Group – Safety Population**

			Teduglutide							
	Standard of Care		0.0125 mg/kg/day		0.025 mg/kg/day		0.05 mg/kg/day		Total Teduglutide	
System Organ Class / Preferred Term	Subjects (N=5) n (%)	Events	Subjects (N=8) n (%)	Events	Subjects (N=14) n (%)	Events	Subjects (N=15) n (%)	Events	Subjects (N=37) n (%)	Events
Any TEAE										
No	0		0		0		0		0	
Yes	5 (100.0)	28	8 (100.0)	55	14 (100.0)	92	15 (100.0)	211	37 (100.0)	358
Blood and lymphatic system disorders	0		0		2 (14.3)	7	1 (6.7)	2	3 (8.1)	9
Neutropenia	0		0		2 (14.3)	2	0		2 (5.4)	2
Thrombocytopenia	0		0		2 (14.3)	2	0		2 (5.4)	2
Cardiac disorders	1 (20.0)	1	0		2 (14.3)	2	2 (13.3)	2	4 (10.8)	4
Tachycardia	1 (20.0)	1	0		1 (7.1)	1	1 (6.7)	1	2 (5.4)	2
Eye disorders	0		0		0		3 (20.0)	4	3 (8.1)	4
Eyes sunken	0		0		0		2 (13.3)	2	2 (5.4)	2
Gastrointestinal disorders	1 (20.0)	4	4 (50.0)	14	10 (71.4)	23	10 (66.7)	72	24 (64.9)	109
Vomiting	0		0		5 (35.7)	8	7 (46.7)	29	12 (32.4)	37
Abdominal pain	1 (20.0)	1	1 (12.5)	1	1 (7.1)	5	4 (26.7)	15	6 (16.2)	21
Nausea	0		1 (12.5)	3	2 (14.3)	2	2 (13.3)	8	5 (13.5)	13
Diarrhoea	1 (20.0)	1	0		1 (7.1)	1	3 (20.0)	6	4 (10.8)	7
Faecal volume increased	0		1 (12.5)	1	1 (7.1)	1	2 (13.3)	2	4 (10.8)	4
Abdominal distension	0		1 (12.5)	2	1 (7.1)	1	1 (6.7)	2	3 (8.1)	5
Flatulence	0		2 (25.0)	2	1 (7.1)	1	0		3 (8.1)	3
Haematochezia	0		2 (25.0)	2	1 (7.1)	1	0		3 (8.1)	3
Constipation	1 (20.0)	2	0		0		2 (13.3)	2	2 (5.4)	2
Painful defaecation	0		0		0		2 (13.3)	2	2 (5.4)	2
Retching	0		0		2 (14.3)	2	0		2 (5.4)	2
General disorders and administration site conditions	3 (60.0)	5	5 (62.5)	8	9 (64.3)	9	12 (80.0)	33	26 (70.3)	50
Catheter related complication	1 (20.0)	1	3 (37.5)	4	4 (28.6)	4	2 (13.3)	3	9 (24.3)	11
Pyrexia	2 (40.0)	3	0		2 (14.3)	2	7 (46.7)	8	9 (24.3)	10
Fatigue	0		0		1 (7.1)	1	4 (26.7)	11	5 (13.5)	12
Injection site haemorrhage	0		0		0		3 (20.0)	4	3 (8.1)	4
Immune system disorders	0		0		2 (14.3)	2	1 (6.7)	1	3 (8.1)	3
Drug hypersensitivity	0		0		2 (14.3)	2	0		2 (5.4)	2
Infections and infestations	4 (80.0)	7	8 (100.0)	14	10 (71.4)	16	10 (66.7)	14	28 (75.7)	44
Upper respiratory tract infection	2 (40.0)	2	2 (25.0)	3	4 (28.6)	6	4 (26.7)	4	10 (27.0)	13
Central line infection	0		0		3 (21.4)	5	1 (6.7)	2	4 (10.8)	7
Gastroenteritis viral	1 (20.0)	1	1 (12.5)	1	0		2 (13.3)	2	3 (8.1)	3
Nasopharyngitis	0		2 (25.0)	2	0		1 (6.7)	1	3 (8.1)	3
Influenza	0		1 (12.5)	1	1 (7.1)	1	0		2 (5.4)	2
Overgrowth bacterial	0		2 (25.0)	2	0		0		2 (5.4)	2
Parainfluenzae virus infection	0		0		1 (7.1)	1	1 (6.7)	1	2 (5.4)	2
Rhinovirus infection	0		0		2 (14.3)	2	0		2 (5.4)	2
Injury, poisoning and procedural complications	0		0		4 (28.6)	4	4 (26.7)	8	8 (21.6)	12

Gastrointestinal stoma complication*	0		0		0		1 (100.0)	5	1 (25.0)	5
Feeding tube complication	0		0		2 (14.3)	2	0		2 (5.4)	2
Incision site erythema	0		0		1 (7.1)	1	1 (6.7)	1	2 (5.4)	2
Investigations	2 (40.0)	6	2 (25.0)	2	5 (35.7)	7	6 (40.0)	32	13 (35.1)	41
Blood bicarbonate decreased	2 (40.0)	2	1 (12.5)	1	1 (7.1)	1	3 (20.0)	4	5 (13.5)	6
Weight decreased	0		1 (12.5)	1	1 (7.1)	1	1 (6.7)	1	3 (8.1)	3
Alanine aminotransferase increased	0		0		1 (7.1)	1	1 (6.7)	1	2 (5.4)	2
Aspartate aminotransferase increased	0		0		1 (7.1)	1	1 (6.7)	1	2 (5.4)	2
Bacteria urine	1 (20.0)	1	0		0		2 (13.3)	2	2 (5.4)	2
Blood urine present	0		0		0		2 (13.3)	2	2 (5.4)	2
Protein urine present	0		0		0		2 (13.3)	2	2 (5.4)	2
Red blood cells urine positive	0		0		0		2 (13.3)	2	2 (5.4)	2
White blood cells urine positive	0		0		0		2 (13.3)	2	2 (5.4)	2
Metabolism and nutrition disorders	1 (20.0)	1	3 (37.5)	4	2 (14.3)	2	6 (40.0)	6	11 (29.7)	12
Anorexia	0		0		0		2 (13.3)	2	2 (5.4)	2
Dehydration	1 (20.0)	1	1 (12.5)	1	0		1 (6.7)	1	2 (5.4)	2
Hypoglycaemia	0		0		1 (7.1)	1	1 (6.7)	1	2 (5.4)	2
Musculoskeletal and connective tissue disorders	0		1 (12.5)	1	1 (7.1)	1	2 (13.3)	3	4 (10.8)	5
Pain in extremity	0		1 (12.5)	1	0		1 (6.7)	1	2 (5.4)	2
Nervous system disorders	0		1 (12.5)	6	4 (28.6)	6	3 (20.0)	15	8 (21.6)	27
Headache	0		1 (12.5)	5	2 (14.3)	2	2 (13.3)	10	5 (13.5)	17
Dizziness	0		0		1 (7.1)	1	2 (13.3)	3	3 (8.1)	4
Renal and urinary disorders	0	0	0	0	1 (7.1)	1	1 (6.7)	1	2 (5.4)	2
Respiratory, thoracic and mediastinal disorders	1 (20.0)	1	2 (25.0)	5	4 (28.6)	6	6 (40.0)	10	12 (32.4)	21
Cough	1 (20.0)	1	1 (12.5)	3	2 (14.3)	3	4 (26.7)	5	7 (18.9)	11
Rhinorrhoea	0		0		1 (7.1)	1	1 (6.7)	1	2 (5.4)	2
Tonsillar hypertrophy	0		0		2 (14.3)	2	0		2 (5.4)	2
Skin and subcutaneous tissue disorders	2 (40.0)	2	0		2 (14.3)	5	5 (33.3)	7	7 (18.9)	12
Rash	0		0		1 (7.1)	3	2 (13.3)	3	3 (8.1)	6
Dermatitis diaper	1 (20.0)	1	0		1 (7.1)	1	1 (6.7)	1	2 (5.4)	2
Vascular disorders	1 (20.0)	1	0		1 (7.1)	1	1 (6.7)	1	2 (5.4)	2

MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects in dosing cohort; n = number of subjects within parameter indicated
Note: Percentages are based on the Safety population in each treatment arm.
Note: Treatment-emergent adverse events are defined as any adverse events whose onset occurs, severity worsens or intensity increases after receiving the study medication and within 30 days after discontinuation of study medication.
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 are coded using MedDRA 12.0.
*Percentages are based on the number of subjects with a stoma in the Safety population in each treatment arm.
Source: Study TED-C13-003 CSR, Table 12-3

Table 4 Number of Treatment Emergent Adverse Events for Each Patient in TED 0.025 mg/kg/daily and TED 0.05 mg/kg/daily dose groups

0.025 mg/kg/daily (n=14 with 92 TEAEs)		0.05 mg/kg/daily (n=15 with 211 TEAEs)	
Patient	no of TEAEs	Patient	no of TEAEs
[redacted]	9	[redacted]	4
	7		5
	11		13
	3		14
	11		5
	12		4
	4		4
	4		4
	4		20
	4		7
	2		**54**
	9		**31**
	3		**38**
	9		2
			6
Total	**92**		**211**
Mean	**6.57 TEAE/patient**		**14.07 TEAE/patient[a]**
Median	**5.50 TEAE/patient**		**6.0 TEAE/patient[a]**

[a]When patients [redacted] are removed from the 0.05 mg/kg/day group, the Mean = 7.33 TEAEs/patient and the Median = 5.0 TEAEs/patient.

To further evaluate whether the increased number of TEAE terms/patient reported at site [redacted] reflected a unique safety profile in these patients, an evaluation of TEAE terms, by PT, for these 3 patients was conducted (Table 5). Overall, the TEAEs reported in the 3 patients ≥ 5 times included: vomiting (17 events), abdominal pain (12 events), fatigue (10 events), headache (10 events), GI stoma complication (5 events) and nausea (5 events).

Table 5 Number of TEAE by Preferred Term for Patients [redacted]

Dictionary-Derived Term (AEDECOD)	[redacted]	[redacted]	[redacted]	Overall of the 3 patients
Vomiting	11	4	2	17
Abdominal pain	0	6	6	12
Fatigue	2	2	6	10
Headache	8	0	2	10
Gastrointestinal stoma complication	0	5	0	5
Nausea	5	0	0	5
Cough	2	1	1	4
Diarrhoea	3	0	0	3
Dizziness	1	0	2	3
Dyspepsia	0	0	3	3
Injection site haematoma	3	0	0	3
Injection site haemorrhage	2	1	0	3

Serious adverse event / deaths / other significant events

Seventeen of 37 subjects (45.9%) in the active dosing cohorts reported 34 TESAEs during the study (8/15 subjects [53.3%] in the 0.05 mg/kg/day cohort, 6/14 [42.9%] in the 0.025 mg/kg/day cohort, and 3/8 [37.5%] in the 0.0125 mg/kg/day cohort). Three of 5 subjects (60.0%) had TESAEs in the standard of care cohort. None of the TESAEs was thought to be related to teduglutide treatment by the investigator. The system organ class with the most frequently reported TESAEs were Infections and Infestations (10/37 [27.0%] subjects) and general disorders and administration site conditions (9/37 [24.3%] subjects) (Table 3).

The most frequently reported TESAEs were central line infection and pyrexia, each reported by 4 of 37 (10.8%) subjects. Catheter-related complication was reported by 3 (8.1%) subjects and parainfluenza virus infection was reported by 2 (5.4%) subjects. All other TESAEs were reported by one subject each.

Table 3 Summary of Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term – Safety Population

System Organ Class Preferred Term	Standard of Care Subjects (N=5) n (%)	Events	Teduglutide 0.0125 mg/kg/day Subjects (N=8) n (%)	Events	0.025 mg/kg/day Subjects (N=14) n (%)	Events	0.05 mg/kg/day Subjects (N=15) n (%)	Events	Total Teduglutide Subjects (N=37) n (%)	Events
Any TESAE										
No	2 (40.0)		5 (62.5)		8 (57.1)		7 (46.7)		20 (54.1)	
Yes	3 (60.0)	6	3 (37.5)	3	6 (42.9)	16	8 (53.3)	15	17 (45.9)	34
Blood and lymphatic system disorders	0		0		0		1 (6.7)	1	1 (2.7)	1
Pancytopenia	0		0		0		1 (6.7)	1	1 (2.7)	1
Gastrointestinal disorders	0		0		1 (7.1)	2	1 (6.7)	1	2 (5.4)	3
Abdominal distension	0		0		1 (7.1)	1	0		1 (2.7)	1
Frequent bowel movements	0		0		0		1 (6.7)	1	1 (2.7)	1
Haematochezia	0		0		1 (7.1)	1	0		1 (2.7)	1
General disorders and administration site conditions	3 (60.0)	3	0		3 (21.4)	3	6 (40.0)	6	9 (24.3)	9
Pyrexia	2 (40.0)	2	0		1 (7.1)	1	3 (20.0)	3	4 (10.8)	4
Catheter related complication	1 (20.0)	1	0		2 (14.3)	2	1 (6.7)	1	3 (8.1)	3
Fatigue	0		0		0		1 (6.7)	1	1 (2.7)	1
Irritability	0		0		0		1 (6.7)	1	1 (2.7)	1
Immune system disorders	0		0		0		1 (6.7)	1	1 (2.7)	1
Anaphylactic reaction[a]	0		0		0		1 (6.7)	1	1 (2.7)	1
Infections and infestations	2 (40.0)	3	3 (37.5)	3	4 (28.6)	7	3 (20.0)	4	10 (27.0)	14
Central line infection	0		0		3 (21.4)	5	1 (6.7)	2	4 (10.8)	7
Parainfluenzae virus infection	0		0		1 (7.1)	1	1 (6.7)	1	2 (5.4)	2
Adenovirus infection	0		1 (12.5)	1	0		0		1 (2.7)	1
Catheter related infection	0		1 (12.5)	1	0		0		1 (2.7)	1
Catheter sepsis	0		0		0		1 (6.7)	1	1 (2.7)	1
Influenza	0		1 (12.5)	1	0		0		1 (2.7)	1
Rhinovirus infection	0		0		1 (7.1)	1	0		1 (2.7)	1
Fungaemia	1 (20.0)	1	0		0		0		0	
Gastroenteritis viral	1 (20.0)	1	0		0		0		0	
Viral infection	1 (20.0)	1	0		0		0		0	
Investigations	0		0		1 (7.1)	1	0		1 (2.7)	1
Blood creatinine increased	0		0		1 (7.1)	1	0		1 (2.7)	1
Metabolism and nutrition disorders	0		0		0		1 (6.7)	1	1 (2.7)	1
Dehydration	0		0		0		1 (6.7)	1	1 (2.7)	1
Nervous system disorders	0		0		1 (7.1)	1	1 (6.7)	1	2 (5.4)	2
Depressed level of consciousness	0		0		0		1 (6.7)	1	1 (2.7)	1
Grand mal convulsion	0		0		1 (7.1)	1	0		1 (2.7)	1
Skin and subcutaneous tissue disorders	0		0		1 (7.1)	1	0		1 (2.7)	1
Rash	0		0		1 (7.1)	1	0		1 (2.7)	1
Vascular disorders	0		0		1 (7.1)	1	0		1 (2.7)	1
Hypovolaemic shock	0		0		1 (7.1)	1	0		1 (2.7)	1

N = total number of subjects in dosing cohort; n = number of subjects within parameter indicated; TESAE = treatment-emergent serious adverse event
Note: Percentages are based on the Safety population in each treatment arm.
Note: Treatment-emergent adverse events are defined as any adverse events whose onset occurs, severity worsens or intensity increases after receiving the study medication and within 30 days after discontinuation of study medication.
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 are coded using MedDRA 12.0.
[a] Anaphylaxis occurred following administration of fondaparinux and was considered by the investigator to not be related to teduglutide treatment.
Source: Study TED-C13-003 CSR, Table 12-4

Laboratory findings

Mean and median changes from baseline in laboratory values by visit are provided for serum chemistry, hematology, and urinalysis analytes, and no clinically meaningful changes from baseline in the analytes were seen overall.

Liver function tests

Liver disease is a co-morbidity associated with PN/IV treatment. Table 12-6 displays an example of the change from baseline in alanine and alkaline phosphatases to Week 12. Liver function test values showed improvement or little or no change from baseline in the active treatment cohorts. There were 10 shifts from normal at baseline to high at Week 12, which occurred in across all dosing cohorts. However, there were 19 shifts from high at baseline to normal at Week 12 across the 3 dosing cohorts. There were no shifts from high to normal in the standard of care cohort.

One subject had increases in hepatobiliary enzymes that were reported as a TEAE. This subject had elevated alanine aminotransferase and aspartate aminotransferase reported on Study Day 30. They were not considered related to study drug by the investigator and were not considered to be clinically significant.

There were no clinically meaningful mean changes from baseline in lipid levels, haematology, or urinalysis, nor did shift tables for these parameters suggest any meaningful trends.

Nutritional status was maintained over the 12-week treatment period, as evidenced by stable levels of albumin, calcium, magnesium, and phosphate. In addition, weight also remained stable.

No clinically meaningful differences in other vital sign parameters or physical examinations were observed during the study period.

One subject had an electrocardiogram (ECG) abnormality that was considered clinically significant at the Week 16 visit (off teduglutide), but the results of a follow-up echocardiogram for a suspected heart murmur was normal. The event was reported as an AE. No medical intervention was needed, and the event resolved. No other abnormal, clinically significant ECG results were reported.

Table 12-6 Summary of Liver Function Analytes and Change from Baseline at Week 12 – Safety Population

Lab Parameter (unit) Visit Category	Statistic	Standard of Care (N=5)	Teduglutide 0.0125 mg/kg/day (N=8)	Teduglutide 0.025 mg/kg/day (N=14)	Teduglutide 0.0 mg/kg/day (N=15)	Total Teduglutide (N=37)
Alanine aminotransferase (U/L)						
Baseline Actual	n	5	8	14	15	37
	Mean (SD)	29.2 (12.42)	74.1 (41.52)	50.3 (48.70)	56.5 (28.47)	57.9 (39.86)
	Median	25.0	71.0	35.0	50.0	46.0
	Min, Max	21, 51	19, 140	11, 179	24, 136	11, 179
Week 12 Actual	n	5	7	13	13	33
	Mean (SD)	31.2 (9.04)	66.7 (39.60)	34.1 (16.99)	50.6 (20.73)	47.5 (26.86)
	Median	35.0	58.0	30.0	46.0	40.0
	Min, Max	21, 40	24, 142	11, 77	23, 98	11, 142
Change	n	5	7	13	13	33
	Mean (SD)	2.0 (9.14)	-13.6 (40.52)	-12.6 (34.91)	-5.4 (31.53)	-10.0 (33.94)
	Median	0.0	-8.0	-3.0	-3.0	-3.0
	Min, Max	-11, 13	-82, 44	-102, 19	-91, 34	-102, 44
Alkaline phosphatase (U/l)						
Baseline Actual	n	5	8	14	15	37
	Mean (SD)	303.4 (197.06)	309.3 (103.15)	225.5 (66.67)	305.9 (85.15)	276.2 (90.02)
	Median	221.0	338.0	227.0	288.0	270.0
	Min, Max	167, 649	181, 423	120, 396	163, 482	120, 482
Week 12 Actual	n	5	7	13	13	33
	Mean (SD)	233.8 (118.02)	293.0 (84.95)	191.1 (53.53)	261.7 (102.80)	240.5 (90.38)
	Median	186.0	296.0	203.0	248.0	237.0
	Min, Max	119, 424	172, 388	89, 247	84, 482	84, 482
Change	n	5	7	13	13	33
	Mean (SD)	-69.6 (88.25)	-30.6 (55.51)	-21.3 (54.15)	-32.4 (84.82)	-27.6 (66.35)
	Median	-44.0	-15.0	-9.0	-51.0	-35.0
	Min, Max	-225, -12	-131, 32	-120, 66	-135, 194	-135, 194

Immunological events

One subject developed non-neutralising teduglutide-specific antibodies at the Week-16 follow-up visit. The subject had no evidence of hypersensitivity or immune-related clinical symptoms. Follow-up testing done 3 months later was negative.

Discontinuation due to adverse events

Neither of the two early discontinuations from the study were due to adverse events.

Post marketing experience

Teduglutide (as Revestive) was first approved in the EU on 30 Aug 2012 for the treatment of adult patients with SBS. It was approved in the United States on 21 Dec 2012, for the treatment of adults with SBS who are dependent on parenteral support. On 09 Oct 2013, the Marketing Authorization in the EU for Revestive was transferred to NPS Pharma Holdings Limited. Approval was granted in Israel for teduglutide on 13 Aug 2014.

From 01 Sep 2012 through the data cutoff date of 30 Aug 2015 as recorded in the Periodic Safety Update Report (PSUR) 6 submitted to Regulatory Authorities (dated 06 Nov 2015), the cumulative postmarketing exposure was estimated at 690 person-years of exposure, in 900 patients who received either commercial product, compassionate use product, or named patient program product, in the US, EU, Norway, Israel and Argentina. Of the exposure of 900 patients from the postmarketing experience, approximately 7 patients were age < 17.

There were no AEs reported amongst children and adolescents in the latest PSUR interval (01 Sep 2012 through 30 Aug 2015). Cumulatively, the most commonly reported adverse drug reactions (ADRs) occurred in the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) of Gastrointestinal disorders, with a cumulative total of 1,055 AEs, 408 of which were serious. The most commonly reported (≥ 25) Preferred terms were Nausea (172 AEs), Abdominal pain (165 AEs), Abdominal distention, (104 AEs), Diarrhoea (95 AEs), Vomiting (86 AEs), Fatigue (47 AEs), Constipation (44 AEs), Abdominal pain upper (41 AEs), Flatulence (34 AEs), Intestinal obstruction (28 AEs), and Abdominal discomfort (25 AEs). For the MedDRA SOC of General disorders and administration site conditions, 631 AEs cumulatively were reported of which 225 were serious.

Commonly reported terms (≥ 25) included Pyrexia (58 AEs), Oedema peripheral (57 AEs), Malaise (44 AEs), Pain (38 AEs), Asthenia and Chills (33 AEs for each), Drug ineffective (31 AEs), andDeath (26 AEs). For the Injury, poisoning and procedural complications SOC, 343 AEs were reported cumulatively, 99 of which were serious; the most commonly reported AEs were Drug dose omission (121 AEs), followed by Gastrointestinal stoma complication (74 AEs). In the MedDRA SOC of Infections and infestations, 254 AEs were reported cumulatively, 177 of which were serious. The most commonly reported terms (≥15) were Device-related infection (59 AEs), followed by Pneumonia (20 AEs), Sepsis (19 AEs), Nasopharyngitis (17 AEs), and Urinary tract infection (16 AEs).

The summary of safety concerns for the product as per the categorization of important identified risks, important potential risks, and important missing information is included in the EU-RMP. Of note, for the missing information category of “Lack of experience in the paediatric population”, there had been no reports of AEs for patients aged ≤ 18 in the interval period of 01 Mar 2015 through 30 Aug 2015, inclusive, as reported in PSUR 6. Lastly, as summarized in PSUR 6, there had been no change in the risk profile for the product’s approved treatment indications during the report interval.

2.4.1. Discussion on clinical safety

Safety information in the paediatric population of 42 paediatric patients aged 1-14 years were collected for 16 weeks (12 weeks on study treatment and 4 weeks follow-up). Vomiting, nausea and diarrhoea were those preferred terms most frequently reported. Fatigue (very common), painful defaecation (very common), and dizziness (common) were reported at a higher frequency in paediatric subjects when compared to adults and this is mentioned in the SmPC for the attention of the prescriber.

The majority of TEAEs were mild to moderate and no patients discontinued the study due to adverse events. Also, no deaths occurred during the study. The safety database in children is considered limited and this is outlined in the SmPC for the attention of the prescriber.

As mentioned in the efficacy discussion disease characteristics in adults and children are similar and the same AE pattern was observed in the paediatric population. There were no new safety signals in the paediatric population as compared with the adult population in previous trials. Events of special interest seen in the adult population, namely biliary complications and colonic polyp formation, were not seen in the paediatric study population. In study TED-C13-003 all patients with positive results in the fecal occult blood testing at the Screening visist and at week 12 were to undergo confirmatory colonoscopy / sigmoidoscopy to evaluate for GI polyps or other sources of GI blood loss. Additionally, patients age 12 and older underwent a colonoscopy/sigmoidoscopy at screening (or within 1 year prior to Visit 1). The frequency of colorectal polyps is very low in paediatric patients, especially in younger children and due to the short-term treatment with teduglutide in this study, it was not justified to perform colonoscopies in children, unless the patient had a positive fecal occult blood test. In view of this safety concern from the adult population recommendation for follow up (test for faecal occult blood and colonoscopies) in children was included for the prescriber in section 4.4 in the SmPC.

Also the study duration was too short to show relevant long term effects particularly on developmental parameters within the relatively large age range of children included in the studyAn abrupt withdrawal of parenteral nutrition and fluids due to the effects of teduglutide could lead to a delay in weight gain, growth and maturation in these children. The SmPC addresses the risk with a precautionary statement on the management of fluids during treatment with Revestive. However further data on long term effects, including developmental parameters will be generated post authorisation with studies TED-C14-006 and the SBS registry as described in the RMP. The studies will also contribute to further characterise the overall safety profile of Revestive in the authorized dose which is acceptable from a safety perspective.

An apparently higher incidence of TEAEs was reported in the 0.05 mg/kg group. However, the Applicant has been able to show that the difference was mainly driven by AEs reporting in 3 patients from the same centre. When excluding these three patients, a comparable safety profile between the 0.025 mg/kg and the 0.05 mg/kg group is observed. The three patients were all 100% weaned off PN/IV and the main AEs were vomiting, abdominal pain, fatigue and headache. These events are well-known and reflected in the SmPC.

2.4.2. Conclusions on clinical safety

The safety database in children is considered limited both in terms of short and long term exposure and this is outlined in the SmPC for the attention of the prescriber. Adequate precautionary statements are included for re-evaluation of the treatment effect and fluid status following parenteral support reduction by the expert prescriber.
Further data on long term effects, including developmental parameters will be generated post authorisation with studies TED-C14-006 and the SBS registry as described in the RMP. The studies will also contribute to further characterise the overall safety profile of Revestive in the authorized dose which is acceptable for marketing authorisation.

During the procedure the applicant has taken the opportunity to amend the due dates for the SBS registry outlined in Annex II of the marketing authorization. The CHMP considered this amendment acceptable as the first patient was enrolled in the study a year later than expected.

2.4.3. PSUR cycle

Due to the extension of indication to include the paediatric population, the PSUR cycle for the medicinal product should continue to follow a half-yearly cycle until otherwise set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

The next data lock point will be 06-11-2015.

2.5. Risk management plan

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

The PRAC considered that the risk management plan version 7.3 is acceptable. The joint assessment report is attached. Further changes were implemented in part III of the RMP in order to align the categorisation of the studies with the current annex II condition.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed the Risk Management Plan version 7.4 with the following content:

Safety concerns

Important Identified Risks	Biliary AEs such as cholecystitis.
	Pancreatic AEs such as chronic and acute pancreatitis, pancreatic duct stenosis, pancreas infection and increased blood amylase and lipase.
	Cardiovascular AEs associated with fluid overload.
	GI stenosis and obstruction.
	GI stoma complications.
	Growth of pre-existing polyps of the colon.
	Benign neoplasia of the GI tract including the hepatobiliary system.
	Tumour promoting ability.
	Occurrence of anti-teduglutide antibodies, cross reactivity with GLP-2 and occurrence of anti-ECP antibodies (and associated clinical immunogenicity reactions).
	Anxiety.
Important Potential Risks	AEs associated with increased absorption of oral concomitant medications.
	Increased CRP.
	Local skin reactions.
	Potential for off-label use in patients with active Crohn's disease.
	Medication errors.
	Compromised nutritional status.
Missing Information	Lack of experience for administration of teduglutide in subjects with severe, clinically unstable concomitant diseases, e.g. cardiovascular, respiratory, renal, infectious, endocrine, hepatic or CNS, or in patients with malignancies within the last 5 years.
	Lack of experience in pregnant or lactating women.
	Lack of experience in the paediatric population.
	Long-term safety in the paediatric population.
	Limited long-term safety data over 1 year of exposure.
	Lack of data in subjects with pre-existing severe hepatic impairment.

Pharmacovigilance plan

Study / Activity, Type, Title and Category (1-3)	**Objectives**	**Safety Concerns Addressed**	**Status (Planned, Started)**	**Date for Submission of Interim or Final Reports (Planned or Actual)**
Clinical 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 (Category 3)	To evaluate the safety, tolerability, pharmacokinetics, and efficacy/pharmacodynamics of teduglutide in pediatric subjects through 17 years of age with short bowel syndrome (SBS) and who are dependent on parenteral support	Lack of experience in the paediatric population Long-term safety in the paediatric population	Planned	Final study report: December 2017
Registry protocol TED-R13-002: A Prospective, Multi-centre Registry for Patients with Short Bowel Syndrome (Category 1)	Primary: To evaluate the long-term safety profile for patients (adults and children) with SBS who are treated with teduglutide in a routine clinical setting. Secondary: To evaluate long-term clinical outcome in subjects with SBS.	The primary safety outcome is the occurrence of colorectal cancer in SBS subjects with a remnant colon taking teduglutide.	Started. Five years of enrolment with at least 10 years of follow-up per subject. The goal is to enrol at least 655 SBS patients of whom 393 will have any remnant colon treated with teduglutide who are at risk for colorectal cancer.	Final study report Q3/2031 Interims reports are planned
Clinical Study 2: Parallel group, placebo-controlled study to assess efficacy of teduglutide in weaning acceleration at least 1 month after major intestinal resection (Category 3)	Primary endpoint is time to wean off PN, main secondary endpoints are PK, persistent efficacy after discontinuation of teduglutide, change in body composition, somatic growth, nutritional status and survival, formation of antibodies against *E.coli* and teduglutide, safety and tolerability	To determine the time to wean off PN. Main secondary endpoints: PK and safety profile in the paediatric population aged 4 months to 6 years.	Study is planned after completion of TED-C13-003. The initiation of the study is deferred.	Study initiation deferred

E.coli=Escherichia coli; IV=intravenous; PK=pharmacokinetics; PN=parenteral nutrition; SBS=short

bowel syndrome

Risk minimisation measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Biliary adverse events such as cholecystitis	Per the current SmPC: Gallbladder and bile ducts Cases of cholecystitis, cholangitis, and cholelithiasis have been reported in clinical studies. In case of gallbladder or bile duct-related symptoms, the need for continued REVESTIVE treatment should be reassessed. Monitoring of small bowel, gallbladder and bile ducts, and pancreas SBS patients are to be kept under close surveillance according to clinical treatment guidelines. This usually includes the monitoring of small bowel function, gallbladder and bile ducts, and pancreas for signs and symptoms, and, if indicated, additional laboratory investigations and appropriate imaging techniques. Cholestasis, cholecystitis and pancreatitis are listed as common undesirable effects.	None.
Pancreatic adverse events such as chronic and acute pancreatitis, pancreatic duct stenosis, pancreas infection and increased blood amylase and lipase	Per the current SmPC: Monitoring of small bowel, gallbladder and bile ducts, and pancreas SBS patients are to be kept under close surveillance according to clinical treatment guidelines. This usually includes the monitoring of small bowel function, gallbladder and bile ducts, and pancreas for signs and symptoms, and, if indicated, additional laboratory investigations and appropriate imaging techniques. Pancreatic diseases Pancreatic AEs such as chronic and acute pancreatitis, pancreatic duct stenosis, pancreas infection and increased blood amylase and lipase have been reported in clinical studies. In case of pancreatic AEs, the need for continued REVESTIVE treatment should be reassessed. Cholestasis, cholecystitis and pancreatitis are listed as common undesirable effect.	None.
Cardiovascular Adverse Events associated with fluid overload	Per the current SmPC: Cardiovascular Due to increased fluid absorption, patients with cardiovascular disease, such as cardiac insufficiency and hypertension,	None.

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	should be monitored with regard to fluid overload, especially during initiation of therapy. Patients should be advised to contact their physician in case of sudden weight gain, swollen ankles and/or dyspnoea. In general, fluid overload can be prevented by appropriate and timely assessment of parenteral nutrition needs. This assessment should be conducted more frequently within the first months of treatment. In case of a significant deterioration of the cardiovascular disease, the need for continued REVESTIVE treatment should be reassessed. Management of fluids during treatment with Revestive In patients receiving Revestive, parenteral support should be reduced carefully and should not be discontinued abruptly. The subject's fluid status should be evaluated following parenteral support reduction and corresponding adjustment performed, as needed.	
Gastrointestinal stenosis and obstruction	Per the current SmPC: Intestinal obstruction Cases of intestinal obstruction have been reported in clinical studies. In case of recurrent intestinal obstructions, the need for continued REVESTIVE treatment should be reassessed. Monitoring of small bowel, gallbladder and bile ducts, and pancreas SBS patients are to be kept under close surveillance according to clinical treatment guidelines. This usually includes the monitoring of small bowel function, gallbladder and bile ducts, and pancreas for signs and symptoms, and, if indicated, additional laboratory investigations and appropriate imaging techniques. Intestinal obstruction is a common undesirable effect.	None.
Gastrointestinal Stoma Complications	Per the current SmPC: GI stoma complication is an undesirable effect. GI stoma complication (swelling of the stoma and associated complications) is considered to be rather a sign of efficacy than an adverse reaction.	None.
Growth of pre-existing polyps of the colon	Per the current SmPC: Contraindications Patients with a history of malignancies in the GI tract including the hepatobiliary system within the last 5 years. Colorectal polyps	None.

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	A colonoscopy with removal of polyps should be performed at the time of starting treatment with REVESTIVE. Once yearly follow-up colonoscopies (or alternate imaging) are recommended during the first 2 years of REVESTIVE treatment. Subsequent colonoscopies are recommended at a minimum of 5-year intervals. An individual assessment whether increased frequency of surveillance is necessary should be performed based on the patient characteristics (e.g. age, underlying disease). If a polyp is found, adherence to current polyp follow-up guidelines is recommended. In case of malignancy, REVESTIVE therapy should be discontinued. <u>Gastrointestinal neoplasia including hepatobiliary tract</u> In the rat carcinogenicity study, benign tumours were found in the small bowel and the extrahepatic bile ducts. These observations were not confirmed in clinical studies of more than 1-year duration. If a neoplasia is detected, it should be removed. In case of malignancy, Revestive treatment should be discontinued Paediatric population <u>*Colorectal polyps/Neoplasia*</u> Prior to initiating treatment with Revestive, faecal occult blood testing should be performed in all children. Subsequent testing should be conducted annually in children while they are receiving Revestive. Prior to initiating treatment with Revestive, children 12 years of age and older should have undergone a colonoscopy/sigmoidoscopy, unless one has been done within the past year.. Children under 12 years of age should also have the procedure if they have unexplained blood in their stool. Colonoscopy is recommended for all children after one year of treatment, and at least every 5 years thereafter of continuous treatment with Revestive. <u>Pharmacodynamic properties</u> Based on the concerns derived from nonclinical studies and the proposed mechanism of action with the trophic effects on intestinal mucosa, there appear to be a risk for the promotion of small intestinal and/or colonic neoplasia. The clinical studies conducted could neither exclude nor confirm such an increased	

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	risk. Several cases of benign colonic polyps occurred during the course of the trials; however, the frequency was not increased compared to placebo-treated patients. In addition to the need for a colonoscopy with removal of polyps by the time of the initiation of the treatment, every patient should be assessed for the need of an enhanced surveillance schedule based on the patient characteristics (e.g. age and underlying disease, previous occurrence of polyps etc.).	

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Benign neoplasia of the gastrointestinal tract including the hepatobiliary system	Per the current SmPC: Gastrointestinal neoplasia including hepatobiliary tract In the rat carcinogenicity study, benign tumours were found in the small bowel and the extrahepatic bile ducts. These observations were not confirmed in clinical studies of more than 1-year duration. If a neoplasia is detected, it should be removed. In case of malignancy, Revestive treatment should be discontinued. Monitoring of small bowel, gallbladder and bile ducts, and pancreas SBS patients are to be kept under close surveillance according to clinical treatment guidelines. This usually includes the monitoring of small bowel function, gallbladder and bile ducts, and pancreas for signs and symptoms, and, if indicated, additional laboratory investigations and appropriate imaging techniques. Paediatric population *Colorectal polyps/Neoplasia* Prior to initiating treatment with Revestive, faecal occult blood testing should be performed in all children. Subsequent testing should be conducted annually in children while they are receiving Revestive. Prior to initiating treatment with Revestive, children 12 years of age and older should have undergone a colonoscopy/sigmoidoscopy, unless one has been done within the past year. Children under 12 years of age should also have the procedure if they have unexplained blood in their stool. Colonoscopy is recommended for all children after one year of treatment, and at least every 5 years thereafter of continuous treatment with Revestive. Pharmacodynamic properties Based on the concerns derived from nonclinical studies and the proposed mechanism of action with the trophic effects on intestinal mucosa, there appear to be a risk for the promotion of small intestinal and/or colonic neoplasia. The clinical studies conducted could neither exclude nor confirm such an increased risk. Several cases of benign colonic polyps occurred during the course of the trials; however, the frequency was not increased compared to placebo-treated	None.

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	patients. In addition to the need for a colonoscopy with removal of polyps by the time of the initiation of the treatment, every patient should be assessed for the need of an enhanced surveillance schedule based on the patient characteristics (e.g. age and underlying disease, previous occurrence of polyps etc.).	
Tumour promoting ability	Per the current SmPC: Contraindications Patients with a history of malignancies in the GI tract including the hepatobiliary system within the last 5 years. Gastrointestinal neoplasia including hepatobiliary tract In the rat carcinogenicity study, benign tumours were found in the small bowel and the extrahepatic bile ducts. These observations were not confirmed in clinical studies of more than 1-year duration. If a neoplasia is detected, it should be removed. In case of malignancy, Revestive treatment should be discontinued Monitoring of small bowel, gallbladder and bile ducts, and pancreas SBS patients are to be kept under close surveillance according to clinical treatment guidelines. This usually includes the monitoring of short bowel function, gallbladder and bile ducts, and pancreas for signs and symptoms, and, if indicated, additional laboratory investigations and appropriate imaging techniques. Paediatric population *Colorectal polyps/Neoplasia* Prior to initiating treatment with Revestive, faecal occult blood testing should be performed in all children. Subsequent testing should be conducted annually in children while they are receiving Revestive. Prior to initiating treatment with Revestive, children 12 years of age and older should have undergone a colonoscopy/sigmoidoscopy, unless one has been done within the past year. Children under 12 years of age should also have the procedure if they have unexplained blood in their stool. Colonoscopy is recommended for all children after one year of treatment, and at least every 5 years thereafter of continuous treatment with Revestive.	None.

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	Pharmacodynamic properties Based on the concerns derived from nonclinical studies and the proposed mechanism of action with the trophic effects on intestinal mucosa, there appear to be a risk for the promotion of small intestinal and/or colonic neoplasia. The clinical studies conducted could neither exclude nor confirm such an increased risk. Several cases of benign colonic polyps occurred during the course of the trials; however, the frequency was not increased compared to placebo-treated subjects. In addition to the need for a colonoscopy with removal of polyps by the time of the initiation of the treatment, every patient should be assessed for the need of an enhanced surveillance schedule based on the patient characteristics (e.g. age and underlying disease, previous occurrence of polyps etc.).	
Occurrence of anti-teduglutide antibodies, cross reactivity with GLP-2, and occurrence of anti-ECP antibodies (and associated clinical immunogenicity reactions)	Per the current SmPC: Immunogenicity Consistent with the potentially immunogenic properties of medicinal products containing peptides, administration of REVESTIVE may potentially trigger the development of antibodies. In Phase 3 studies with SBS, patients who received REVESTIVE for ≥ 2 years, 39% of patients developed anti-teduglutide antibodies and 21% of patients developed antibodies against ECP (residual host cell protein from the manufacture). The antibody formation has not been associated with clinically relevant safety findings, reduced efficacy or changed PK of REVESTIVE.	None.
Anxiety	Per the current SmPC: Anxiety is listed as a common undesirable effect.	None.

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Adverse events associated with increased absorption of oral concomitant medications	Per the current SmPC: Concomitant medication Patients receiving oral concomitant medicinal products requiring titration or with a narrow therapeutic index should be monitored closely due to potential increased absorption. Interaction with other medicinal products and other forms of interaction No clinical drug-drug interaction studies have been performed. An in vitro study indicates that teduglutide does not inhibit CYP450 drug metabolising enzymes. Based upon the PD effect of teduglutide, there is a potential for increased absorption of concomitant medicinal products.	None.
Increased C-Reactive Protein	Per the current SmPC: C-reactive protein increased CRP increased is listed as a common undesirable effect under Investigations. Modest increases of CRP of approximately 25 mg/L have been observed within the first 7 days of REVESTIVE treatment, which decreased continuously under ongoing daily injections. After 24 weeks of REVESTIVE treatment, subjects showed small overall increase in CRP of approximately 1.5 mg/L on average. These changes were neither associated with any changes in other laboratory parameters nor with any reported clinical symptoms. There were no clinically relevant mean increases of CRP from baseline following long-term treatment with REVESTIVE for up to 30 months.	None.

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Local skin reactions	Per the current SmPC: General disorders and administration site conditions Oedema peripheral and injection site reactions are listed as very common. Injection site reactions Injection site reactions occurred in 21% of SBS patients treated with REVESTIVE. The reactions appeared to be dose dependent and occurred with similar frequency in patients given the recommended dose of 0.05 mg/kg/day REVESTIVE and in subjects given placebo (injection site reactions were experienced by 12% of the placebo-treated subjects, by 13% of the patients who received 0.05 mg/kg/day REVESTIVE and by 41% of the subjects who received 0.10 mg/kg/day REVESTIVE). The reactions included injection site erythema, injection site haematoma and injection site pain.	None.
Potential for off-label use on patients with active Crohn's disease	Per the current SmPC: REVESTIVE is indicated for the treatment of patients aged 1 year and above with SBS. Patients should be stable following a period of intestinal adaptation. *Adults:* Treatment should be initiated under the supervision of a medical professional with experience in the treatment of SBS. *Paediatric population (≥1 year)* Treatment should be initiated under the supervision of a medical professional with experience in the treatment of paediatric SBS.	None.

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Medication errors	Per the current SmPC: *Adults* The recommended dose of REVESTIVE is 0.05 mg/kg body weight once daily. A table with the injection volume per body weight is provided. Due to the heterogeneity of the SBS population, a carefully monitored down-titration of the daily dose may be considered for some patients to optimise tolerability of the treatment. If a dose is missed, that dose should be taken as soon as possible on that day. *Paediatric population (≥1 year)* The recommended dose of Revestive in children and adolescents (aged 1 to 17 years) is the same as for adults (0.05 mg/kg body weight once daily). *Overdose* The maximum dose of teduglutide studied during clinical development was 86 mg/day for 8 days. No unexpected systemic adverse reactions were seen. In the event of an overdose, the patient should be carefully monitored by the medical professional. Determination of the number of vials needed for administration of one dose must be based on the individual patient's weight and the recommended dose of 0.05 mg/kg/day. The physician should at each visit weigh the patient, determine the daily dose to be administered until next visit and inform the patient accordingly. Tables with the injection volumes based on the recommended dose per body weight for both adults and paediatric patients are provided in section 4.2 of the SmPC.	None.
Compromised nutritional status	The SmPC recommends optimising nutrition before starting therapy and evaluating treatment effects after 6 months. This includes nutritional status.	None.
Lack of experience for administration of teduglutide in subjects with severe, clinically unstable concomitant diseases e.g., cardiovascular, respiratory, renal, infectious, endocrine, hepatic, or CNS	Per the current SmPC: Special clinical conditions REVESTIVE has not been studied in patients with severe, clinically unstable concomitant diseases, (e.g., cardiovascular, respiratory, renal, infectious, endocrine, hepatic, or CNS), or in patients with malignancies within the last 5 years. Caution should be exercised when prescribing REVESTIVE.	None.

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Lack of experience in pregnant or lactating women	Per the current SmPC: Pregnancy There are no data from the use of REVESTIVE in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of REVESTIVE during pregnancy. Breast-feeding It is unknown whether teduglutide is excreted in human milk. In rats, mean teduglutide concentration in milk was less than 3% of the maternal plasma concentration following a single SC injection of 25 mg/kg. A risk to the breastfed new-born/infant cannot be excluded. As a precautionary measure it is preferable to avoid the use of REVESTIVE during breastfeeding.	None.
Lack of experience in paediatric the population	Per the current SmPC: Paediatric population In one completed clinical study, there were 37 paediatric subjects (aged 1 to 14 years) enrolled and exposed to REVESTIVE for duration of 12 weeks. No significant hepatobiliary events or events related to intestinal obstruction or fluid overload occurred. No subject discontinued the study due to an AE. Overall, the safety profile of REVESTIVE in children and adolescents (ages 1-17 years) was similar to that in adults. The following terms were reported at a higher frequency in paediatric subjects when compared to adults: fatigue (very common), painful defaecation (very common), dizziness (common), rash (common).Long-term safety data are not yet available for this paediatric population. No data are available for children under 1 year of age\	None.
Long-term safety in the paediatric population	Long-term safety data are not yet available for this paediatric population. No data are available for children under 1 year of age.	None.
Limited longer-term safety data over one year of exposure	No risk minimisation activities are proposed at this time.	None.

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Lack of data in subjects with pre-existing severe hepatic impairment	Per the current SmPC: Special populations Hepatic impairment No dose adjustment is necessary for subjects with mild and moderate hepatic impairment based on a study conducted in Child-Pugh grade B subjects. REVESTIVE has not been studied in subjects with severe hepatic impairment	None.

AE=adverse event; CNS=central nervous system; CRP=C-reactive protein; CYP450=cytochrome P450; ECP=E. coli protein; GI=gastrointestinal; GLP-2=glucagon-like peptide; PD=pharmacodynamic; PK=pharmacokinetic(s); SBS=short bowel syndrome; SC=subcutaneous; SmPC=Summary of Product Characteristics

2.6. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC have been updated. The Package Leaflet has been updated accordingly. Please refer to the new amended PI.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s) [e.g. Excipients guideline, storage conditions, Braille, etc…], which were reviewed by QRD and accepted by the CHMP.

2.6.1. User consultation

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

- The content of the current PL has been fully tested and assessed for readability.
- The proposed revisions to the PL are minor: the proposed dose for paediatrics is the same as the recommended dose in adults and the side effect profile is similar to that seen in adults.
- Many paediatric patients administering Revestive are likely to be assisted by carers/parents and the PL has already been tested in this population.

2.6.2. Paediatric data

The CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0245/2015 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

3. Benefit-Risk Balance

Benefits

Beneficial effects
Overall, 12 weeks teduglutide treatment was associated with a reduction in parenteral nutrition PN/IV support in terms of volume and calories in paediatric patients aged 1-14 years, when compared with the group of children treated with standard of care. Three different dose levels were evaluated: 0.0125, 0.025, and 0.05 mg/kg. The adult dose of 0.05 mg/kg was also chosen for the paediatric population. The number of patients achieving a 10% and 20% reduction in PN/IV volume and calories use were higher in the 0.025 mg/kg (71%) and 0.05 mg/kg (53%) dose groups compared with the lowest dose of 0.0125 mg/kg (12.5%) and the standard of care group (0%). The absolute and percent changes in PN/IV volume and calories were about 2.7 L/week and 1800 kcal/week, translating into a percent change of about 37% in the two highest dose groups. Furthermore days of PN/IV usage was estimated to be reduced by 1.3 days per week in the 0.05 mg/kg dose group and 0.69 days per week in the 0.025 mg/kg group. Four patients were completely weaned off at 12 weeks. These subjects included 3 of 15 (20.0%) subjects in the 0.05 mg/kg/day cohort and 1 of 14 (7.1%) subjects in the 0.025 mg/kg/day cohort.

The clinical manifestation of the disease in adults and children are similar and is due to diminished absorption, which leads to malabsorption and diarrhoea, leading to dehydration and malnutrition, abdominal pain, fluid and electrolyte disturbances. Also the management and complications of SBS are similar between adults and children. Based on the disease characteristics, course of disease, the preclinical and clinical data from the adult population, there is sufficient data to conclude that the data observed in adults can be used to draw conclusions on efficacy in the paediatric population.

In the adult studies, a 20% reduction in the PN/IV support is considered clinically relevant, and a superior effect of teduglutide was seen already after 8-12 weeks. The effect increased over time with more than 70% of patients reaching a 20% reduction in PN/IV volume at 6 months. Similar results after 12 weeks were seen for the doses 0.025 and 0.05 mg/kg in the paediatric population, supporting that also the paediatric population accordingly benefits in the long term from teduglutide treatment. Furthermore, one day off PN/IV support per week is also considered clinically relevant for paediatric patients.

Uncertainty in the knowledge about the beneficial effects
The study duration was short (3 months only) and the numbers of included patients was small, however the durability and further course of the beneficial effects of teduglutide in paediatric patients comprised by the indication can be reasonably assumed from the effect seen in adults based on the totality of data in this rare disease.

Risks

Unfavourable effects
Gastrointestinal disorders (vomiting, nausea and diarrhoea) were most frequently reported, followed by general disorders and administration site conditions, and infections and infestations. While these events are important, their risk is well known and described in the RMP. Fatigue (very common), painful defaecation (very common), and dizziness (common) were reported at a higher frequency in paediatric subjects when compared to adults and this is mentioned in the SmPC for the attention of the prescriber.

There were no new safety signals in the paediatric population as compared with the adult population in previous trials. Events of special interest seen in the adult population, namely biliary complications and colonic polyp formation, were not seen in the paediatric study population but due to the limited safety database precautionary statements were included in 4.4 of the SmPC for their screening in the paediatric population namely regular testing of faecal occult blood and colonoscopy / sigmoidoscopy to evaluate for GI polys or other sources of occult blood.

Uncertainty in the knowledge about the unfavourable effects

Adverse events were only evaluated for 16 weeks, hence no long-term safety data for the paediatric population was provided. Due to the low number of subjects included into the trial and the restricted observation period it is possible that events of clinical concern have not been observed within the study and long term safety in the paediatric population has been added as missing information to the RMP. No differences were found in the pivotal study for the "developmental" parameters body weight, height, and height-Z-scores, with a small numerical disadvantage for the higher dosing groups.

Theoretically a to abrupt withdrawal of parenteral nutrition and fluids due to the effects of teduglutide could lead to a delay in weight gain, growth and maturation in these children. The SmPC addresses the risk with a precautionary statement on the management of fluids during treatment with Revestive. However further data on long term unfavourable effects, including developmental parameters will be generated post authorisation with studies TED-C14-006 and its long term extension as described in the RMP.
Furthermore it is noted that paediatric patients are to be enrolled in the already existing SBS registry which was established at the time of the initial marketing authorisation as outlined in Annex II and described in the RMP. These studies will also contribute to the further characterisation of the overall safety profile of Revestive in the authorized dose in this patient population.

Effects Table

Table 2. . Effects Table for Revestive (data cut-off: 05 February 2015)

Effect	Short Description	Unit	Revestive	Standard of care	Uncertainties / Strength of evidence	References
Favourable Effects						
20% reduction in PN/IV volume	From baseline to week 12	n/N (%)	**0.05 mg/kg:** 8/15 (53%)	0/5 (0%)	Endpoint used in adult studies	
Absolute change in PN volume	From baseline to week 12	L/week Mean (SD)	**0.05 mg/kg:** -2.57 (3.564)	0.43 (0.746)	The dose of 0.05 mg/kg was chosen for the pediatric population. This is the dose recommended for the adults. The dose of 0.025 appeared to have the same effect as the 0.05 mg/kg dose.	
Percent change in PN volume	From baseline to week 12	% Mean (SD)	**0.05 mg/kg:** -39.11 (40.792)	7.38 (12.756)		
Change in EN volume	From baseline to week 12	L/week Mean (SD)	**0.05 mg/kg:** 0.67 (1.4)	1.11 (0.70)	Patients in the 0.05 mg/kg group had less small intestine as those patients in the 0.025 mg/kg	
Percent change in	From baseline to week 12	% Mean (SD)	**0.05 mg/kg:** 26 (42)	54 (57)	Patients in the 0.05 mg/kg group had	

Effect	Short Description	Unit	Revestive	Standard of care	Uncertainties / Strength of evidence	References
EN volume					less small intestine as those patients in the 0.025 mg/kg	

Unfavourable Effects						
Gastrointestinal disorders	Vomiting, nausea, diarrhoea mostly reported	N/events (events per patient)	**0.05 mg/kg:** 10/72 (7.2)	1/4 (4)	Patients treated with 0.05 mg/kg reported more TEAEs within gastrointestinal disorders compared to the other groups.	
General disorders and administration site conditions	Fatigue mostly reported	N/events (events per patient)	**0.05 mg/kg:** 12/33 (2.8)	3/5 (1.7)	Patients treated with 0.05 mg/kg reported more TEAEs within general disorders and administration site conditions compared to the other groups.	

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Short bowel syndrome is a state of intestinal failure following major intestinal resection. Currently limited treatment options are available restricted to pharmacological therapy aiming at reduction of secretory losses and parenteral nutrition (PN: fluid/energy). PN is associated with a significant impact on quality of life in addition to risk of serious complications (e.g. central catheter sepsis and thrombosis, complications related to bacterial overgrowth of the small intestine, significant liver toxicity and biliary disease).

For patients with short-bowel-syndrome (SBS), a reduction in PN/IV support is valuable along with an increase in enteral intake leading to an improved quality of life particularly following a reduction in numbers of days on PN/IV usage per week and reducing the complications related to parenteral nutrition.

Benefit-risk balance

The benefit-risk balance of teduglutide for the treatment of paediatric patients aged one year and above with SBS with PN need is positive.

Discussion on the Benefit-Risk Balance

Long term PN/IV support is associated with serious complications, such as infections and liver damage. The risk for these effects increases over time with longer duration of PN/IV support. Achievement of enteral autonomy avoids the significant morbidity associated with long-term dependence on PN and is therefore the primary aim of modern management of intestinal failure.

The applicant could show clinical relevant effects in paediatric patients aged one year and above on the reduction in PN/IV volume and calories as well as on the potentially clinically most relevant parameters, the complete weaning from PN need. In adult studies the effect on reduction in PN/IV volume increased even further at 6 months. The applicant provided convincing arguments that the efficacy data observed in adults can be used to support to this paediatric indication.

The same AE pattern was observed in the paediatric population. Gastrointestinal disorders (vomiting, nausea and diarrhoea) were most frequently reported, followed by general disorders and administration site conditions, and infections and infestations. While these events are important, their risk is well known and described in the RMP. Also monitoring of potential colonic polyp formation and careful fluid management are addressed in the product information and their risk can be considered balanced. No differences were found in the pivotal study for developmental parameters such as body weight, height,

and height-Z-scores. However, due to the low number of subjects included into the trial and the restricted observation period long term safety in the paediatric population will be carried out with in the already existing NIS as well as with study TED-C14-006 as described in the RMP. These studies will also contribute to the further characterisation of the overall safety profile of Revestive in the authorized dose in this patient population.

4. Recommendations

Outcome

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

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include the treatment of patients aged 1 year and above with short bowel syndrome who are stable following a period of intestinal adaptation. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet has been updated accordingly.

The Risk Management Plan was also updated to reflect the study completion and results and the MAH took the opportunity to update due dates of the International Short Bowel Syndrome Registry reflected in Annex II.

Furthermore, the PI is brought in line with the latest QRD template.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

This CHMP recommendation is subject to the following conditions, with amended submission dates for the International Short Bowel Syndrome Registry:

Conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

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

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

- **Risk management plan (RMP)**

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

An updated RMP should be submitted:

At the request of the European Medicines Agency;

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

- **Obligations to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
International Short Bowel Syndrome Registry Non-interventional study (NIS) to gather further safety data, in order to further elucidate the potential and identified risk as outlined in the RMP, based on a CHMP approved protocol. Interim data for the NIS should be provided every second year. Final study report	 Four interim reports will be provided within six months after the data lock points (i.e., Q4 2016, Q4 2018, Q4 2020, and Q4 2022). Q3 2031

5. EPAR changes

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

Scope

Extension of Indication to include the treatment of patients aged 1 year and above with short bowel Syndrome who are stable following a period of intestinal adaptation. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance.

Summary

Please refer to the scientific discussion Revestive EMEA/H/C/002345/II/20 for further information.