EU RISK MANAGEMENT PLAN (RMP)

for

Revestive® (Teduglutide)

RMP Version number: 9.2

Date: 14-February-2022

[redacted]

EU Risk Management Plan for Revestive (teduglutide)

Administrative Information

RMP version to be assessed as part of this application:

RMP Version number: 9.2

Data lock point for this RMP: 30-April-2021

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Rationale for submitting an updated RMP: Removal of missing information 'Lack of experience in children aged less than 1 year' to maintain consistency throughout the document, addition of risk minimization information from package leaflet (PL).

Summary of significant changes in this RMP:

RMP Module:	Significant Changes:
Part I Product Overview	Not applicable.
Part II Safety Specification	
• **Module SI Epidemiology of the indication(s) and target population(s)**	Proposed indication wording mentioned in the epidemiology table.
• **Module SII Non-clinical part of the safety specification**	Not applicable.
• **Module SIII Clinical trial exposure**	Not applicable.
• **Module SIV Populations not studied in clinical trials**	Not applicable.
• **Module SV Post-authorisation experience**	Not applicable.
• **Module SVI Additional EU requirements for the safety specification**	Not applicable.
• **Module SVII Identified and potential risks**	Year of initial RMP submission updated from 2013 to 2012. "Risks with minimal clinical impact on patients (in relation to the severity of the indication treated)" was updated to "Not applicable".
• **Module SVIII Summary of the safety concerns**	Not applicable.
Part III Pharmacovigilance plan	Removal of missing information 'Lack of experience in children aged less than 1 year'.
Part IV Plans for post-authorisation efficacy studies	This section was updated to "Not applicable".
Part V Risk minimisation measures	Routine risk minimization measure details from

RMP Module:	Significant Changes:
	"package leaflet" have been added.
Part VI Summary of the risk management plan	Routine risk minimization measure details from "package leaflet" have been added.
Part VII Annexes	Annex 8 – updated to reflect the changes made from 9.1 to 9.2. Version 9.1 has been marked as "not approved".

Other RMP versions under evaluation: Not applicable.

RMP Version number: Not applicable.

Submitted on: Not applicable.

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Details of the currently approved RMP:

Version number: 9.0

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QPPV name: Sumit Munjal

Please note that e-signature may also be performed by Deputy EU QPPV [redacted] or Deputy EU QPPV [redacted] on behalf of the EU QPPV (i.e. 'per procurationem').

QPPV signature: Refer to the electronic signature at the end of the document.

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List of Abbreviations

Abbreviation	Definition
ADR	Adverse drug reaction
AE	Adverse event
AIDS	Acquired immune deficiency syndrome
ATC	Anatomical therapeutic chemical classification
AUC	Area under the curve
AUC_{inf}	Area under the concentration versus time curve from time 0 to infinity = AUC_{0-inf}
AUC_{ss}	Area under the curve at steady state
BANS	British Artificial Nutrition Survey
BAPEN	British Association for Parenteral and Enteral Nutrition
BMI	Body mass index
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
C_{max}	Observed maximum plasma concentration
$C_{max,ss}$	Observed maximum plasma concentration at steady state
$C_{min,ss}$	Observed minimum plasma concentration at steady state
CNS	Central nervous system
CRP	C-reactive protein
CSR	Clinical study report
CYP450	Cytochrome P450
DPP-IV	Dipeptidyl peptidase IV
ECG	Electrocardiogram
E. coli	*Escherichia coli*
ECP	*E. coli* protein

Abbreviation	Definition
EEA	European economic area
EGF	Epidermal growth factor
EMA	European Medicines Agency
EPAR	European Public Assessment Reports
EU	European Union
GFR	Glomerular filtration rate
GI	Gastrointestinal
GLP-2	Glucagon-like peptide 2
GLP-2R	Glucagon-like peptide 2 receptor
GLUT-2	Glucose transporter 2
hERG	Human ether-à-go-go-related gene
hGH	Human growth hormone
HPN	Home parenteral nutrition
ICD-9	International Classification of Diseases-9
IGF-1	Insulin-like growth factor 1
INN	International non-proprietary name
IV	Intravenous
KGF	Keratinocyte growth factor
MA	Marketing authorisation
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	Messenger ribonucleic acid
PBRER	Periodic Benefit-Risk Evaluation Report
PD	Pharmacodynamic(s)
Ph. Eur.	Pharmacopoeia Europaea

Abbreviation	Definition
PL	Package leaflet
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic(s)
PN	Parenteral nutrition
PRAC	Pharmacovigilance Risk Assessment Committee
PT	Preferred term
PY	Person-years
QPPV	Qualified person for pharmacovigilance
QTc	Corrected QT interval
QTcF	Fredericia corrected QT interval
rDNA	Recombinant deoxyribonucleic acid
RMP	Risk management plan
SAE	Serious adverse event
SBS	Short bowel syndrome
SC	Subcutaneous
SGLT-1	Sodium-dependent glucose transporter 1
SmPC	Summary of Product Characteristics
SOC	Standard of care
$t_{1/2}$	Elimination half-life
TEAE	Treatment-emergent adverse event
TPN	Total parenteral nutrition
UK	United Kingdom
ULN	Upper limit of normal
US	United States

Abbreviation	Definition
V/F	Apparent volume of distribution

[redacted]

Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) (INN or common name)	Teduglutide
Pharmacotherapeutic group(s) (ATC Code)	Other alimentary tract and metabolism products, various alimentary tract and metabolism products (A16AX08)
Marketing Authorisation Holder	Shire Pharmaceuticals Ireland Limited
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Revestive
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Teduglutide is a novel recombinant analogue of the human Glucagon-like peptide 2 (GLP-2), a peptide secreted by the lower Gastrointestinal (GI) tract.
	Summary of mode of action: Native GLP-2 facilitates efficient GI movement, digestion and absorption of food. GLP-2 is mainly responsible for the maintenance and expansion of the GI mucosal surface area through the regulation of proliferation and apoptosis of the intestinal epithelium. Furthermore, GLP-2 promotes energy absorption through a number of mechanisms including enhanced capacity for carbohydrate, amino acid, and lipid absorption, increased activity and expression of brush border digestive enzymes, and increased mucosal hexose and nutrient transport via up-regulation of Glucose transporter 2 (GLUT-2) and the Sodium-dependent glucose transporter 1 (SGLT-1). In addition, GLP-2 reduces gastric motility, inhibits gastric acid secretion, enhances mucosal barrier function, and acutely increases intestinal and portal blood flow. The naturally occurring human 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.
	Important information about its composition: The active ingredient in Revestive is teduglutide (rDNA origin), which

[redacted]

	is a 33 amino acid glucagon-like peptide-2 (GLP-2) analogue manufactured using a strain of *Escherichia coli* modified by recombinant DNA technology. Similar to GLP-2, teduglutide is 33 amino acids in length with an amino acid substitution of alanine by glycine at the second position of the N-terminus. The single amino acid substitution relative to naturally occurring GLP-2 results in resistance to in vivo degradation by the enzyme DPP-IV, resulting in an extended half-life. Teduglutide increases villus height and crypt depth of the intestinal epithelium.
Hyperlink to the Product Information (PI)	Refer to eCTD Module 1.3.1 for proposed PI.
Indication(s) in the EEA	Current (if applicable): Revestive is indicated for the treatment of patients aged 1 year and above with Short Bowel Syndrome (SBS). Patients should be stable following a period of intestinal adaptation after surgery.
	Proposed (if applicable): Revestive is indicated for the treatment of patients 4 months corrected gestational age and above with Short Bowel Syndrome (SBS). Patients should be stable following a period of intestinal adaptation after surgery.
Dosage in the EEA	Current (if applicable): <u>Adults</u> The recommended dose of Revestive is 0.05 mg/kg body weight once daily. The injection volume per body weight are provided in section 4.2 of the SmPC. 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 injected as soon as possible on that day. Treatment effect should be evaluated after 6 months. Limited data from clinical studies have shown that some patients may take longer to respond to treatment (i.e., those who still have presence of colon-in-continuity or distal/terminal ileum); if no overall improvement is achieved after 12 months, the need for continued treatment should be reconsidered. <u>Paediatric population (≥1 year):</u> 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). The injection volume per body weight when using the 5 mg strength vial is provided in Section 4.2 of the Summary of Product Characteristics (SmPC). A 1.25 mg strength vial is available for paediatric use (patients with a body weight <20 kg). A treatment period of 6 months is recommended after which treatment effect should be evaluated. There are no data available in paediatric patients after 6 months. If a dose is missed, that dose should be taken as soon as possible on that day.

[redacted]

	Method of administration: The reconstituted solution should be administered by subcutaneous (SC) injection once daily, alternating sites between 1 of the 4 quadrants of the abdomen. In case the injection into the abdomen is hampered by pain, scarring or hardening of the tissue, the thigh can also be used. Revestive should not be administered intravenously or intramuscularly.
	Proposed (if applicable): *Paediatric population (≥4 months)* The recommended dose of Revestive in children and adolescents (aged 4 months corrected gestational age to 17 years) is 0.05 mg/kg body weight once daily. The injection volume per body weight when using the 1.25 mg strength vial is provided in Section 4.2 of the SmPC. For paediatric patients with a body weight >20 kg, the 5 mg strength vial should be used. A treatment period of 6 months is recommended after which treatment effect should be evaluated. In children below the age of two years, treatment should be evaluated after 12 weeks. If a dose is missed, that dose should be injected as soon as possible on that day. Method of administration The reconstituted solution should be administered by subcutaneous injection once daily, alternating sites between 1 of the 4 quadrants of the abdomen. In case the injection into the abdomen is hampered by pain, scarring or hardening of the tissue, the thigh can also be used. Revestive should not be administered intravenously or intramuscularly.
Pharmaceutical form(s) and strengths	Current (if applicable): ***5 mg Strength*** Each single-use vial contains 5 mg of teduglutide as a white lyophilized powder for solution for subcutaneous injection. After reconstitution, each vial contains 5 mg teduglutide in 0.5 ml of solution, corresponding to a concentration of 10 mg/ml. ***1.25 mg Strength*** Each single-use vial contains 1.25 mg of teduglutide as a white lyophilized powder for solution for subcutaneous injection. After reconstitution, each vial contains 1.25 mg teduglutide in 0.5 ml of solution, corresponding to a concentration of 2.5 mg/ml. The reconstituted drug product also contains the following excipients: L-histidine, mannitol, sodium phosphate monohydrate, disodium phosphate heptahydrate, sodium hydroxide (pH adjustment) and hydrochloric acid (pH adjustment).
	Proposed (if applicable): Not applicable.
Is/will the product be subject to additional monitoring in the EU?	Yes.

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Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Epidemiology for SBS patients 4 months corrected gestational age and above	
Incidence and prevalence:	SBS is a serious, disabling, socially incapacitating and potentially life-threatening condition, which may result from surgical resection, congenital defect, or disease-associated loss of absorption. It is characterised by the inability to maintain protein-energy, fluid, electrolyte or micronutrient balances when on a conventionally accepted, normal diet [1]. Other clinically important manifestations of SBS can include malnutrition, dehydration, gastric acid hypersecretion, metabolic acidosis, cholelithiasis, nephrolithiasis, steatorrhoea, diarrhoea, and small bowel bacterial overgrowth [2]. Among the factors associated with the prognosis of SBS-associated intestinal failure is the length of the residual small bowel, the presence of residual underlying disease, the presence or absence of the colon in continuity and of the ileocecal valve, the nature of the primary disorder, the age of the subjects, and the status of dependence or independence of parenteral nutrition (PN) [1]. As SBS is a rare condition, most prevalence and incidence estimates are based on data describing only subjects on long-term PN and vary substantially between countries. Moreover, the differences in health care systems also affect the way patients are treated. In some countries the treatment is centralised with a few specialised centres treating most of the subjects, while in other countries treatment is decentralised, with many centres treating very few patients each. Market research commissioned by Nycomed in March 2009 estimated about 4000 adult patients with SBS (who are or who have been at least temporarily on PN) in all target European countries (assumed prevalence of 15 in 1 million). Estimates of SBS incidence in Europe vary from 2-3/million [3,4]. The incidence of SBS in infants has been estimated at 24.5 cases of SBS per 100,000 live births [5]. In one Italian population-based study, the incidence of SBS intestinal failure was 0.1% in all live births and 0.5% among neonatal intensive care unit admissions [6]. In 2016 a recent cross-sectional study in the Netherlands (the nationwide The Dutch Register of Intestinal Failure and Intestinal Transplantation (DRIFT) registry study) covered data till January 2013, the prevalence of chronic intestinal failure requiring home parenteral support was 12.24/1,000,000 in adults and 9.56/1,000,000 in children [7]. Refer to table below for the incidence and prevalence of SBS as reported in relevant medical publications.

Epidemiology for SBS patients 4 months corrected gestational age and above	
Demographics of the target population in the indication:	While the target patient population for the indication of SBS is small and clinically challenging, it is not specific regarding age or gender.
Risk factors for the disease:	SBS is due to surgical removal of portions of the GI tract for different reasons, to congenital defect or to disease-associated loss of absorption.
Main existing treatment options:	In the past, the clinical care of SBS subjects has mainly focused on optimising remnant intestinal function through dietary interventions, oral rehydration solutions, anti-diarrhoeal and anti-secretory agents. Current treatment of SBS is supportive and primarily based upon PN therapy. PN-treated subjects have indwelling catheters with inherent risks of catheter-related infections and sepsis, as well as a risk of intestinal failure-associated liver disease. Intravascular catheter-related blood stream infections are the main acute PN-related morbidity and occur at a rate of 0.33-20.06 infections/1000 catheter days [8]. It has been reported that patients with long-term PN developed end stage liver disease at a rate of approximately 15% with an associated high rate of morbidity and mortality [9]. Long-term PN has also been associated with a higher risk of biliary complications such as cholecystitis and gallstone formation. Acalculous cholecystitis has been reported in approximately 4% of patients receiving PN for more than 3 months [10]. PN use is associated with high cost, significant quality of life impairment and economic impediments. Surgical options also exist. Anastomosis of excluded bowel should be performed when possible. Surgical procedures such as bowel lengthening surgery can increase surface area and improve motility. In cases where central venous access is lost, intestinal transplantation may be an option. In the setting of combined intestinal and liver failure, multivisceral transplantation may be an option. Intestinal transplantation and multivisceral transplantation are associated with significant morbidity and mortality, and are considered only in selected patients [11].
Natural history of the indicated condition in the untreated population, including mortality and morbidity:	The overall survival rate of patients with intestinal failure due to non-malignant causes is approximately 70% at 5 years. Mortality directly related to home parenteral nutrition (HPN) itself accounts only for 5-15% of the deaths [12]. In a study following 268 patients with non-malignant SBS requiring HPN for varying lengths of time over 25 years, the actuarial survival probabilities were 94%, 70% and 52% at 1, 5 and 10 years respectively. Furthermore, the 10-year survival was significantly higher in patients that became HPN free compared with those who remained HPN dependent (67.0% + 0.6% versus 40.7% + 0.5%, p<0.001). Thirteen (13%) of the 105 deaths were related to HPN (sepsis and liver failure) and 14 (13%) of the deaths were due to the SBS (cachexia and metabolic complications) [13].

[redacted]

Epidemiology for SBS patients 4 months corrected gestational age and above	
	Long-term survival has been improving due to advances in central line care and understanding of the pathogenesis of intestinal failure-associated liver disease. In a large single-center cohort, 10 year survival of children with intestinal failure due to primary digestive diseases (predominantly SBS), was approximately 85% [14].
Important co-morbidities and concomitant medication(s) in the target population:	Among the subjects in the adult Phase 2/3 studies, the most common medical histories were surgical and medical procedures mainly consisting of colectomy, small intestinal resection, intestinal anastomosis and intestinal resection {teduglutide: 170 (89.0%) subjects, placebo: 28 (92.7%) subjects), as well as GI disorders with a majority of subjects with Crohn's disease {teduglutide: 163 (85.3%) subjects, placebo: 37 (90.2%)}. This is to be expected in a study population of SBS and Crohn's disease patients. No obvious differences in medical history were observed between teduglutide treatment groups and placebo. As SBS is an outcome of surgery for different background conditions and diseases, the target subject population is very heterogeneous. To Shire's knowledge there are no epidemiological data regarding co-morbidity in the SBS population. The most commonly used concomitant medications received by at least 20% of all subjects treated with teduglutide in adult Phase 2/3 studies were antipropulsives, proton pump inhibitors, heparin group, vitamin D and analogues, calcium, anilides, benzodiazepine derivatives, electrolyte solutions, H_2-receptor antagonists, multivitamins, opium alkaloids and derivatives. The extent of their use was similar between placebo and teduglutide and among the teduglutide dose groups.

HPN=home parenteral nutrition; GI: Gastrointestinal; SBS: Short Bowel Syndrome.

The incidence and prevalence of SBS as reported in relevant medical publications is presented below:

Incidence and Prevalence in Medical Publications			
Study Title	**Author, Date**	**Target Population**	**Prevalence and/or Incidence**
The year 2002 national register on home-based parenteral nutrition	Moreno 2005 [15]	Patients receiving HPN	Spain: The programme had an enrolment of 74 subjects, resulting in a prevalence of 1.8 subjects/million in the general population.
National Registry of Patients with Short Bowel Syndrome	Kurlberg, 2004 [16]	All patients (adults and children/neonatals)	Sweden: 400 people/9 million population = 44 people/million prevalence.

[redacted]

Incidence and Prevalence in Medical Publications			
Study Title	**Author, Date**	**Target Population**	**Prevalence and/or Incidence**
Home parenteral nutrition in Denmark in the period of 1996 – 2001	Ugur, 2006 [17]	202 patients (115 female, 87 male)	This retrospective study included a total of 202 patients who had been receiving HPN between 01 January 1996 and 31 December 2000 and is a follow-up of a study describing 129 HPN patients receiving HPN from 1991 to 1996. In 1991, 1996 and towards the end of 2000, the prevalence of HPN has increased from 9.0 to 13.9 and to 19.2 patients per million inhabitants, respectively. The average annual incidence has increased from 3.0 to 5.0 patient inhabitants/year within the two 5-year periods.
Indications and need for long-term parenteral nutrition: implications for intestinal transplantation	Lennard-Jones 1990 [3]	Patients requiring long-term total HPN for SBS	UK: incidence of SBS requiring HPN therapy 2/million.
Annual BANS Report, 2008	BANS, a committee of BAPEN 2008 [18]	Adults requiring HPN	UK: SBS remains the main reason for HPN (41.3% new cases; 53.6% established cases) - about half subjects on HPN have SBS. From 2003 to 2007, point prevalence/million registered patients on HPN rose from 8.8 to 13.1 while new registrations rose from 2.0 to 2.3/million.
Annual BANS Report, 2009	BANS, a committee of BAPEN 2009 [19]	Adults requiring HPN	UK: SBS remains the main reason for HPN (42.7% new cases; 55.7% established cases). New registrations of patients on HPN rose in 2008 by 14% to 157. Point and period prevalence fell significantly to 413 (-47%) and 521 (-40%) respectively, but according to the report,

Incidence and Prevalence in Medical Publications			
Study Title	**Author, Date**	**Target Population**	**Prevalence and/or Incidence**
			this was due to a new law requiring subject consent before submitting any data to BANS.
Home parenteral nutrition in adults: a multicentre survey in Europe in 1993	Van Gossum, 1996 [20]	496 adult HPN cases	A retrospective survey was performed in 1994, involving 496 adult HPN cases, newly enrolled in the year 1993 from 13 European countries from 75 centres. From the 8 countries having registered more than 80% of cases (423 patients), incidence and prevalence ranged from 0.2 to 4.6 and 0.3 to 12.2 patients/108 population/year. In the patients studied, the diagnosis was cancer (42%), Crohn's disease (15%), vascular diseases (13%), radiation enteritis (8%), AIDS (4%) and other non-malignant non-AIDS diseases (18%). SBS and intestinal obstruction were the 2 major indications for HPN in 31% and 22%, respectively.
Home parenteral nutrition in adults: a European multicentre survey in 1997	Van Gossum, 1999 [4]	494 adults requiring HPN	A total of 494 patients were registered in 73 centres from 9 countries: Belgium, Denmark, France, Poland, Spain, Sweden, UK, The Netherlands and Germany. The underlying diseases for HPN in 494 patients were cancer (39%), Crohn's (19%), vascular diseases (15%), radiation enteritis (7%), AIDS (2%), other diseases with intestinal failure (18%). Incidence (patients/million inhabitants/year) was 3 in The Netherlands, 2.9 in France, 2.8 in Denmark, 2.6 in Belgium, 1.2 in UK, 0.7 in Spain and 0.36 in Poland. Prevalence was 12.7 in Denmark, 3.7 in UK, 3.7 in The Netherlands, 3.6 in

Incidence and Prevalence in Medical Publications			
Study Title	**Author, Date**	**Target Population**	**Prevalence and/or Incidence**
			France, 3.0 in Belgium, 1.1 in Poland and 0.65 in Spain.
The Medical and Surgical Management of Short Bowel Syndrome	Buchman, 2004 [21]	All subjects (adults and children/neonates)	In the absence of registry data, it is impossible to know the precise incidence and prevalence of SBS in the US. On the basis of European data, the incidence of TPN-dependent short-bowel patients is estimated between 2 and 3 per million per year, with the prevalence at approximately 4 per year per million.
Classification, epidemiology and aetiology	Koffeman, 2003 [22]	Adults and children	The incidence of HPN in adults varies from 2 to 3 per million, with a prevalence of 4 per million. In children, highly variable figures for HPN incidence (0.2-4.9/ million), and prevalence (0.3-8.9/million) have been noted. Estimated incidence and prevalence of SBS can be extrapolated from these data because SBS patients form the most important group of HPN patients (35%). The incidence of SBS can be estimated to be approximately 2 per million and the prevalence close to 3 per million. However, SBS patients who do not survive after surgery or who exhibit adequate intestinal adaptation during hospitalisation will not require HPN and will not be included in such data. Because as many as 27% of adult SBS patients can be weaned off TPN within 1 month, there may be a significant underestimation of both incidence and prevalence of SBS.
Epidemiology and Healthcare	Pant C 2015 [23]	Children	In the Kids' Inpatient Database 2680 children aged

[redacted]

Incidence and Prevalence in Medical Publications			
Study Title	**Author, Date**	**Target Population**	**Prevalence and/or Incidence**
Resource Utilization Associated With Children With Short Bowel Syndrome in the United States			0-3 were identified with SBS for the year 2012.
Presentation of a nationwide multicenter registry of intestinal failure and intestinal transplantation	Neelis, 2016 [7]	Adults and children	The prevalence of chronic intestinal failure requiring home parenteral support was 12.24/1,000,000 in adults and 9.56/1,000,000 in children.

AIDS=acquired immune deficiency syndrome; BANS=British artificial nutrition survey; BAPEN=British Association of Parenteral and Enteral Nutrition; HPN=home parenteral nutrition; SBS=short bowel syndrome; TPN=total parenteral nutrition; UK=United Kingdom; US=United States.

Part II: Module SII - Non-clinical part of the safety specification

The nonclinical development programme, addressing the safety pharmacology and toxicity of teduglutide, comprises studies on cardiovascular, respiratory and central nervous system (CNS) effects, single-dose toxicity, repeat-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, studies in juvenile animals, and local tolerance. All pivotal studies were conducted in compliance with Good Laboratory Practice, with the exception of the nonclinical C-reactive protein (CRP) study, using lyophilised formulations of teduglutide containing histidine and mannitol in phosphate buffer, comparable to the formulations used in clinical studies and to be marketed.

Teduglutide has shown primary pharmacodynamic (PD) activity in mice, rats, ferrets, dogs, minipigs and cynomolgus monkeys. Pivotal repeat-dose toxicity studies were conducted in mice and monkeys, genotoxicity was studied in vitro and in mice, carcinogenicity was investigated in rats and mice, reproductive and developmental toxicity were investigated in rats and rabbits, and toxicity in juvenile animals was investigated in minipigs. The nonclinical safety evaluation of teduglutide is complemented by a comprehensive investigation of its toxicokinetic properties in the abovementioned animal species.

The below table outlines the safety concerns which have arisen during the nonclinical programme and their possible relevance to human usage.

Key Safety Findings	Relevance to human usage
Repeat-dose toxicity studies The pattern of toxicity after repeated dosing has been consistent amongst the various species studied, with the majority of the findings observed being associated with the pharmacological activity of the drug or with an extended pharmacological effect. In studies ranging from 14 days to 26 weeks in mice, and up to 1 year in monkeys, the primary findings have been an increase in intestinal weight and length, associated with structural changes in the intestinal mucosa. A hyperplastic and/or hypertrophic response has been reported in the intestines (the target organ for the pharmacological activity of the drug). Hyperplasia/hypertrophy was also found in intrahepatic and extrahepatic bile ducts in mouse and monkey, gallbladder in mouse and monkey, stomach in monkey, and pancreatic ducts in monkey. The intestinal changes in the toxicity studies occurred in a non-dose-related manner and were reported at all teduglutide doses. The lack of dose-related effects was expected as the lowest doses selected in toxicity studies were above those that produced the maximal pharmacological effect. For the non-target organs, the findings are considered to represent an extension of the pharmacology of the drug. The intestinal changes were partially resolved during the recovery period. The effects in the other organs either partially	AEs associated with the gallbladder, biliary ducts, and pancreas, were observed in humans.

Key Safety Findings	Relevance to human usage
or completely resolved during the recovery period.	
Epithelial hyperplasia in the gallbladder, biliary ducts, and pancreatic ducts In the repeat dose-toxicity studies, hyperplasia of the gallbladder and biliary ducts was seen in mice and monkeys but did not lead to obstruction. Following a recovery period, these changes often resolved partially, if not completely. No clinical signs or symptoms were associated with these findings, and there were no associated changes in clinical chemistry that would suggest possible related adverse effects. This observation is in line with the known pharmacological activity of teduglutide.	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, Teduglutide treatment should be discontinued. 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 teduglutide treatment should be reassessed. 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 teduglutide treatment should be reassessed. 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.
Intestinal polyps Described in nonclinical studies in the literature [24-26]. In animals, repeated administration of GLP-2 promotes the expansion of the intestinal mucosa via the stimulation of crypt cell growth and the reduction of enterocyte apoptosis [27]. GLP-2 binds to a specific G-protein coupled receptor, known as GLP-2R. Expression of the GLP-2R contributes to the tissue specific action of GLP-2 [28]. The effects on the intestinal epithelium upon GLP-2R stimulation are likely the result of secretion of down-stream mediators such as Insulin like growth factor (IGF)-1, ErbB signalling and Keratinocyte growth factor (KGF) [27,29-31]. Thus, based on mediator release, teduglutide bears the potential risk to enhance the growth of colon polyps. Teduglutide did not show a genotoxic potential in nonclinical studies.	Teduglutide may potentially enhance the growth of polyps and may pose a risk for subjects with known and unidentified colonic adenomas.

[redacted]

Key Safety Findings	Relevance to human usage
Increased occurrence of benign intestinal neoplasms was observed in rats after life-long teduglutide treatment at a dose that was 700-fold higher than the anticipated clinical dose in humans. Increased benign tumours of the gallbladder were noted in mice following life-long teduglutide administration. Additionally, adenocarcinoma in the jejunum was observed at a dose that was 250-fold higher than the recommended therapeutic dose.	
Benign neoplasia of the GI tract including the hepatobiliary system In animals, repeated administration of GLP-2 promotes the expansion of the intestinal mucosa via the stimulation of crypt cell growth and the reduction of enterocyte apoptosis [27,32]. In a 2-year rat carcinogenicity study, increased occurrence of jejunal adenoma and cholangioma was observed in rats after life-long teduglutide treatment. The neoplasms occurred primarily in the 35 mg/kg/day treatment group. However, 1 jejunal adenoma was observed in an animal of the 3 mg/kg/day treatment group and 1 cholangioma was observed in an animal of the 10 mg/kg/day treatment group. In a mouse carcinogenicity study, an increased occurrence of papillary adenoma in the gallbladder at doses ≥ 1 mg/kg/day was observed in mice following life-long teduglutide treatment. The effects on the intestinal epithelium are likely mediated through secretion of down-stream trophic factors such as IGF-1, ErbB signaling and KGF [27,29-31].	Due to the properties of teduglutide, which are potentially mediated through trophic factor release, teduglutide may potentially enhance the growth of benign tumours in the GI tract and the hepatobiliary system.
Tumour-promoting ability In animals, repeated administration of GLP-2 promotes the expansion of the intestinal mucosa via the stimulation of crypt cell growth and the reduction of enterocyte apoptosis [27,32]. The effects on the intestinal epithelium are likely mediated through secretion of down-stream trophic factors such as IGF-1, ErbB signalling and KGF [27,30,31]. In a 2-year rat carcinogenicity study, an increase in benign tumours in the bile duct and jejunum was observed. In a 2-year mouse study, an increase in papillary adenoma was noted. Adenocarcinoma in the jejunum was also	Due to the properties of teduglutide, which are potentially mediated through trophic factor release, teduglutide may potentially enhance the growth of benign tumours in the GI tract and the hepatobiliary system.

Key Safety Findings	Relevance to human usage
observed at the highest dose.	
Inflammation at the site of injection Treatment-related inflammatory lesions at the injection sites were observed in all nonclinical animal species. In the juvenile minipig and monkeys, treatment-related granulomatous inflammation at injection sites was observed with dose-dependent increases in severity. The lesions were most pronounced in the monkey and were consistently observed in all monkey studies (14 days to 52 weeks). Macroscopically, the lesions were described as increased thickness of injection sites, raising, swelling, and ulcers. Histopathologically, the lesions are characterised by minimal to severe granulomatous inflammation associated with haemorrhage, oedema, degeneration/necrosis, arteritis/periarteritis and fibrinoid necrosis of the arterial wall. The severity of the injection site changes improved significantly at the end of the recovery phases.	Non-serious mild to moderate skin reactions were seen in subjects exposed to teduglutide clinical trials, although these occurred at a similar rate to the placebo group.
Genotoxicity and carcinogenicity Teduglutide was negative in standard in vitro and in vivo genotoxicity studies. In a 2-year rat carcinogenicity study, an increase in benign tumours in the bile duct and jejunum was observed. In a 2-year mouse carcinogenicity study an increased occurrence of papillary adenoma in the gallbladder was noted. Adenocarcinoma in the jejunum at the highest dose was also observed.	The current label notes the drug is contraindicated in patients with active or suspected malignancy and in patients with a history of malignancies in the GI tract including the hepatobiliary system and pancreas within the last 5 years. 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. Based on the concerns derived from preclinical studies and the proposed mechanism of action with the trophic effects on intestinal mucosa, there appears 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.
Reproductive toxicity studies Teduglutide did not affect reproductive performance, early embryonic development or sperm parameters in rats, did not increase malformations or produce developmental toxicity in rats and rabbits, and did not affect pre and postnatal development in rats.	There are no data from the use of teduglutide in pregnant women. As a precautionary measure it is preferable to avoid the use of teduglutide during pregnancy. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. It is unknown whether teduglutide is excreted in human milk. In rats, mean teduglutide concentration in milk was less than 3% of the

[redacted]

Key Safety Findings	Relevance to human usage
	maternal plasma concentration following a single SC injection of 25 mg/kg. A risk to the breastfed newborn/infant cannot be excluded. As a precautionary measure it is preferable to avoid the use of teduglutide during breastfeeding. There are no data on the effects of teduglutide on human fertility. Animal data do not indicate any impairment of fertility.
Toxicity Studies in Juvenile Animals The same toxicological responses were observed in a 90-day juvenile toxicity study in minipigs at all doses as were observed in adult mice, rats and monkeys. There were no new or unique toxicities that suggested a specific risk in the paediatric population.	Two studies of teduglutide in paediatric subjects aged 1 to 17 years have been completed (TED-C13-003 and TED-C14-006). Overall, the safety profile of teduglutide in children and adolescents was similar to that in adults. There are no clinical data on toxic effects of teduglutide in juveniles or children. Animal data do not indicate a specific toxic risk in the paediatric population.
Antigenicity Teduglutide is considered non-immunogenic in rats and rabbits, while it induces a weak humoral immune response in monkeys. Occurrence of anti-teduglutide antibodies in monkeys was neither associated with a reduction in its pharmacological activity in the intestine, nor was it consistently associated with a decline in the systemic exposure to teduglutide. In the mouse carcinogenicity study, there was evidence of an immunogenic response to teduglutide. Occurrence of neutralizing antibodies was observed; however, there was no apparent impact on teduglutide effects or exposure.	Consistent with the potentially immunogenic properties of medicinal products containing peptides, administration of teduglutide may potentially trigger the development of antibodies. In Studies CL0600-020 and CL0600-021 in SBS subjects who received teduglutide for up to 2.5 years, 49% of subjects developed anti-teduglutide antibodies and 30% of subjects developed antibodies against *Escherichia coli* protein (ECP) (residual host cell protein from the manufacture). In the Paediatric TED-C14-006 study, 16% of children developed anti-teduglutide antibodies after 24 weeks of treatment. The anti-drug antibody formation seen in both adults and Paediatric clinical studies has not been associated with clinically relevant safety findings, reduced efficacy or changed Pharmacokinetic (PK) of teduglutide. The conclusions drawn from available data are limited by lack of neutralising antibody data and potential free drug interference in the assays performed.
Pharmacokinetics In vivo PK studies showed that, following SC administration, teduglutide was rapidly absorbed into the systemic circulation in all species with median C_{max} occurring between 20 and 60 minutes after dosing. Subsequently plasma teduglutide concentrations declined	<u>Absorption</u> Teduglutide was rapidly absorbed from SC injection sites with maximum plasma levels occurring approximately 3-5 hours after dose administration at all dose levels. The absolute bioavailability of SC teduglutide is high (88%). No accumulation of teduglutide was observed

[redacted]

Key Safety Findings	Relevance to human usage
rapidly with a mean terminal phase $t_{1/2}$ ranging from 0.36 to 3.1 hours across the species studied. Consistent with this $t_{1/2}$, teduglutide did not accumulate in plasma upon multiple dosing. Teduglutide is predominantly confined to the systemic circulation, and the clearance values across species were approximately equivalent to the Glomerular filtration rate (GFR), which is consistent with a renal route of clearance. A study performed in rats showed penetration of teduglutide through the blood-brain barrier of 2% to 5%. In addition, there was placental transfer of 0.1% teduglutide into the foetus of pregnant rabbits and secretion ranging from 0.9% to 2.9% of plasma concentrations into milk of lactating rats.	following repeated SC administration. Distribution Following SC administration, teduglutide has a V/F of 26 litres in patients with SBS. Biotransformation The metabolism of teduglutide is not fully known. Since teduglutide is a peptide it is likely that it follows the principal mechanism for peptide metabolism. Elimination Teduglutide has a terminal $t_{1/2}$ of approximately 2 hours. Following IV administration teduglutide plasma clearance was approximately 127 mL/hr/kg, which is equivalent to the GFR. Renal elimination was confirmed in a study investigating PK in subjects with renal impairment. No accumulation of teduglutide was observed following repeated SC administrations. Dose linearity The rate and extent of absorption of teduglutide is dose-proportional at single and repeated SC doses up to 20 mg. *Paediatric population* Following SC administration, similar C_{max} of teduglutide across age groups was demonstrated by population PK modelling. However, lower exposure (AUC) and shorter half-life were seen in paediatric patients 1 to 17 years of age, as compared with adults. The PK 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.
General safety pharmacology *Cardiovascular and Respiratory* With regard to cardiovascular and respiratory effects, IV doses of up to 10 mg/kg did not result in teduglutide-related abnormalities in dogs. Doses up to 300 µg/mL did not affect the human Ether-à-go-go-Related Gene (hERG) channel current. No effects were observed in canine Purkinje fibers in vitro at perfusion concentrations up to 5.8 µg/mL teduglutide.	No safety issue relevant to humans has been identified from nonclinical studies. However, due to increased fluid absorption, patients with cardiovascular disease, such as cardiac insufficiency and hypertension, should be monitored with regard to fluid overload, especially during the initiation of therapy.

[redacted]

Key Safety Findings	Relevance to human usage
Neurologic The neuropharmacological profile of teduglutide has been investigated in rats. An SC dose of up to 25 mg/kg did not produce any apparent neuropharmacological signs, although it is expected that about 2% to 5% of the C_{max} of teduglutide will penetrate the blood-brain barrier.	No safety issue relevant to humans has been identified.
Mechanisms for drug interactions While the native GLP-2(1-33) peptide is rapidly cleaved into the biologically inactive form GLP-2(3-33) by the serine protease DPP-IV, teduglutide shows resistance to DPP-IV cleavage. Nevertheless, the expected metabolism of teduglutide is degradation into smaller peptide fragments, which are eliminated via the kidneys (glomerular filtration). Teduglutide did not cause any significant in vitro inhibition of the individual recombinant CYP450 isoenzymes 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 or 3A4, suggesting that the drug would not be involved in any clinically relevant drug-drug interactions involving hepatic CYP450 mediated metabolism.	No clinical drug-drug interactions are expected to occur. However, there may be a potential for increased absorption of concomitant oral medication use due to the mechanism of action of teduglutide. Subjects receiving oral concomitant medicinal products requiring titration or with a narrow therapeutic index should be monitored closely due to potential increased absorption.
Other toxicity-related information or data In monkey studies, there was an ECP content-related temporary increase in CRP concentrations, peaking at the 24 hours post-treatment sample. Even though a mechanism is not proven, the CRP effect seems to be related to the ECP content in the teduglutide product rather than teduglutide itself.	In clinical studies, modest increases of CRP of approximately 25 mg/L have been observed within the first 7 days of teduglutide treatment, which decreased continuously under ongoing daily injections. After 24 weeks of teduglutide 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 teduglutide for up to 30 months.

AE: Adverse event; IGF-1: Insulinlike growth factor – 1; SC: Subcutaneous; AUC: Area Under the Curve; hERG: The human Ether-à-go-go-Related Gene; CRP: C-Reactive Protein; ECP: Escherichia coli protein; GLP: Glucagon like peptide; SBS: Short Bowel Syndrome.

[redacted]

Part II: Module SIII - Clinical trial exposure

Within the clinical development program, the safety and tolerability of teduglutide was investigated in healthy volunteers, in subjects with SBS, in subjects with Crohn's disease, in subjects with moderately impaired hepatic function and in renally impaired subjects (with moderate renal impairment, severe renal impairment or end stage renal disease).

The overall clinical development program for teduglutide included 27 clinical studies: 15 phase 3 studies, 3 phase 2 studies, 9 phase 1 studies; additionally, there is 1 ongoing registry study. As of May 2021, a total of 718 subjects have been treated with teduglutide and 247 subjects have been treated with placebo/standard of care in the overall clinical development program for teduglutide. Of the 718 subjects treated with teduglutide in the clinical studies, 613 were adult subjects, 97 were paediatric subjects, and 8 were infant subjects.

This represents the studies used to support the adult and the Paediatric indication.

Table SIII.1: Duration of exposure

Cumulative for SBS indications (person time):		
Duration of exposure	**Patients**	**Person time (years)***
Cumulative any exposure	313	422.22
Cumulative at least 4 weeks	290	421.21
Cumulative at least 12 weeks	271	418.41
Cumulative at least 24 weeks	241	408.84
Cumulative at least 52 weeks	174	364.82
Cumulative at least 104 weeks	97	253.73

*Subject-time is calculated as the total exposure for all subjects within a study, converted to years (total exposure/365.25).
Studies for SBS included: ALX-0600-92001, CL0600-020 (core study), CL0600-004 (core study), CL0600-021 (extension study), CL0600-005 (extension study), TED-C13-003 and TED-C14-006, TED-C14-004, SHP633-301 (core study), SHP633-302, SHP633-303 (extension study), SHP633-304 (extension study), SHP633-306.
Subjects can contribute to more than one dose based on incorrectly rechallenged subjects in ALX-0600-92001.

All Phase 2/3 Trials for SBS and Phase 2 Trials for Crohn's Disease - Exposure by Duration

Duration of exposure[1]	**Persons**	**Person time (years)[2]**
Indication: SBS		
Cumulative any exposure	313	422.22
Cumulative at least 4 weeks	290	421.21
Cumulative at least 12 weeks	271	418.41
Cumulative at least 24 weeks	241	408.84
Cumulative at least 52 weeks	174	364.82

Duration of exposure[1]	Persons	Person time (years)[2]
Cumulative at least 104 weeks	97	253.73
Indication: Crohn's Disease		
Cumulative any exposure	94	21.91
Cumulative at least 4 weeks	69	21.08
Cumulative at least 12 weeks	50	18.04
Cumulative at least 24 weeks	1	0.47
Cumulative at least 52 weeks	0	0.00

SBS=short bowel syndrome.
[1] Duration of exposure is defined as: (last dose date – first dose date +1)/7.
[2] Subject-time is calculated as the total exposure for all subjects within a study, converted to years (total exposure/365.25).
Note: Studies for SBS included: ALX-0600-92001, CL0600-020 (core study), CL0600-004 (core study), CL0600-021 (extension study), CL0600-005 (extension study), TED-C13-003, and TED-C14-006. Subjects can contribute to more than 1 dose based on incorrectly rechallenged subjects in ALX-0600-92001.
Note: Studies for Crohn's disease included: CL0600-008 (core study), CL0600-009 (extension study). Subjects with Crohn's disease can contribute to more than 1 dose.

Table SIII.2: Age group and gender

Cumulative exposure (All Phase 2/3 Trials for SBS) for all age/gender groups (person time):				
Age group	**Patients**		**Person time (years)***	
	Male	**Female**	**Male**	**Female**
Infants and toddlers (28 days to <2 years)	9	4	5.61	5.52
Children (2 to <12 years)	60	25	100.95	47.62
Adolescents (12 - <18 years)	6	2	8.67	3.76
Adults (18 - <65 years)	86	96	112.21	104.71
Elderly				
65 - <75 years	7	12	11.87	13.73
75 - <85 years	3	3	1.10	6.46

*Subject-time is calculated as the total exposure for all subjects within a study, converted to years (total exposure/365.25).
Studies for SBS included: ALX-0600-92001, CL0600-020 (core study), CL0600-004 (core study), CL0600-021 (extension study), CL0600-005 (extension study), TED-C13-003 and TED-C14-006, TED-C14-004, SHP633-301 (core study), SHP633-302, SHP633-303 (extension study), SHP633-304 (extension study), SHP633-306. Subjects can contribute to more than one dose based on incorrectly rechallenged subjects in ALX-0600-92001.

All Phase 2/3 Trials for SBS and Phase 2 Trials for Crohn's Disease – Exposure by Age Group and Gender

Age group	Persons		Person time (years)[1]	
	Male	Female	Male	Female
Indication: SBS				
Infants and toddlers (28 days to <2 years)	9	4	5.61	5.52
Children (2 to <12 years)	60	25	100.95	47.62
Adolescent (12 - <18 years)	6	2	8.67	3.76
Adults (18 - <65 years)	86	96	112.21	104.71
Elderly				
65 - <75 years	7	12	11.87	13.73
75 - <85 years	3	3	1.10	6.46
Indication: Crohn's Disease				
Age group	**Persons**		**Person time (years)[1]**	
<65 years of age	45	48	10.00	11.52
≥65 years of age	0	1	0	0.39

SBS=short bowel syndrome.
[1]Subject-time is calculated as the total exposure for all subjects within a study, converted to years (total exposure/365.25).
Studies for SBS included: ALX-0600-92001, CL0600-020 (core study), CL0600-004 (core study), CL0600-021 (extension study), CL0600-005 (extension study), TED-C13-003 and TED-C14-006, TED-C14-004, SHP633-301 (core study), SHP633-302, SHP633-303 (extension study), SHP633-304 (extension study), SHP633-306.
Subjects can contribute to more than one dose based on incorrectly rechallenged subjects in ALX-0600-92001.
Note: Studies for Crohn's included: CL0600-008 (core study), CL0600-009 (extension study). Subjects with Crohn's can contribute to more than 1 dose.

Table SIII.3: Dose

Cumulative for all doses of exposure (person time) for SBS:		
Dose of exposure	**Patients**	**Person time (years)***
0.0125 mg/kg/day	8	1.72
0.025 mg/kg/day	38	14.41
0.03 mg/kg/day	3	0.17
0.05 mg/kg/day	244	373.84

Cumulative for all doses of exposure (person time) for SBS:		
Dose of exposure	**Patients**	**Person time (years)***
0.10 mg/kg/day	49	31.67
0.15 mg/kg/day	5	0.40

*Subject-time is calculated as the total exposure for all subjects within a study, converted to years (total exposure/365.25).
Studies for SBS included: ALX-0600-92001, CL0600-020(core study), CL0600-004(core study), CL0600-021(extension study), CL0600-005 (extension study), TED-C13-003 and TED-C14-006, TED-C14-004, SHP633-301(core study), SHP633-302, SHP633-303(extension study), SHP633-304(extension study), SHP633-306.
Subjects can contribute to more than one dose based on incorrectly rechallenged subjects in ALX-0600-92001.

All Phase 2/3 Trials for SBS and Phase 2 Trials for Crohn's Disease - Exposure by Dose

Indication: SBS		
Dose of exposure	**Persons**	**Person time (years)[1]**
0.0125 mg/kg/day	8	1.72
0.025 mg/kg/day	38	14.41
0.03 mg/kg/day	3	0.17
0.05 mg/kg/day	244	373.84
0.10 mg/kg/day	49	31.67
0.15 mg/kg/day	5	0.40
Indication: Crohn's Disease		
Dose of exposure	**Persons**	**Person time (years)[1]**
0.05 mg/kg/day	24	3.19
0.10 mg/kg/day	77	15.64
0.20 mg/kg/day	25	3.08

SBS=short bowel syndrome.
[1]Subject-time is calculated as the total exposure for all subjects within a study, converted to years (total exposure/365.25).
Studies for SBS included: ALX-0600-92001, CL0600-020 (core study), CL0600-004 (core study), CL0600-021 (extension study), CL0600-005 (extension study), TED-C13-003 and TED-C14-006, TED-C14-004, SHP633-301 (core study), SHP633-302, SHP633-303 (extension study), SHP633-304 (extension study), SHP633-306.
Subjects can contribute to more than one dose based on incorrectly rechallenged subjects in ALX-0600-92001.
Note: Studies for Crohn's disease included: CL0600-008 (core study), CL0600-009 (extension study).
Subjects with Crohn's disease can contribute to more than 1 dose.

[redacted]

Table SIII.4: Ethnic origin

All Phase 2/3 Trials for SBS - Exposure By Ethnic Origin		
Ethnic origin	**Patients**	**Person time (years)***
White	250	331.24
Asian	33	40.55
Black or African American	19	29.93
Not allowed based on local regulations	5	12.36
Other	5	7.91
Not applicable	1	0.23

*Subject-time is calculated as the total exposure for all subjects within a study, converted to years (total exposure/365.25).
Studies for SBS included: ALX-0600-92001, CL0600-020 (core study), CL0600-004 (core study), CL0600-021 (extension study), CL0600-005 (extension study), TED-C13-003 and TED-C14-006, TED-C14-004, SHP633-301 (core study), SHP633-302, SHP633-303 (extension study), SHP633-304 (extension study), SHP633-306.
Subjects can contribute to more than one dose based on incorrectly rechallenged subjects in ALX-0600-92001.

All Phase 2/3 Trials for SBS and Phase 2 Trials for Crohn's Disease - Exposure by Ethnic Origin

Ethnic origin	Persons	Person time (years)[1]
Indication: SBS		
White	250	331.24
Asian	33	40.55
Black or African American	19	29.93
Not allowed based on local regulations	5	12.36
Other	5	7.91
Not applicable	1	0.23
Indication: Crohn's Disease		
White	81	19.17
Black	5	1.23
Other	8	1.51

SBS=short bowel syndrome.
[1]Subject-time is calculated as the total exposure for all subjects within a study, converted to years (total exposure/365.25).

[redacted]

Studies for SBS included: ALX-0600-92001, CL0600-020 (core study), CL0600-004 (core study), CL0600-021 (extension study), CL0600-005 (extension study), TED-C13-003 and TED-C14-006, TED-C14-004, SHP633-301 (core study), SHP633-302, SHP633-303 (extension study), SHP633-304 (extension study), SHP633-306.
Subjects can contribute to more than one dose based on incorrectly rechallenged subjects in ALX-0600-92001.
Studies for Crohn's disease included: CL0600-008 (core study), CL0600-009 (extension study). Subjects with Crohn's disease can contribute to more than 1 dose.

Part II: Module SIV - Populations not studied in clinical trials

SIV.1. Exclusion criteria in pivotal clinical studies within the development programme

Exclusion Criteria Pivotal Clinical Studies within the Development Programme

Exclusion criterion	Reason for exclusion	Included as missing information	Justification for NOT including as missing information or for NOT being Contraindication
Hypersensitivity to the active substance or to any of the excipients listed in the current label, or trace residues of tetracycline.	Standard exclusion criteria - a general safety precaution.	No	Included as contraindication.
Active or suspected malignancy.	As a trophic factor, a potential for increased risk for accelerating active or suspected malignancy cannot be excluded.	No	Included as contraindication.
Subjects with a history of malignancies in the GI tract including the hepatobiliary system and pancreas within the last 5 years.	As a trophic factor with high specificity for intestinal epithelium which may be present in the intestinal tract and hepatobiliary system a potential for exacerbation cannot be excluded.	No	Included as contraindication.
Female subjects of child-bearing potential not willing to use contraception. Pregnant or lactating women.	Standard requirement to prevent exposing a developing foetus or infant to a drug that has not yet been shown to be effective.	Yes	Not applicable.
Subjects who had a history of multiple drug allergies or current evidence of clinically relevant allergies or idiosyncrasy to drugs or food.	During clinical trials, a hypothetical concern may be that active allergies may impact outcomes often seen in the target SBS	No	This is of no concern in real world clinical practice since subjects are being monitored for symptoms as it relates to diet and

Exclusion criterion	Reason for exclusion	Included as missing information	Justification for NOT including as missing information or for NOT being Contraindication
	population such as abdominal pain and output/diarrhoea.		new medications on a regular basis.
A history of cancer or clinically significant lymphoproliferative disease with fewer than 5 years documented disease-free state. This did not include resected cutaneous basal or squamous cell carcinoma, or in situ cervical cancer.	As a trophic factor, there existed a potential that teduglutide may promote the growth of pre-existing neoplasm in an at-risk population.	No	The available nonclinical data indicated that teduglutide may promote the growth of pre-existing neoplasms in an at-risk population. However, it is believed that this potential mechanism is limited to the GI tract including the hepatobiliary system, i.e., the site of pharmacological activity of teduglutide. Revestive is contraindicated for patients with active or suspected malignancy and for patients with a history of malignancies in the gastrointestinal tract, including the hepatobiliary system and pancreas within the last five years.
Bowel obstruction or any condition that may predispose to its development (e.g., clinically significant unresolved intestinal stricture, adhesions, or any condition that would place the subject at risk for developing overt bowel obstruction), intestinal perforation, or significant GI haemorrhage. A history of structural abnormality or pathology of the GI tract or diseases/conditions that could affect GI motility.	Theoretical concerns existed that utilising an intestinal trophic factor may exaggerate known obstructions or dysmotility.	No	This is an expected potential complication of the SBS population with a history of multiple surgeries and its underlying aetiology that led to SBS. A low number of obstructions/stenosis occurred during clinical trials. These obstructions/stenoses were adequately managed during clinical trials where subjects were conservatively

Exclusion criterion	Reason for exclusion	Included as missing information	Justification for NOT including as missing information or for NOT being Contraindication
Subjects who had a previous or present history of gallstone disease and surgery involving the GI tract (including the gallbladder). However, appendectomy was acceptable. Intestinal or other major surgery scheduled within the time frame of the study. Current ileostomy or colostomy or extensive external fistulisation (> 3 external fistulae that were expressible with gentle compression).			managed by giving bowel rest and decompression. All subjects were able to continue teduglutide and complete clinical trials. Only 1 subject required a surgical intervention. Listed as intestinal obstruction in Special warnings and precautions for use. "Gastrointestinal stenosis and obstruction" is characterised as important identified risk. Disease of the gallbladder is common to the SBS population with up to 30% of subjects with SBS having their gallbladder removed prior to participation in clinical trials. No significant differences in subjects with or without gallbladder disease were seen in terms of safety or efficacy. Listed as gallbladder and biliary tract disease in Special Warnings and Precautions for Use. Biliary AEs is characterised as important identified risk.
SBS subjects who had < 50% of colon in continuity More than 4 SBS-related or PN-related hospital admissions (e.g., catheter	This was considered an indicator of severity of SBS and marker of instability in participating in a long-	No	Teduglutide results in clinical trials revealed that clear efficacy was seen in a range of subjects with varying

Exclusion criterion	Reason for exclusion	Included as missing information	Justification for NOT including as missing information or for NOT being Contraindication
sepsis, bowel obstruction, severe water-electrolytes disturbances) within 12 months prior to the screening.	term outpatient study.		lengths of remnant bowel and with/without colon in continuity. This included subjects who were able to achieve complete parenteral support independence. More than 70% of teduglutide subjects were able to complete long-term trials up to 30 months after first exposure.
Subjects with a previous or present history of malabsorption, pancreatic disease and GI disorders such as irritable bowel syndrome, Crohn's disease or ulcerative colitis. Nutritionally compromised subjects requiring enteral/parenteral therapy to maintain weight. Special dietary requirements that would have precluded a subject's acceptance of a high fat or high caloric, standardised meal.	Active GI conditions and specialised diets leading to malabsorption related to insufficiency or active inflammation were considered to be potential confounders in clinical trials where SBS population had similar symptoms of diarrhoea and abdominal pain.	No	There was no apparent exacerbation of underlying GI conditions that may have been part of the underlying aetiology for SBS such as Crohn's disease in clinical trials (up to 20% of trial participants had history of Crohn's disease). There was no difference appreciated in safety and efficacy in these conditions. In summary, conditions that result from decreased absorptive capacity benefit from teduglutide intestinotrophic effect. Subjects' clinical nutritional statuses were maintained throughout clinical trials despite significant parenteral support reductions. This indicates that teduglutide was able to enhance intestinal rehabilitation and allow more efficient uptake of orally

Exclusion criterion	Reason for exclusion	Included as missing information	Justification for NOT including as missing information or for NOT being Contraindication
			ingested diets.
Subjects who had a previous or present history of any clinically significant neurological, GI, renal, urologic, hepatic, cardiovascular, psychological, pulmonary, metabolic, endocrine, immunologic, dermatologic (e.g., psoriasis, eczema, atopic dermatitis), or hematologic disorder or disease, or any other major disorder or disease. The presence of any of the excluded disease states: On-going radiation enteritis or the presence of damaged enteral tissue due to radiation enteritis, celiac disease, refractory or tropical sprue, pseudo-obstruction, active inflammatory bowel disease which required chronic systemic immunosuppressant therapy that had been introduced or changed during the last 3 months, inflammatory bowel disease that required chronic systemic immunosuppressant therapy for symptom control. A history of thromboembolic disease (e.g., phlebitis, pulmonary embolus) or known congenitally or acquired prothrombotic disorder (e.g., protein C deficiency). Subjects who had received any treatment agents known to alter the major organs or systems, such as barbiturates, phenothiazines, and cimetidine, within 30 days of the start of dosing. A proneness to orthostatic dysregulation, fainting, or	Standard requirement for clinical trial participants in placebo-controlled trials aimed at assessing safety and efficacy to be considered otherwise clinically stable to undergo investigational drug intervention and maintain compliance with study procedures. Active medical conditions as listed here may have confounding effects on assessing endpoints and outcomes in otherwise stable SBS population.	No	Teduglutide has been shown to be safe and effective in conditions related to SBS and inadequate absorptive capacity. 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 is included as missing information.

Exclusion criterion	Reason for exclusion	Included as missing information	Justification for NOT including as missing information or for NOT being Contraindication
blackouts.			
A history of hepatitis, pancreatitis or cholecystitis. Subjects with the acceptable Child-Pugh score (Grade B, score of 7 to 9), which was associated with conditions such as metastatic cancer, rather than impaired hepatic function.	The SBS population is at high risk for comorbid conditions related to gallbladder and pancreatic disorders.	No	SBS subjects require close monitoring for hepatobiliary and pancreatic conditions. "Pancreatic AEs" is characterized as an important identified risk. Listed in PI as monitoring of small bowel, gallbladder and bile ducts, and pancreas in general precautions.
A history of angina or cardiac arrhythmia requiring drug or device intervention or clinically significant congestive heart failure or other clinically significant cardiac disease. A history of myocardial infarction within 12 months of screening. ECG abnormalities of clinical relevance (e.g., QTc according to Bazett's >450 ms in men and in women, PR ≥210 ms; or QRS ≥120 ms). A history of additional risk factors for torsades de pointes, (e.g., heart failure, hypokalaemia, and family history of long QT syndrome). Subjects with a resting heart rate <50 bpm, systolic blood pressure <90 mmHg, diastolic blood pressure <50 mmHg.	Standard requirement for clinical trial participants in placebo-controlled trials aimed at assessing safety and efficacy to be considered otherwise clinically stable to undergo investigational drug intervention and maintain compliance with study procedures.	No	Subjects who have a cardiac history are at risk for fluid overload. These subjects should continue to be monitored closely for continued evaluation. "Cardiovascular AEs associated with fluid overload" is characterized as an Important identified risk. Listed as a special consideration in Special warnings and Precautions for Use.
Clinically relevant abnormalities in clinical chemical, haematological or in any other laboratory	Standard requirement for clinical trial participants in placebo-controlled trials aimed at	No	It is expected the SBS population is considered medically complex and may

Exclusion criterion	Reason for exclusion	Included as missing information	Justification for NOT including as missing information or for NOT being Contraindication
variables at the time of randomisation. Haemoglobin level <10.0 g/dL at screening. Total bilirubin ≥2x ULN (for subjects with Gilbert's disease, direct (conjugated) bilirubin ≥2xULN), aspartate aminotransferase ≥5xULN, serum creatinine ≥2xULN. A history or evidence of congenital non-haemolytic hyperbilirubinemia.	assessing safety and efficacy to be considered otherwise clinically stable to undergo investigational drug intervention and maintain compliance with study procedures.		have as a consequence of inadequate absorptive capacity significant other co morbidities in real world clinical setting. There is no safety reason to contraindicate use in these subjects.
Previous or concomitant use of native GLP-2 or hGH, IV glutamine, octreotide, GLP-1 analogue, or DPP-IV.	The use of these compounds may be confounding factors in assessing endpoints of safety and efficacy in randomised placebo-controlled trials.	No	There are no expected safety concerns in the real-world clinical practice.
Chronic or clinically relevant acute infections, especially of the intestinal tract requiring antibiotic therapy at the time of screening or baseline. Positive human immunodeficiency virus or hepatitis virus tests.	Standard requirement for clinical trial participants to be considered otherwise clinically stable to undergo investigational drug intervention and maintain compliance with study procedures. Signs and symptoms of these chronic diseases may be confounding factors in the SBS study population including diarrhoea, nausea, weight loss, abdominal pain.	No	There are no expected safety concerns in the real-world clinical practice.
BMI <15 kg/m^2 or >30 kg/m^2.	Subjects with a BMI < 15 kg/m^2 may be malnourished and may also be hypoproteinaemic and more susceptible to fluid overload and its consequent effects. Subjects with BMI	No	As long as the subject is being carefully monitored, there are no expected safety concerns in the real-world clinical practice. There is no safety reason to

Exclusion criterion	Reason for exclusion	Included as missing information	Justification for NOT including as missing information or for NOT being Contraindication
	>30 kg/m^2 are more likely to be obese and suffer from other medical conditions like type 2 diabetes mellitus and cardiovascular disease.		contraindicate use in these subjects.

BMI=body mass index; ECG=electrocardiogram; GI=gastrointestinal; GLP-2=glucagon-like peptide 2; hGH=human growth hormone; QTc=corrected QT interval; ULN=upper limit of normal; SBS=short bowel syndrome.

SIV.2. Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

Limitations of adverse drug reaction detection in the clinical development programme are presented in below table.

Limitations of Adverse Drug Reaction Detection Common to Clinical Study Development Programmes

Ability to Detect Adverse Reactions	Limitation of Study Programme	Discussion of Implications for Target Population
Which are common	Based on 313 subjects in clinical trials for SBS and 94 for Crohn's disease.	ADR with a frequency >1 in 95 could be detected if there were no background incidence.
Due to prolonged exposure	106 individuals with SBS had a cumulative exposure of at least 52 weeks and 43 individuals have had a cumulative exposure for at least 104 weeks.	The duration of exposure for subjects who started teduglutide in Study CL0600-020 and continued in Study CL0600-021 and Study TED-C11-001 is shown in the table below. In long-term Study TED-C11-001, 14 subjects were enrolled following up to 30 months of treatment with teduglutide (24 weeks of exposure in the in the placebo-controlled study, CL0600-020, and 24 months of exposure in the open label extension study, CL0600 021). Safety and efficacy data from this study indicated that long-term treatment with teduglutide continues to be safe and well tolerated while efficacy is maintained or further enhanced. The SAE profile for the subjects with this exposure is similar to the SAE
Due to cumulative effects		
Which have a long latency		

Ability to Detect Adverse Reactions	Limitation of Study Programme	Discussion of Implications for Target Population
		profile seen with shorter exposures. No safety signals were identified with long-term use.

ADR=adverse drug reaction; SAE=serious adverse event; SBS=short bowel syndrome. Source: NYC-046-01.

Duration of Continuous Exposure in Studies CL0600-020, CL0600-021 and TED-C11-001

Parameter	Statistic	CL0600-020 Not Treated/Placebo (N=51)	CL0600-020/ Teduglutide (N=37)	All Teduglutide (N=88)
≥ 1 year	n (%)	36 (70.6%)	34 (91.9%)	70 (79.5%)
≥ 2 years	n (%)	29 (56.9%)	31 (83.8%)	60 (68.2%)
≥ 3 years	n (%)	2 (3.9%)	2 (5.4%)	4 (4.5%)

Source: GATTEX® PBRER (Periodic Benefit Risk-Evaluation Report) #3, Table 9

SIV.3. Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.2: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development program.
Breastfeeding women	
Patients with relevant comorbidities:	
Patients with hepatic impairment	Teduglutide has not been studied in patients with severe hepatic impairment. A total of 12 subjects (0.03 PY) with moderate hepatic impairment received a single dose of 20 mg teduglutide in a phase 1 study (CL0600-017).
Patients with renal impairment	Phase 1 Study CL0600-018 was conducted in subjects with moderate, severe or end stage renal. Trial was conducted with 6 groups in total with 6 subjects in each group. All subjects received a single subcutaneous injection of 10 mg teduglutide. - 6 subjects with moderate renal impairment (0.016 PY); - 6 subjects with severe renal

[redacted]

Type of special population	Exposure
	impairment (0.016 PY); - 6 subjects with end-stage renal diseases (0.016 PY); - Matched health subjects: 3 groups of 6 subjects.
Patients with cardiovascular impairment	Not included in the clinical development program. A Phase 1 study (C09-001) was conducted on healthy volunteers to determine the effect of a single dose of teduglutide (5 mg or 20 mg) on cardiac repolarisation, heart rate and conduction revealed no prolongation of the QTcF. The results of the thorough QT study (study C09-001) were negative for both doses.
Immunocompromised patients	Not included in the clinical development program.
Patients with a disease severity different from inclusion criteria in clinical trials	Not applicable.
Population with relevant different ethnic origin	In completed SBS trials, the majority of subjects were white (250, 331.24 PY), followed by Asians (33, 40.55 PY), and black (19, 29.93 PY). See above Table SIII.4 for exposure in person-years for each race exposed to teduglutide in SBS clinical studies.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program.
Subjects with severe, clinically unstable concomitant diseases	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 five years.
Other	
Children under 18 years of age	There were 106 paediatric patients (age 4 months to less than 18 years) exposed to teduglutide during the clinical development programme till date. Of the 108 patients, 13 patients were infants. The details can be found in Table SIII.2.
Elderly	No specific concerns have been identified for the use of teduglutide in the elderly. The exposure in person-years of elderly

[redacted]

Type of special population	Exposure
	(> 65 years of age) subjects is shown in Table SIII.2.

Children

Per the SmPC, the safety and efficacy of Revestive in children below 4 months of age have not been established.

Elderly

Of the 190 subjects with SBS who received teduglutide in Phase 2/3 clinical studies, 13.2% (25/190) were ≥65 years of age. Six of 190 (3.2%) SBS subjects ≥75 years were exposed to teduglutide in Phase 2/3 SBS studies. In the entire development program, 43/566 subjects (7.6%) ≥65 years of age were included in clinical studies, although not specifically studied. No specific concerns have been identified for the use of teduglutide in the elderly. Population PK analysis of data from study CL0600-004 indicated that age does not have an effect on the PK of teduglutide; therefore, subjects aged 65 and older are not expected to have different teduglutide exposure than subjects less than 65 years of age because of age alone. Study CL0600-018 also included a description of the PK of teduglutide following SC administration of 10 mg teduglutide in elderly (≥65 years) healthy subjects compared to non-elderly healthy subjects. No difference in the plasma PK parameters AUC_{inf} or C_{max} was detected between subjects younger than 65 years versus subjects older than 65 years and there was no marked difference in the frequency of AEs regarding age. However, older subjects may have a potentially higher risk of fluid overload, because the prevalence of underlying cardiovascular disease is greater in this subject group [33].

No dose adjustment is necessary in subjects above the age of 65 years.

Pregnant or Breastfeeding Women

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.

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 newborn/infant cannot be excluded. As a precautionary measure, it is preferable to avoid the use of Revestive during breastfeeding.

Subjects with Hepatic Impairment

In a Phase 1 study (CL0600-017) the effect of hepatic impairment on the PK of teduglutide following subcutaneous administration of 20 mg teduglutide was investigated. The maximum exposure and the overall extent of exposure to teduglutide following single 20 mg subcutaneous doses were lower (10-15%) in subjects with moderate hepatic impairment relative to those in healthy matched controls. No dose adjustment is necessary for patients with mild and moderate hepatic impairment based on a study conducted in Child-Pugh grade B subjects. The data from use in subjects with moderate hepatic impairment do not suggest a need for restricted use. Revestive has not been studied in subjects with severe hepatic impairment.

Subjects with Renal Impairment

A specific study (CL0600-018) has been conducted in renally impaired subjects. This study conducted in subjects with moderate, severe or end-stage renal impairment has demonstrated that the total exposure to teduglutide (C_{max} and AUC_{inf}) increases with the severity of the renal impairment. The primary PK parameters of teduglutide increased up to a factor of 2.6 (AUC_{inf}) and 2.1 (C_{max}) for the subjects with end stage renal impairment compared to healthy subjects. In a Phase 1 study, the effect of renal impairment on the PK of teduglutide following subcutaneous administration of 10 mg teduglutide was investigated. With progressive renal impairment up to and including end stage renal disease the primary pharmacokinetic parameters of teduglutide increased up to a factor of 2.6 (AUC_{inf}) and 2.1 (C_{max}) compared with healthy subjects. No dose adjustment is

necessary for adult or paediatric patients with mild renal impairment. In adult or paediatric patients with moderate and severe renal impairment (creatinine clearance less than 50 mL/min), and end-stage renal disease, the daily dose should be reduced by 50%.

Subjects with Other Relevant Comorbidity

Cardiac Impairment

Safety pharmacology studies did not reveal any changes that would indicate a potential risk for QT prolongation in humans at the recommended clinical dose of 0.05 mg/kg/day. Teduglutide has not specifically been studied in subjects with cardiac disease to date.

A Phase 1 study (C09-001) to determine the effect of a single dose of teduglutide (5 mg or 20 mg) on cardiac repolarisation, heart rate and conduction revealed no prolongation of the QTcF. Thus, the results of the thorough QT study (study C09-001) were negative for both doses.

Due to the recognised risk of changes in electrolyte and fluid balances which may be associated with increased cardiovascular risk in susceptible subjects with SBS, a clinical safety assessment of teduglutide was initially performed focusing on the 6 largest studies of the teduglutide program including all studies with a duration of longer than 7 days (i.e., studies CL0600-022, ALX-0600-92001, CL0600-008, CL0600-009, CL0600-004 and CL0600-005). As a result, a tendency in the occurrence of treatment-emergent adverse events (TEAEs) associated with fluid overload under teduglutide treatment compared with placebo treatment was seen, which can possibly be explained by the mechanism of action of teduglutide. No clear trends in the occurrence of 'cardiovascular AEs' could be identified. However, it cannot be excluded that in single cases in predisposed subjects, the fluid overload may lead to cardiovascular AEs such as congestive heart failure. Subjects with underlying conditions predisposing to fluid retention may become hypervolemic when responding to teduglutide therapy due to increased GI fluid and sodium absorption.

A re-analysis of these events in the Phase 2/3 SBS studies (ALX-0600-92001, CL0600-004, CL0600-005, CL0600-020, and CL0600-021) confirmed these findings. Overall, 49/190 subjects (25.8%) treated with teduglutide 0.05 or 0.10 mg/kg/day had 108 events associated with fluid overload in these studies. Most of the events were mild or moderate with only 10 subjects (5.3%) having 11 severe events. The severe events included pleural effusion, weight increased, oedema peripheral (4 events), pulmonary hypertension, dyspnoea, hyponatremia, hypertension, and portal hypertension. The most frequently occurring events (i.e., occurring in greater than 3% of the subjects) were oedema peripheral {23/190 (12.1%)}, weight increased {8/190 (4.2%)}, hypokalaemia {8/190 (4.2%)}, dyspnoea {7/190 (3.7%)}, and hypertension {6/190 (3.2%)}. There does not appear to be a pattern to the occurrence of these events in relation to exposure, with the onset of the events occurring throughout the duration of exposure (≥ 72 weeks).

Due to increased fluid absorption, subjects with cardiovascular disease, such as cardiac insufficiency and hypertension, should be monitored with regard to fluid overload, especially during initiation of therapy. Subjects 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 PN 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 teduglutide treatment should be reassessed.

Benign and malignant neoplasia

Teduglutide is an analogue of human GLP-2, a peptide which is believed to accelerate growth of crypts and microvilli and to inhibit apoptosis of the intestinal epithelium. In a 2-year rat carcinogenicity study, an increase in benign tumours in the bile duct and jejunum was observed. In a 2-year mouse carcinogenicity study, an increased occurrence of papillary adenoma in the gallbladder was noted. Adenocarcinoma in the jejunum at the highest dose was also observed. 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. As a precaution, in clinical studies all subjects underwent a full colonoscopy with removal of all detected polyps prior to teduglutide therapy. Subjects with a history of cancer within

the last 5 years before start of the studies were excluded from the clinical development program. Although not seen in clinical studies, the potential of teduglutide to enhance the growth of pre-existing polyps is considered a risk for humans. In addition, a general tumour promoting ability affecting benign and malignant tumours cannot be excluded. The SmPC informs that Revestive has not been studied in subjects with malignancies within the last 5 years. Revestive is contraindicated in subjects with active or suspected malignancy. Revestive is also contraindicated in subjects with a history of malignancies in the GI tract including the hepatobiliary system and pancreas within the last 5 years. The SmPC advises that a colonoscopy with removal of polyps should be done 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 five-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. The SmPC also advises that subjects should be monitored clinically for small bowel neoplasia. If GI or hepatobiliary neoplasia is found, it should be removed. In case of malignancy, Revestive therapy should be discontinued. In children and adolescents, prior to initiating treatment with Revestive, faecal occult blood testing should be done. Colonoscopy/sigmoidoscopy is required if there is evidence of unexplained blood in the stool. Subsequent faecal occult blood testing should be done annually in children and adolescents while they are receiving Revestive.

History or presence of any clinically significant GI (other than colorectal cancer, polyposis, active Crohn's disease or indication for treatment), psychological, pulmonary, metabolic (other than diabetes), urologic or hematologic diseases

These exclusion criteria were applied to the completed and on-going clinical studies of teduglutide. The impact of teduglutide on these disease conditions has not been specifically evaluated. Where the condition has been treated, is not likely to recur or forms only part of the subject's medical history, risk minimisation is not considered necessary. Where the disease is ongoing, subjects receiving oral concomitant medications requiring titration or with a narrow therapeutic index should be monitored closely due to potential increased absorption. As far as possible the underlying medical condition should be optimally treated and stable prior to treatment with teduglutide. Teduglutide should only be introduced if the benefits of treatment outweigh any potential risks (based on the known safety profile of teduglutide).

Uncontrolled, untreated systemic diseases of respiratory, endocrine, or neurological origin

Teduglutide has not been evaluated in subjects with active, uncontrolled, untreated systemic diseases of respiratory, endocrine, or neurological origin due to the exclusion criteria utilised in the clinical development program. It is possible that the pharmacological action of teduglutide may result in deterioration of these untreated concomitant conditions, especially where fluid overload or altered absorption or nutrition may be symptoms or features of the disease. However, it is not possible to predict the response to medication in this subject group without specific studies. In line with Good Clinical Practice, it is advisable that all conditions that are identified are treated appropriately and stabilised prior to introducing teduglutide to the subject's medication regime. The SmPC states that Revestive has not been studied in subjects with severe, clinically unstable concomitant diseases, (e.g., cardiovascular, respiratory, renal, infectious, endocrine, hepatic, or CNS), or in subjects with malignancies within the last 5 years. The SmPC advises that caution should be exercised when prescribing Revestive.

Subpopulations Carrying Known and Relevant Polymorphisms

Not applicable.

Subjects of different racial and/or ethnic origin

See Table SIII.4 for exposure in person-years for each race exposed to teduglutide in SBS clinical studies.

In clinical studies conducted, none of the covariates specifically age, gender, race, and dosing occasion had an effect on the clearance of distribution (CL/F), the volume of distribution (V/F) and the constant of absorption (Ka).

Body Mass Index

In the majority of the clinical studies (but not all), the subject's BMI was used to help define the population to be treated through either inclusion or exclusion criteria. The range of BMI's employed generally excluded subjects with a BMI less than 18 kg/m^2 (in studies CL0600-020 and CL0600-021: less than 15) and subjects were excluded if BMI exceeded more than 27, 29, 34, 35 and 40 depending on the study. It would be expected that subjects with a BMI of less than 18 are those most likely to be malnourished and to benefit most from treatment with teduglutide. However, caution would need to be exercised in these subjects as they may also be hypoproteinaemic and more susceptible to fluid overload and its consequent effects. For subjects that would be considered obese (BMI >30 kg/m^2), the conditions associated with obesity such as diabetes and cardiovascular disease may be affected detrimentally by treatment with teduglutide and the absorption of concomitant medications used to treat these conditions may also be altered. A subject's BMI at either end of the scale should not exclude that subject from treatment with teduglutide, but close monitoring of the subject's condition would be advisable.

Part II: Module SV - Post-authorisation experience

SV.1. Post-authorisation exposure

SV.1.1. Method used to calculate exposure

The method and formula for calculating patient exposure is described below:

Person-Years = (Number of vials sold/Average Number of vials used per person per day (1vial)/365.25 days.

SV.1.2. Exposure

Based on the marketing data, the estimated worldwide patient exposure to teduglutide is estimated to 10,777 person-years (PY) of treatment cumulatively through 30 April 2021.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

At present, there are no potential properties of teduglutide that would lead to its misuse for illegal purposes and so this risk is considered to be small.

[redacted]

Part II: Module SVII - Identified and potential risks

SVII.1. Identification of safety concerns in the initial RMP submission

The below table lists the safety concerns as identified in the initial RMP submission (EU RMP version 5.0).

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.
	Pre-existing moderate or severe renal impairment, or end stage renal disease.
	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.
Missing information	Lack of experience for administration of teduglutide in patients with severe, clinically unstable concomitant diseases e.g., cardiovascular, respiratory, renal, infectious, endocrine, hepatic, or CNS
	Lack of experience in pregnant or lactating women
	Lack of experience in paediatric population

[redacted]

	Limited long-term safety data over one year of exposure
	Lack of data in patients with pre-existing severe hepatic impairment

Reported in EU RMP version 5.0 approved on 30 August 2012

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated)

Not applicable.

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

Not applicable.

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered to by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):

Not applicable.

Known risks that do not impact the risk-benefit profile:

Not applicable.

Other reasons for considering the risks not important:

Not applicable.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important identified risk	Risk-benefit impact
Biliary adverse events	Teduglutide-induced hyperplasia in the gallbladder and the biliary ducts (shown in nonclinical studies) may theoretically lead to concentration of the bile with increased risk for the occurrence of sludge and stones. In contrast, no obstruction of the bile ducts has been observed in clinical and nonclinical studies with teduglutide. Evidence of a causal association between biliary adverse events and teduglutide is based on a small number of cases and exposure to the drug has not been extensive to date. Biliary events are also relatively common in SBS as well as the general population. To date, the benefit-risk profile of teduglutide is assessed as positive. For patients that develop gallbladder or bile duct-related signs or symptoms, the need for continued treatment with teduglutide should be reassessed, to ensure the benefit-risk remains favourable for the patient. In severe cases of hepatobiliary or cholestatic disease the physician should reassess if an interruption or continued

Important identified risk	Risk-benefit impact
	treatment with teduglutide is suitable.
Pancreatic AEs	Teduglutide-induced hyperplasia in the gallbladder and the biliary ducts (shown in nonclinical studies) may theoretically lead to concentration of the bile with increased risk for the occurrence of sludge and stones, which are in turn risk factors for pancreatitis. Pancreatic adverse events such as chronic and acute inflammation of the pancreas (pancreatitis), narrowing of the pancreatic duct, pancreas infection and increased blood amylase and lipase have been reported in clinical studies. Pancreatitis (acute and chronic) and pancreatic duct stenosis are common undesirable effects for Revestive per the SmPC. The benefit-risk balance is assessed as positive. For patients who present with pancreatic adverse events, the need for continued Revestive treatment should be reassessed to ensure the benefit-risk balance remains positive for the patient.
Cardiovascular AEs associated with fluid overload	A probable relationship of fluid overload with teduglutide treatment was observed in clinical studies. This overload could lead to cardiovascular AEs in predisposed subjects such as aggravation of heart failure. Cardiovascular events are also relatively common in the general population. Fluid overload adverse events occurred most frequently during the first 4 weeks of therapy and decreased over time. The benefit-risk balance is assessed as positive. Due to increased fluid absorption, patients with cardiovascular disease, such as cardiac insufficiency and hypertension, 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 to determine if the benefit-risk balance remains positive for that individual. 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. Congestive heart failure has been observed in clinical trials and is listed as a common undesirable side effect in the SmPC. In case of a significant deterioration of the cardiovascular disease, the need for continued treatment with Revestive should be reassessed to determine if the benefit-risk balance remains positive for that patient.
GI stenosis and obstruction	A higher frequency of gastrointestinal stenosis and obstruction was noted in the teduglutide groups in the adult clinical studies conducted to date when compared to placebo. The benefit-risk balance is assessed as positive. Patients with SBS generally are at a high risk of gastrointestinal stenosis/obstruction due to prior surgical procedures with intestinal adhesions and concurrent bowel conditions (e.g., Crohn's disease). Small intestinal stenosis, Colonic stenosis and Intestinal obstruction are common undesirable effects per the

Important identified risk	Risk-benefit impact
	SmPC. In case of recurrent intestinal obstructions, the need for continued Revestive treatment should be reassessed to assess if the benefit-risk balance remains positive for the patient.
GI stoma complications	Gastrointestinal stoma complications have been observed in the clinical trials with the use of teduglutide and are listed as very common undesirable effects. Approximately 38% of the treated patients with a stoma experienced gastrointestinal stoma complication. The majority of these reactions were mild or moderate. Stomal complications are common in the SBS patient population. Most stoma complications are preventable and result from poor stoma placement. Up to 20% of patients with stoma complications require surgical revision of the stoma. All patients with ostomies require ongoing, accurate assessment and, if needed, early intervention by trained clinicians. The benefit-risk balance remains positive for the individual patient due to the clinical benefits of ongoing teduglutide treatment.
Intestinal polyps	The available nonclinical data indicates that teduglutide may promote the growth of intestinal cells including pre-existing neoplasms. Those neoplasms are limited to the GI tract and hepatobiliary system. Colorectal polyp (common), Duodenal Polyps (uncommon), and Gastric polyp (frequency not known) are listed as undesirable effect in the SmPC. The benefit-risk balance is assessed as positive. The SmPC provides instructions for polyp surveillance prior to and during treatment. Also included are instructions to discontinue Revestive in case of malignancy and precautionary language regarding gastrointestinal neoplasia including the hepatobiliary tract. An individual assessment whether increased frequency of surveillance is necessary should be performed based on the patient characteristics (e.g., age, underlying disease) to ensure the benefit-risk balance remains positive for the individual patient. If a polyp is found, adherence to current polyp follow-up guidelines is recommended. In case of malignancy, the benefit-risk balance would be considered negative and Revestive therapy must be discontinued.
Benign neoplasia of the GI tract including the hepatobiliary system	The available nonclinical data indicates that teduglutide may promote the growth of pre-existing neoplasms in an at-risk population. Those neoplasms are believed to be limited to the GI tract including the hepatobiliary system. These observations were not confirmed in clinical studies of more than 1 year duration. The benefit-risk balance is assessed as positive. If a neoplasia is detected, it should be removed. In case of malignancy, the benefit-risk balance would be considered negative and Revestive therapy must be discontinued.

Important identified risk	Risk-benefit impact
Tumour promoting ability	The risk of a tumour-promoting ability associated with the use of teduglutide was derived from its mode of action, namely the promotion of growth and the inhibition of apoptosis of the intestinal epithelium. With regards to a tumour promoting effect in the GI tract, limited nonclinical data are available and the respective risks are presented above. Those neoplasms are believed to be limited to the GI tract including the hepatobiliary system. These observations were not confirmed in clinical studies of more than one year duration. The benefit-risk balance is assessed as positive. If a neoplasia is detected, it should be removed. In case of malignancy, the benefit-risk balance would be considered negative and Revestive therapy must be discontinued.
Anxiety	Anxiety is a common undesirable effect in the SmPC. The potential mechanism for anxiety is unknown. In rats, messenger ribonucleic acid (mRNA) of the GLP-2 receptor has been shown in some areas of CNS primarily in the hypothalamus [34]. It is not known, however, whether GLP-2 receptors exist in the human brain. The physiology of GLP-2 in the CNS is not fully understood and the mechanism for anxiety is unknown. The potential effect of teduglutide on the development of anxiety is not known. In the placebo-controlled studies CL0600-004 and CL0600-020, a higher reporting rate of subjects with anxiety has been observed in the teduglutide group (2.8%) compared with the placebo group (0%). A potential mechanism for this observation is unknown. However, due to the facts that anxiety can have severe consequences and that no reports occurred in the placebo group, anxiety is considered an important identified risk and on-going vigilance for signs and symptoms of anxiety should be practiced by subjects and their physicians. The benefit-risk balance is assessed as positive.

AE: Adverse event; GI: Gastrointestinal; SBS: short bowel syndrome

Important potential risk	Risk-benefit impact
AEs associated with increased absorption of oral concomitant medications	Due to the trophic activity of teduglutide there is a potential for increased intestinal absorption of concomitant drugs which can lead to higher bioavailability and an increased risk for developing side effects of those concomitant drugs. The efficacy response and the risk of increased absorption of individual subjects are difficult to predict. In general, subjects with concomitant medications with narrow therapeutic index are believed to be at increased risk, and therefore subjects receiving oral concomitant medication requiring titration or with a narrow therapeutic index should be monitored closely due to potential increased absorption. The physician should assess each individual patient's concomitant medications and monitor as appropriate to ensure a positive benefit-risk balance is maintained. As clinical data are limited, further data collection and analysis are considered appropriate due to the low number of subjects

[redacted]

Important identified risk	Risk-benefit impact
	included in clinical trials.
Local skin reactions	Subcutaneous injection of teduglutide, which is a peptide, may lead to activation of the immune system which may cause symptoms such as injection site erythema, injection site haematoma and injection site pain. The development of local skin reactions is considered an important potential risk. Injection site reactions occurred in 26% of SBS patients treated with teduglutide, compared to 5% of patients in the placebo arm. The reactions included injection site haematoma, injection site erythema, injection site pain, and injection site swelling and injection site haemorrhage. The majority of reactions were moderate in severity and no occurrences led to drug discontinuation. Injection site reaction is a common undesirable side effect listed in the SmPC. The benefit-risk balance is assessed as positive.
Potential for off-label use in patients with active Crohn's disease	This has not been fully studied, so it is unknown if any negative effects would arise in patients with Crohn's disease without concomitant SBS. Results from clinical studies with teduglutide in subjects with active Crohn's disease were published including a claim for a potential effect of teduglutide [35]. Although teduglutide may be used off-label to treat Crohn's disease, the risk profile for SBS subjects and active Crohn's disease subjects as determined in clinical trials is believed to be comparable, i.e. no increased clinical risk is expected in case of off label use of teduglutide in active Crohn's disease. However, the potential off-label use in patients with active Crohn's disease is considered an important potential risk. Consequently, further data collection and analysis are considered appropriate due to the low number of subjects included in clinical trials. Teduglutide was also shown to be safe in a pilot study conducted in 100 subjects with moderate to severe Crohn's disease (Protocol CL0600-008) who received SC doses of 0.05, 0.10, or 0.20 mg/kg/day teduglutide or placebo for 8 weeks, but the primary efficacy endpoint was not met because the study results did not establish significant differences in response rates between any of the teduglutide treatment groups and placebo. In a follow-up study of 67 subjects with Crohn's disease (Protocol CL0600-009), teduglutide administered at a dose of 0.10 mg/kg/day was associated with clinical remission rates at Study Week 12 ranging from 21.1% to 43.8% across treatment groups, with a 35.8% rate for the total number of subjects (n = 24). Teduglutide was well-tolerated during this 12-week extension study. The benefit-risk balance is assessed as positive.
Medication errors	Medication errors related to confusion regarding the pharmaceutical form, the route of administration, the strength, the setting for dispensing and use, reading errors, problems with the handling of the SmPC and the PL or prescription errors can never be fully excluded and are deemed to occur less frequent during clinical trials and potentially more frequent in post

[redacted]

Important identified risk	Risk-benefit impact
	marketing. Medication errors can be various and as such require trend analysis once they are reported during the post marketing period. Consequently, further data collection and analysis are considered appropriate. Impact on individual patient varies depending on the nature of the medication error but has the potential to lead to mild/moderate morbidity due to insufficient drug being delivered with exacerbation of GI symptomatology. All the events of medication error reviewed had no clinically significant outcome resulting from the medication error/misuse. The benefit-risk balance is assessed as positive.
Compromised nutritional status	As patients begin to obtain (partial) independence from PN/IV, they may require adjustments in the method of delivery of nutrition, in order to prevent an imbalance of micronutrients/ minerals/ vitamins. Due to the trophic activity of teduglutide there is a potential for higher absorption of micronutrients/ minerals/ vitamins which can lead to higher bioavailability. On the other hand, reduction of PN/IV may result in lack of micronutrients/ minerals/vitamins once not adequately compensated by nutrition. Further data collection and analysis are considered appropriate due to the low number of subjects included in clinical trials. The benefit-risk balance is assessed as positive.

Missing information	Risk-benefit impact
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	Teduglutide has not specifically been studied in subjects with cardiac disease to date. Safety pharmacology studies did not reveal any changes that would indicate a potential risk for QT prolongation in humans at the recommended clinical dose of 0.05 mg/kg/day. Teduglutide has not been evaluated in subjects with active, uncontrolled, untreated systemic diseases of respiratory, endocrine, or neurological origin due to the exclusion criteria utilized in the clinical development program. It is possible that the pharmacological action of teduglutide may result in deterioration of these untreated concomitant conditions, especially where fluid overload or altered absorption or nutrition may be symptoms or features of the disease. However, it is not possible to predict the response to medication in this subject group without specific studies. In line with Good Clinical Practice, it is advisable that all conditions that are identified are treated appropriately and stabilised prior to introducing teduglutide to the subject's medication regime. The SmPC states that Revestive has not been studied in subjects with severe, clinically unstable concomitant

Missing information	Risk-benefit impact
	diseases, (e.g., cardiovascular, respiratory, renal, infectious, endocrine, hepatic, or CNS), or in subjects with malignancies within the last 5 years. The SmPC advises that caution should be exercised when prescribing Revestive. The objective is to further understand the response to teduglutide in subjects with severe, clinically unstable concomitant medications.
Lack of experience in pregnant or lactating women	No pregnant and/or lactating women have been included in the teduglutide clinical development program. There are no data from the use of teduglutide 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 teduglutide during pregnancy. 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 newborn/infant cannot be excluded. As a precautionary measure it is preferable to avoid the use of teduglutide during breastfeeding. The objective is to characterize the safety profile among pregnant and breast-feeding patients.
Long-term safety in the paediatric population	Limited Long-term data in the paediatric population has been available since marketing authorisation. Potential long-term safety and efficacy issues in relation to paediatric use include the long-term risks of proliferations in the biliary tract and gastro-intestinal tract. Studies are currently underway to characterize the safety profile for long-term use of teduglutide in the paediatric population.
Limited long-term safety data over 1 year of exposure	A total of 106 individuals were exposed to teduglutide for one year and 43 individuals were exposed to teduglutide at least 2 years or longer. In Study TED-C11-001, 14 subjects in this long-term study were enrolled following up to 30 months of treatment with teduglutide (24 weeks of exposure in the placebo-controlled study, CL0600-020, and 24 months of exposure in the open label extension study, CL0600-021). Safety and efficacy data from this study indicated that long-term treatment with teduglutide continues to be safe and well tolerated while efficacy is maintained or further enhanced. Given the small number of subjects in this study, only descriptive statistics were employed. CL0600-021 was a 2-year open-label extension of CL0600-020 in which 88 subjects received teduglutide 0.05 mg/kg/day. Ninety-seven percent (76/78) of subjects from CL0600-020 elected to enrol in CL0600-021. An additional 12 subjects, who had been optimised and stabilised but not randomised in CL0600-020 because of closed enrolment, entered CL0600-0021. There continued to be evidence of increased response to

[redacted]

Missing information	Risk-benefit impact
	treatment over time in all groups exposed to teduglutide in terms of PN/IV volume reduction, gaining additional days off PN/IV per week, and achieving weaning of parenteral support. The SAE profile for the subjects with this exposure is similar to the SAE profile seen with shorter exposures. No safety signals were identified so far with long-term use. The objective is to further characterize the safety profile for long-term use of teduglutide over 1 year of exposure.
Lack of data in subjects with pre-existing severe hepatic impairment	Revestive has not been studied in subjects with severe hepatic impairment (Child Pugh grade B). The data from use in subjects with moderate hepatic impairment do not suggest a need for restricted use (Phase 1 pharmacokinetics study, CL0600-017). The objective is to characterize the safety profile among subjects with pre-existing severe hepatic impairment.

SAE: serious adverse event; PN: Parenteral nutrition; IV: Intravenous.

SVII.2. New safety concerns and reclassification with a submission of an updated RMP

The following risks were removed, updated, or added since the last approved RMP.

- "Lack of experience in children aged less than 1 year": was removed as missing information from safety concerns based on clinical trials (SHP633-301, SHP633-302, and SHP633-304) results.

SVII.3. Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important Identified Risk – Biliary adverse events

Potential mechanisms:	From literature it is known, that in the majority of subjects, gallstones are the cause of acute cholecystitis. The process is one of physical obstruction of the gallbladder by a gallstone, at the neck or in the cystic duct. This obstruction results in increased pressure in the gallbladder. There are 2 factors which determine the progression to acute cholecystitis: the degree of obstruction and the duration of the obstruction. If the obstruction is partial and of short duration the subject experiences biliary colic. If the obstruction is complete and of long duration the subject develops acute cholecystitis. If the subject does not receive early treatment, the disease becomes more serious and complications occur [36]. Teduglutide-induced hyperplasia in the gallbladder and the biliary ducts (shown in nonclinical studies) may theoretically lead to concentration of the bile with increased risk for the occurrence of sludge and stones. In contrast, no obstruction of the bile ducts has been observed in clinical and nonclinical studies with teduglutide. Also, it has been shown that increased GLP-2 concentrations trigger the increased release of glucagon, which might inhibit peristalsis of the gallbladder with increased risk for cholestasis and cholecystitis [37,38].
Evidence source(s) and strength of evidence:	**Non-clinical**: Teduglutide-induced hyperplasia in the gallbladder and the biliary ducts were observed in nonclinical studies and may theoretically lead to concentration of the bile with increased risk for the occurrence of sludge and stones. **Clinical studies**: Biliary events like cholecystitis, cholangitis, and cholelithiasis have been observed in clinical trials. No obstruction of the bile ducts has been observed in clinical and nonclinical studies with teduglutide.
Characterisation of the risk:	In adult and paediatric clinical studies, no obstruction of the bile ducts has been observed. **Adult population**: In the phase 2/3 adult studies, a total of 24 biliary events were reported for 14 patients in the teduglutide exposed group {N=190; 7.4% Confidence Interval (CI) 4.1% to 12.1 %}. Four biliary events were reported in 1 placebo patient (N= 59, 3.4%, CI 0.0% to 9.1%). *Outcome and Seriousness {% of total number of events (N=24)}* Serious: 13 (54.2%) Recovered: 17 (70.8%) Recovering: 4 (16.7%) Severity/frequency increased: 3 (12.5%) *Severity (% total number of subjects analysed, N=190)*

Important Identified Risk – Biliary adverse events

	Mild: 3 (1.6%) Moderate: 4 (2.1%) Severe: 7 (3.7%) **Paediatric population:** In the paediatric studies TED-C13-003 and TED-C14-006, 2 patients in the teduglutide treatment group experienced 4 biliary events (N= 87, 2.30%, CI 0.2 – 7.0). Of these, one (1/4) event was serious, 2 were mild, and 2 were moderate in severity. One event resolved, 2 remained unresolved, and 1 event had an unknown outcome. There were no biliary events reported in the System Organ Class (SOC) group. No biliary AEs were reported in infants in studies SHP633-301, SHP633-302 and SHP633-304.
Risk factors and risk groups:	The SBS population is too small for stratified data analysis and the existence of risk groups is unknown. Risk factors for cholecystitis mirror those for cholelithiasis. The overall incidence of gallbladder disease was about twice as high in women as in men, and it increased with age in both sexes without any evidence of an excess in the forties. Increase in weight and number of pregnancies were each associated with increased incidence [39]. Additional risk factors include rapid weight loss and pregnancy (elevated progesterone levels during pregnancy may cause biliary stasis). Also, recent operation and consequences of previous intestinal surgery are associated with the occurrence of cholecystitis [40].
Preventability:	Although teduglutide is associated with biliary AEs, it might also be able to decrease these events because it reduces the need for PN. As many of the unwanted biliary effects occur over a long period of time, it is difficult to demonstrate a reduction in these complications especially given the small number of subjects available to participate in clinical studies. However, biliary AEs, such as cholecystitis, have been described usually within the first weeks after start of teduglutide treatment. As it is expected that teduglutide treatment will reduce PN, a reduced occurrence of AEs under long-term treatment may happen. Precautionary language to reassess the need for continued treatment with Revestive in case of gallbladder or bile duct-related symptoms is included in Section 4.4 Special warnings and precautions for use of the SmPC.
Impact on the risk-benefit balance of the product:	Biliary adverse events will continue to be monitored through routine pharmacovigilance and routine risk minimisation measures. The risk-benefit balance remains positive in the overall SBS population. Biliary events would increase the burden of illness in an already ill patient. The need for continued teduglutide treatment should be reassessed at a patient level in case of gallbladder or bile duct-related symptoms.

[redacted]

Important Identified Risk – Biliary adverse events

Public health impact:	None anticipated due to orphan drug status and an estimated SBS prevalence of 15 in 1 million.

ADR=adverse drug reaction; AE=adverse event; CI=confidence interval; GLP-2=glucagon-like peptide; HPN=home parenteral nutrition; MedDRA=Medical Dictionary for Regulatory Activities; PN=parenteral nutrition; PT=preferred term; SBS=short bowel syndrome, SOC=standard of care.
Note: Studies included: ALX0600-92001, CL0600-004 (Core study), CL0600-005 (extension study), CL0600-020 (Core study), and CL0600-021 (extension study), TED-C13-003 (paediatric study), and TED-C14-006 (paediatric study).

Important Identified Risk – Pancreatic adverse events

Potential mechanisms:	In general, sludge and gallstones may contribute to the development of pancreatitis. The process may be one of physical obstruction of the distal pancreatic ducts or the Ampulla of Vater by gallstones, which may cause stasis of digestive juices in conjunction with lysis of pancreatic cells and subsequent pancreatitis. Teduglutide-induced hyperplasia in the gallbladder and the biliary ducts (shown in nonclinical studies) may theoretically lead to concentration of the bile with increased risk for the occurrence of sludge and stones. Also, hyperplasia of the pancreatic duct has been shown in nonclinical studies.
Evidence source(s) and strength of evidence:	**Non-clinical**: Teduglutide-induced hyperplasia in the gallbladder and the biliary ducts were observed in nonclinical studies and may theoretically lead to concentration of the bile with increased risk for the occurrence of sludge and stones. Also, hyperplasia of the pancreatic duct has been shown in nonclinical studies. **Clinical studies:** Pancreatic adverse events such as chronic and acute pancreatitis, pancreatic duct stenosis, pancreas infection and increased blood amylase and lipase have been reported in clinical studies.
Characterisation of the risk:	**Adult population**: In the phase 2/3 adult studies, a total of 18 pancreatic events were reported for 11 patients with SBS in the teduglutide exposed group (N=190; 5.8%, CI 2.9% to 10.1%). One case was reported for 1 placebo patient (N=59, 1.7% CI 0.0% to 9.1%). *Outcome and Seriousness {% of total number of events (N=18)}* Serious: 3 (16.6%) Recovered: 8 (44.4%) Recovering: 10 (55.6%) Severity/frequency increased: 0 *Severity {% total number of subjects analysed (N=190)}* Mild: 5 (2.6%) Moderate: 6 (3.2%) Severe: 0 **Paediatric population**: There were no pancreatic AEs or markedly elevated amylase levels

[redacted]

Important Identified Risk – Pancreatic adverse events

	reported in the Paediatric studies TED-C13-003 and TED-C14-006. In the TED-C14-006 study, 1 patient in 0.025 mg/kg dose group had an isolated elevated lipase value at week 10; this was deemed not clinically significant. A second patient in the 0.025 mg/kg dose group had elevated lipase at baseline, which remained elevated throughout the study without any clinically significant change. No pancreatic AEs were reported in infants in studies SHP633-301, SHP633-302 and SHP633-304.
Risk factors and risk groups:	The SBS population is too small for stratified data analysis and the existence of risk groups is unknown. Pancreatitis is generally caused by toxic-metabolic events (e.g., alcohol, smoking, hyperlipidaemia), by duct obstruction and may also have a genetic, idiopathic or autoimmune aetiology [41]. Thus, risk factors for pancreatitis partially mirror those for cholelithiasis and sludge. The overall incidence of gallbladder disease was about twice as high in women as in men, and it increased with age in both sexes without any evidence of an excess in the forties. Increase in weight and number of pregnancies were each associated with increased incidence [39]. Also, the use of PN and the potential hyperlipidaemia might contribute to the occurrence of pancreatitis.
Preventability:	Stenotic or obstructive events, such as sludge or gallstones, are risk factors for pancreatitis [41]. Although teduglutide may be associated with biliary AEs due to its mechanism of action, it is also expected to decrease these events because it reduces the need for PN. As many of these unwanted effects occur over a long period of time, it is difficult to demonstrate a reduction in these complications especially given the small number of subjects available to participate in clinical studies. Precautionary language to reassess the need for continued Revestive treatment in case of pancreatic adverse events is included in Section 4.4 Special warnings and precautions for use of the EU SmPC.
Impact on the risk-benefit balance of the product:	Pancreatic adverse events will continue to be monitored through routine pharmacovigilance and routine risk minimisation measures. The risk-benefit balance remains positive in the overall SBS population. Pancreatic events would increase the burden of illness in an already ill patient. The need for continued Revestive treatment should be reassessed at a patient level in case of pancreatic adverse events.
Public health impact:	None anticipated due to orphan drug status and an estimated SBS prevalence of 15 in 1 million.

AE=adverse event; ADR=adverse drug reaction; CI=confidence interval; GLP-2=glucagon-like peptide; HPN=home parenteral nutrition; MedDRA=Medical Dictionary for Regulatory Activities; PN=parenteral nutrition; PT=preferred term; SBS=short bowel syndrome, SOC=standard of care.
Note: Studies included: ALX0600-92001, CL0600-004 (Core study), CL0600-005 (extension study), CL0600-020 (Core study), and CL0600-021 (extension study), TED-C13-003 (paediatric study), and TED-C14-006 (paediatric study).

Important Identified Risk - Cardiovascular adverse events associated with fluid overload

Potential mechanisms:	As with GLP-2, teduglutide has been shown to preserve mucosal integrity by promoting repair and normal growth of the intestine. Teduglutide increases villus height and crypt depth of the intestinal epithelium resulting in enhanced digestive absorptive capacity as demonstrated by greater absorption of fluids, electrolytes and nutrients and reduced faecal fluid loss. Teduglutide accelerates intestinal adaptation, increases nutrient transporter activity and enhances barrier function in the small intestine. Given the mechanism of action of teduglutide and the known biology of GLP-2, it is expected that patients with SBS who respond to teduglutide treatment would experience an increase in the amount of fluid absorbed from their GI tract, thereby reducing or eliminating the need to obtain fluid via PN. Thus, there is a theoretical rationale that subjects may become volume expanded if their PN volumes are not appropriately down titrated.
Evidence source(s) and strength of evidence:	**Clinical Trials**: Fluid overload and congestive heart failure have been observed in adults in clinical trials.
Characterisation of the risk:	**Adult Population** Fluid Overload In the phase 2/3 adult studies, a total of 108 fluid overload events were reported for 49 teduglutide patients with SBS in the teduglutide exposed group (N=190, 25.8% CI 19.7% to 32.6%). Twenty-six events were reported in 17 placebo patients (N= 109, 15.6%, CI 9.4% to 23.8%). Congestive heart failure Four cases of congestive heart failure were observed in 3 teduglutide patients (N = 190; 1.6% CI 0.3% to 4.5%) in the teduglutide exposed SBS patients in Phase 2/3 studies. *Seriousness and Outcome {% of total number of events (N=4)}* Serious: 2 (50%) Recovered: 4 (100%) Recovering: 0 Severity/frequency increased: 0 *Severity {% total number of subjects analysed (N=4)}* Mild: 2 (50%) Moderate: 1 (25%) Severe: 1 (25%) **Paediatric population**: In the Paediatric studies TED-C13-003 and TED-C14-006, no reports of fluid overload were observed. In the TED-C13-003 study, 1 event of eyelid oedema was reported in a subject who received 0.05 mg/kg/day. In TED-C14-006, one event of oedema peripheral was reported. Both events were non-serious, mild in severity, and

Important Identified Risk - Cardiovascular adverse events associated with fluid overload

	resolved. No events of congestive heart failure were observed in the Paediatric patients. Cardiac events observed in children and adolescents included 3 events of tachycardia reported in 3 patients (N = 87, 3.4%, CI 0.7 to 9.7). All events resolved, none were serious and the majority (2/3) were mild in severity. No cardiac AEs were reported in infants in studies SHP633-301, SHP633-302 and SHP633-304.
Risk factors and risk groups:	The SBS population is too small for stratification.
Preventability:	Per the current SmPC: Due to increased fluid absorption, patient with cardiovascular disease, such as cardiac insufficiency and hypertension, 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 PN 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. 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.
Impact on the risk-benefit balance of the product:	Cardiovascular adverse events associated with fluid overload will continue to be monitored through routine pharmacovigilance and routine risk minimisation measures. The risk-benefit balance remains positive in the overall SBS population. Such events would increase the burden of illness in an already ill patient. In case of a significant deterioration of the cardiovascular disease, the need for continued treatment with Revestive should be assessed on a case by case basis.
Public health impact:	None anticipated due to orphan drug status and an estimated SBS prevalence of 15 in 1 million.

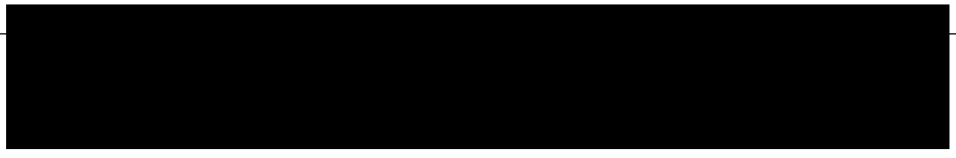
AE=adverse event; ADR=adverse drug reaction; CI=confidence interval; GLP-2=glucagon-like peptide; HPN=home parenteral nutrition; MedDRA=Medical Dictionary for Regulatory Activities; PN=parenteral nutrition; PT=preferred term; SBS=short bowel syndrome, SOC=standard of care.
Note: Studies included: ALX0600-92001, CL0600-004 (Core study), CL0600-005 (extension study), CL0600-020 (Core study), and CL0600-021 (extension study), TED-C13-003 (paediatric study), and TED-C14-006 (paediatric study).

Important Identified Risk - Gastrointestinal stenosis and obstruction

Potential mechanisms:	Subjects with SBS had multiple or extensive intestinal resections. Data for the mechanistic background are scarce and the investigated

Important Identified Risk - Gastrointestinal stenosis and obstruction

	SBS population is very heterogeneous in terms of their intestinal morphology and medical history. However, intestinal obstructive events in the Phase 2/3 SBS studies were mainly located in the small bowel and occurred mainly in the population with stoma. Proliferation of intestinal mucosa and hyperaemia seem to be the most prominent factors, which are behind the observed increased rate of intestinal obstructive events under teduglutide treatment.
Evidence source(s) and strength of evidence:	**Clinical Trials**. Cases of intestinal obstruction have been reported in adult clinical studies.
Characterisation of the risk:	**Adult population**: In the Phase 2/3 adult studies, a total of 20 events of gastrointestinal stenosis and obstruction were reported in 13 teduglutide patients with SBS (N=190; 6.8%, CI 3.7% to 11.4%). There were no events in the placebo group. *Seriousness and Outcome {% of total number of events (N=20)}* Serious: 10 (50.0%) Recovered: 18 (90.0%) Recovering: 2 (10.0%) Severity/frequency increased: 0 *Severity {% total number of subjects analysed (N=190)}* Mild: 1 (0.5%) Moderate: 4 (2.1%) Severe: 8 (4.2%) **Paediatric population**: In the Paediatric studies TED-C13-003 and TED-C14-006, 1 patient in the teduglutide treatment group experienced 1 serious event of ileus. The event was moderate in severity and resolved. {N=87; 1.1 % CI 0.0 to 5.4}. No events of intestinal stenosis or obstruction were recorded. No AEs of intestinal stenosis or obstruction were observed in infants in studies SHP633-301, SHP633-302 and SHP633-304.
Risk factors and risk groups:	The SBS population is too small for stratified data analysis.
Preventability:	The current SmPC lists intestinal obstruction as an undesirable effect and note cases of intestinal obstruction have been reported in clinical studies. In case of recurrent intestinal obstructions, the need for continued treatment with Revestive should be reassessed. On-going vigilance for signs and symptoms of intestinal obstruction should be practiced by subjects and their physicians.
Impact on the risk-benefit balance of the product:	Events of GI stenosis and obstruction will continue to be monitored through routine pharmacovigilance and routine risk minimisation measures. The risk-benefit balance remains positive in the overall



Important Identified Risk - Gastrointestinal stenosis and obstruction

	SBS population. In case of recurrent intestinal obstructions, the need for continued treatment with Revestive should be reassessed on a case-by-case basis.
Public health impact:	None anticipated due to orphan drug status and an estimated SBS prevalence of 15 in 1 million.

AE=adverse event; ADR=adverse drug reaction; CI=confidence interval; GLP-2=glucagon-like peptide; HPN=home parenteral nutrition; MedDRA=Medical Dictionary for Regulatory Activities; PN=parenteral nutrition; PT=preferred term; SBS=short bowel syndrome, SOC=standard of care.
Note: Studies included: ALX0600-92001, CL0600-004 (Core study), CL0600-005 (extension study), CL0600-020 (Core study), and CL0600-021 (extension study), TED-C13-003 (paediatric study), and TED-C14-006 (paediatric study).

Important Identified Risk - Gastrointestinal stoma complications

Potential mechanisms:	The naturally occurring human 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. It is known that GLP-2 (and teduglutide) causes an increase in mucosal surface area, as mesenteric blood flow increases [42]. This may contribute to an increase in the stoma nipple size.
Evidence source(s) and strength of evidence:	**Clinical Studies**: Stoma complications have been observed in clinical studies.
Characterisation of the risk:	**Adult population**: A total of 47 GI stoma complications were reported for 31 teduglutide subjects (45.6%, CI 33.5% to 58.1%) in 68 teduglutide exposed SBS subjects with stoma in the Phase 2/3 studies. In placebo-controlled SBS studies CL0600-004 and CL0600-020, 3 cases of GI stoma complications were reported for 3/22 placebo treated subjects with stoma (13.6%, CI 2.9% to 34.9%) and 19 GI stoma complications were reported for 17/45 teduglutide subjects with stoma (37.8%, CI 23.8% to 53.5%). *Seriousness and Outcome {% of total number of GI stoma complications (N=47)}* Serious: 3 (2.9%) Resolved: 26 (20.6%) On-going: 21 (27.9%) *Severity {% total number of subjects with stoma (N=68)}* Mild: 13 (19.1%) Moderate: 14 (20.6%) Severe: 4 (5.9%)

Important Identified Risk - Gastrointestinal stoma complications

	Paediatric population: In the Paediatric clinical studies, 9 events of stoma complications were reported in 6 patients exposed to teduglutide (N=87, 6.9%, CI 2.2 to 12.5). All of the events were non-serious, and the majority of events were mild in severity (8/9). All patients recovered. There were no events reported in the SOC group. No AEs of GI stoma complications were observed in infants in studies SHP633-301, SHP633-302 and SHP633-304.
Risk factors and risk groups:	The SBS population is too small for stratified data analysis and the existence of risk groups is unknown.
Preventability:	Subjects with SBS had multiple or extensive intestinal resections, which partially lead to the construction of GI stoma. Ongoing vigilance for signs and symptoms of GI stoma complications should be practiced by subjects and their physicians.
Impact on the risk-benefit balance of the product:	Events of GI stoma complications will continue to be monitored through routine pharmacovigilance and routine risk minimisation measures. The risk-benefit balance remains positive in the overall SBS population. The need for continued treatment with Revestive should be reassessed on a case-by-case basis in case of recurrent GI stoma complications.
Public health impact:	None anticipated due to orphan drug status and an estimated SBS prevalence of 15 in 1 million.

AE=adverse event; ADR=adverse drug reaction; CI=confidence interval; GLP-2=glucagon-like peptide; HPN=home parenteral nutrition; MedDRA=Medical Dictionary for Regulatory Activities; PN=parenteral nutrition; PT=preferred term; SBS=short bowel syndrome, SOC=standard of care.
Note: Studies included: ALX0600-92001, CL0600-004 (Core study), CL0600-005 (extension study), CL0600-020 (Core study), and CL0600-021 (extension study), TED-C13-003 (paediatric study), and TED-C14-006 (paediatric study).

Important Identified Risk - Intestinal polyps

Potential mechanisms:	Teduglutide is likely to act like native GLP-2, which effects are the result of secretion of down-stream mediators such as IGF-1, epidermal growth factor (EGF) and KGF [27,30,31]. The available nonclinical data set indicates that teduglutide may promote the growth of intestinal cells including pre-existing neoplasms. Those neoplasms are limited to the GI tract and hepatobiliary system.
Evidence source(s) and strength of evidence:	**Nonclinical:** Teduglutide bears the potential risk to enhance the growth of colon polyps. In the rat carcinogenicity study, benign tumours were found in the small bowel and the extrahepatic bile ducts. **Clinical:** Polyps were observed in adult patient in clinical studies.
Characterisation of the risk:	**Adult population**: A total of 13 cases of polyps were reported for 13 subjects in the 190 teduglutide exposed SBS subjects in Phase 2/3 studies. One subject was on placebo (0.9% CI 0.0% to 5.0%) and 12 subjects were on teduglutide (6.3% CI 3.3% to 10.8%). Of the 12 subjects on

Important Identified Risk - Intestinal polyps

	teduglutide, 1 developed duodenal polyps and 11 developed colorectal polyps. Case reports received from the completion of CL0600-021 (STEPS 2) clinical trial revealed an additional 9 subjects had been diagnosed with intestinal polyps, all of which were removed. **Paediatric population**: No events of polyps were seen in the Paediatric studies TED-C13-003, TED-C14-006, SHP633-301, SHP633-302 and SHP633-304.
Risk factors and risk groups:	The SBS population is too small for stratified data analyses and the existence of risk groups is unknown. However, data from literature and from other populations indicate the following risk factors: **Age** Background prevalence between 23 and 41% in persons between ages of 50 and 82 years [43-46] and between 7 and 40% for persons younger than 50 years of age [47]. **Crohn's Disease / Ulcerative Colitis** The risk for colorectal cancer for subjects with active Crohn's disease/ulcerative colitis is approximately an 18-fold increase greater than for a person without chronic inflammatory bowel disease [48]. **Presence of colon** Within the intestinal tract, colonic neoplasms are most frequent in men. Therefore, SBS subjects with colon may represent a subgroup with increased risk compared with subjects without colon.
Preventability:	Revestive is contraindicated in patients with a history of malignancies in the GI tract including the hepatobiliary system within the last 5 years. Precautionary language Section 4.4 Special warnings and precautions for use of the SmPC include instructions for polyp surveillance prior to and during treatment in adults as well as in children and adolescents. Section 5.1 "Pharmacodynamic properties" informs prescribers about the mechanism of action believed to be associated with the risk for the promotion of small intestinal and/or colonic neoplasia.
Impact on the risk-benefit balance of the product:	Events of growth of pre-existing polyps of the colon will continue to be monitored through routine pharmacovigilance and routine risk minimisation measures. The risk-benefit balance remains positive in the overall SBS population. Such events would increase the burden of illness in an already ill patient. Due to risk of malignancy, close monitoring of small bowel, gallbladder and bile ducts, and pancreas is recommended per the SmPC.
Public health impact:	None anticipated due to orphan drug status and an estimated SBS prevalence of 15 in 1 million.

AE=adverse event; ADR=adverse drug reaction; CI=confidence interval; GLP-2=glucagon-like peptide; HPN=home parenteral nutrition; MedDRA=Medical Dictionary for Regulatory Activities; PN=parenteral nutrition; PT=preferred term; SBS=short bowel syndrome, SOC=standard of care.
Note: Studies included: ALX0600-92001, CL0600-004 (Core study), CL0600-005 (extension study),

Important Identified Risk - Intestinal polyps

CL0600-020 (Core study), and CL0600-021 (extension study), TED-C13-003 (paediatric study), and TED-C14-006 (paediatric study).

Important Identified Risk - Benign neoplasia of the gastrointestinal tract including the hepatobiliary system

Potential mechanisms:	Teduglutide is likely to act like native GLP-2, which effects result through the secretion of down-stream mediators such as IGF-1, EGF and KGF [27,30,31]. The available nonclinical data indicates that teduglutide may promote the growth of pre-existing neoplasms in an at-risk population. Those neoplasms are limited to the GI tract including the hepatobiliary system.
Evidence source(s) and strength of evidence:	**Nonclinical:** In the rat carcinogenicity study, benign tumours were found in the small bowel and the extrahepatic bile ducts. **Clinical:** These observations were not confirmed in clinical studies of more than one year duration.
Characterisation of the risk:	**Adult population:** There was 1case of duodenal polyp in adult Phase 2/3 clinical trials. **Paediatric population:** No events of neoplasia were seen in the Paediatric studies TED-C13-003, TED-C14-006, SHP633-301, SHP633-302, and SHP633-304.
Risk factors and risk groups:	The SBS population is too small for stratified data analyses and the existence of risk factors or groups is unknown. However, data from literature and from other populations indicate the following risk factors and groups: Populations at risk of small bowel neoplasia include subjects with Crohn's disease, celiac disease, polyposis syndromes, or a history of small bowel-diverting surgeries and subjects elder than 50 years of age [43-46,49]. Based on known risk factors for cholangiocarcinoma, it can be assumed that subjects with chronic inflammation of the biliary ducts or with liver cirrhosis of different origin are at increased risk for the occurrence of cholangiomas [50].
Preventability:	The SmPC recommends that neoplasia should be removed if detected. In case of malignancy, Revestive treatment should be discontinued. Section 4.4 "Special warnings and precautions for use" of the SmPC includes: • Precautionary language concerning gastrointestinal neoplasia including hepatobiliary tract; • Instructions for monitoring of small bowel, gallbladder and bile ducts, and pancreas; • Instructions for polyp surveillance prior to and during treatment in adults as well as in children and adolescents.

[redacted]

Important Identified Risk - Benign neoplasia of the gastrointestinal tract including the hepatobiliary system

Impact on the risk-benefit balance of the product:	Events of benign neoplasia of the GI tract including the hepatobiliary events will continue to be monitored through routine pharmacovigilance and routine risk minimisation measures. The risk-benefit balance remains positive in the overall SBS population. Such events would increase the burden of illness in an already ill patient. Due to risk of malignancy, close monitoring of small bowel, gallbladder and bile ducts, and pancreas is recommended per the SmPC.
Public health impact:	None anticipated due to orphan drug status and an estimated SBS prevalence of 15 in 1 million.

AE=adverse event; ADR=adverse drug reaction; CI=confidence interval; GLP-2=glucagon-like peptide; HPN=home parenteral nutrition; MedDRA=Medical Dictionary for Regulatory Activities; PN=parenteral nutrition; PT=preferred term; SBS=short bowel syndrome, SOC=standard of care.
Note: Studies included: ALX0600-92001, CL0600-004 (Core study), CL0600-005 (extension study), CL0600-020 (Core study), and CL0600-021 (extension study), TED-C13-003 (paediatric study), and TED-C14-006 (paediatric study).

Important Identified Risk - Tumour promoting ability

Potential mechanisms:	Teduglutide is likely to act like native GLP-2, which effects result through the secretion of down-stream mediators such as IGF-1, EGF and KGF [27,30,31]. The available nonclinical data indicated that teduglutide may promote the growth of pre-existing neoplasms in an at-risk population. However, it is believed that this potential mechanism is limited to the GI tract including the hepatobiliary system, i.e., the site of pharmacological activity of teduglutide.
Evidence source(s) and strength of evidence:	**Nonclinical**: Teduglutide was negative when tested in the standard battery of tests for genotoxicity. In a rat carcinogenicity study, treatment related benign neoplasms included tumours of the bile duct epithelium in males exposed to teduglutide plasma levels approximately 32- and 155-fold higher than obtained in patients administered the recommended daily dose (incidence of 1 out of 44 and 4 out of 48, respectively). Adenomas of the jejunal mucosa were observed in 1 out of 50 males and 5 out of 50 males exposed to teduglutide plasma levels approximately 10- and 155-fold higher than obtained in patients administered the recommended daily dose. In addition, a jejunal adenocarcinoma was observed in a male rat administered the lowest dose tested (animal: human plasma exposure margin of approximately 10-fold). **Clinical studies:** The clinical studies conducted could neither exclude nor confirm such an increased risk.
Characterisation of the risk:	**Adult population**: In study CL0600-0021 there was 1 report of metastatic adenocarcinoma (subject [redacted]), 1 of non-small cell lung

[redacted]

Important Identified Risk - Tumour promoting ability

	cancer (subject [redacted]) and 1 of squamous cell carcinoma of the lung (subject [redacted] All of the above events in study CL0600-0021 were serious and severe. Subjects [redacted] and [redacted] died as a result of the events. The event was ongoing in subject [redacted] Subject [redacted] in the not treated, placebo/teduglutide group, with a prior history of Hodgkin's disease (treated with chemotherapy and radiation) died within 30 days following discontinuation from the study. [redacted] died 10 days after the reported onset of a metastatic adenocarcinoma, 11 months after the start of study drug. The serious TEAE was considered by the investigator to be treatment-related. Subject [redacted] in the not treated, placebo/teduglutide group, was diagnosed with non-small cell lung cancer 3 months after the start of treatment with teduglutide and died 5 months later. The event was considered by the investigator to be unrelated to treatment with the study drug. Subject [redacted] in the teduglutide/teduglutide group was diagnosed with squamous cell lung carcinoma approximately 2 years after starting teduglutide. The investigator did not consider the event to be related to study drug. The event was still ongoing as of the last follow-up. **Paediatric population**: In the Paediatric clinical studies TED-C13-003, TED-C14-006, SHP633-301, SHP633-302 and SHP633-304 there were no reports of malignancy.
<u>Risk factors and risk groups:</u>	The SBS population is too small for stratified data analyses and the existence of risk factors or groups is unknown. In general, risk groups are subjects with an increased risk for developing any kind of tumours such as an elderly population. In addition, certain subject characteristics like smoking, immune suppression therapy or previous cancers, which are known to be associated to a higher incidence / prevalence of neoplasias, are considered additional risk factors.
<u>Preventability:</u>	Section 4.3 "Contraindication" of the SmPC includes: - Contraindication in Patients with a history of malignancies in the GI tract including the hepatobiliary system and pancreas within the last 5 years. Section 4.4 "Special warnings and precautions for use" of the SmPC includes: - Precautionary language concerning gastrointestinal neoplasia including the hepatobiliary tract; - Instructions for monitoring of small bowel, gallbladder and bile ducts, and pancreas, - Instructions for polyp surveillance at start and during treatment, in adults as well as in children and adolescents.

[redacted]

Important Identified Risk - Tumour promoting ability

	- Instructions to discontinue Revestive in case of malignancy Section 5.1 "Pharmacodynamic properties" informs prescribers of the mechanism of action believed to be associated with the risk for the promotion of small intestinal and/or colonic neoplasia.
Impact on the risk-benefit balance of the product:	Events of tumour promoting ability will continue to be monitored through routine pharmacovigilance and routine risk minimisation measures. The risk-benefit balance remains positive in the overall SBS population. Such events would increase the burden of illness in an already ill patient.
Public health impact:	None anticipated due to orphan drug status and an estimated SBS prevalence of 15 in 1 million.

AE=adverse event; ADR=adverse drug reaction; CI=confidence interval; GLP-2=glucagon-like peptide; HPN=home parenteral nutrition; MedDRA=Medical Dictionary for Regulatory Activities; PN=parenteral nutrition; PT=preferred term; SBS=short bowel syndrome, SOC=Standard of Care.
Note: Studies included: ALX0600-92001, CL0600-004 (Core study), CL0600-005 (extension study), CL0600-020 (Core study), and CL0600-021 (extension study), TED-C13-003 (paediatric study), and TED-C14-006 (paediatric study).

Important Identified Risk: Anxiety

Potential mechanisms	The potential mechanism for anxiety is unknown. In rats, mRNA of the GLP-2 receptor has been shown in some areas of CNS primarily in the hypothalamus [34]. It is not known, however, whether GLP-2 receptors exist in the human brain.
Evidence source(s) and strength of evidence	In the placebo-controlled studies CL0600-004 and CL0600-020, a higher reporting rate of subjects with anxiety has been observed in the teduglutide group compared with the placebo group. A potential mechanism for this observation is unknown. However, due to the facts that anxiety can have severe consequences and that no reports occurred in the placebo group, anxiety is considered an important identified risk.
Characterisation of the risk	**Adult population:** A total of 3 cases of anxiety were reported for 3 teduglutide subjects in the 190 teduglutide exposed SBS subjects in Phase 2/3 placebo-controlled studies. In all Phase 2 SBS studies, the respective incidence proportion was 0.016 (3 subjects/190 patients). There were no reports of anxiety in the placebo group. **Paediatric population**: No events of anxiety (PT) were observed in the teduglutide exposed subjects with SBS in the paediatric clinical studies TED-C13-003, TED-C14-006, SHP633-301, SHP633-302 and SHP633-304.
Risk factors and risk groups	The SBS population is too small for stratified data analysis and the existence of risk groups is unknown.
Preventability	The physiology of GLP-2 in the CNS is not fully understood and the mechanism for anxiety is unknown. Therefore, on-going vigilance for signs and symptoms of anxiety should be practiced by subjects and

Important Identified Risk: Anxiety

	their physicians.
Impact on the risk-benefit balance of the product	Events of anxiety will continue to be monitored through routine pharmacovigilance and routine risk minimisation measures. The risk-benefit balance remains positive in the overall SBS population. Such events would increase the burden of illness in an already ill patient.
Public health impact	None anticipated due to orphan drug status and an estimated SBS prevalence of 15 in 1 million.

AE=adverse event; ADR=adverse drug reaction; CI=confidence interval; GLP-2=glucagon-like peptide; HPN=home parenteral nutrition; MedDRA=Medical Dictionary for Regulatory Activities; PN=parenteral nutrition; PT=preferred term; SBS=short bowel syndrome, SOC=standard of care.
Note: Studies included: ALX0600-92001, CL0600-004 (Core study), CL0600-005 (extension study), CL0600-020 (Core study), and CL0600-021 (extension study), TED-C13-003 (paediatric study), and TED-C14-006 (paediatric study).

Important Potential Risk - Adverse events associated with increased absorption of oral concomitant medications

Potential mechanisms:	It is theoretically possible that teduglutide improved intestinal absorption, which potentially increased benzodiazepine efficacy and toxicity. However, no decrease in benzodiazepine serum levels had been recorded from coma (>300 µg/L) to recovery (>300 µg/L).
Evidence source(s) and strength of evidence:	**Clinical Trials:** Based upon the PD effect of teduglutide, there is a potential for increased absorption of concomitant medicinal products. No confirmed event of increased absorption of concomitant medications has occurred in the teduglutide development program.
Characterisation of the risk:	**Adult population**: In Phase 2/3 SBS studies with an overall population of 190 teduglutide-treated patients, 1 serious adverse event of coma was observed in a teduglutide-treated patient potentially due to hyperabsorption of benzodiazepine leading to a higher bioavailability. This event was considered moderate and the patient recovered from the event. This corresponds to an incidence proportion of 0.005 (1 subject/191 subjects) and an incidence rate of 0.007/year (1 subject/143 subject-years). **Paediatric population**: No events associated with increased absorption of oral concomitant medications were observed in the Paediatric studies TED-C13-003, TED-C14-006, SHP633-301, SHP633-302 and SHP633-304.
Risk factors and risk groups:	The SBS population is too small for stratified data analysis and the existence of risk groups is unknown.
Preventability:	The mechanism of the observed coma is unconfirmed. The benzodiazepine levels suggest that the coma was related to increased absorption of benzodiazepines. The efficacy response and the risk of increased absorption of

[redacted]

Important Potential Risk - Adverse events associated with increased absorption of oral concomitant medications

	individual subjects are difficult to predict. In general, subjects with concomitant medications with narrow therapeutic index are believed to be at increased risk. Subjects receiving oral concomitant medication requiring titration or with a narrow therapeutic index should be monitored closely due to potential increased absorption.
Impact on the risk-benefit balance of the product:	Events of AE associated with increased absorption of oral concomitant medications will continue to be monitored through routine pharmacovigilance and routine risk minimisation measures. Such events would increase the blood level of oral medications which may lead to adverse effects. The risk-benefit balance remains positive in the overall SBS population.
Public health impact:	None anticipated due to orphan drug status and an estimated SBS prevalence of 15 in 1 million.

AE=adverse event; ADR=adverse drug reaction; CI=confidence interval; GLP-2=glucagon-like peptide; HPN=home parenteral nutrition; MedDRA=Medical Dictionary for Regulatory Activities; PN=parenteral nutrition; PT=preferred term; SBS=short bowel syndrome, SOC=standard of care.
Note: Studies included: ALX0600-92001, CL0600-004 (Core study), CL0600-005 (extension study), CL0600-020 (Core study), and CL0600-021 (extension study), TED-C13-003 (paediatric study), and TED-C14-006 (paediatric study).

Important Potential Risk: Local skin reactions

Potential mechanisms	The mechanism is unknown. However, teduglutide is a peptide drug, which in a certain scope also contains impurities from the production process. SC injection of such drug may lead to activation of the immune system which finally may become obvious in the above described symptoms.
Evidence source(s) and strength of evidence	**Non-Clinical**: Treatment-related inflammatory lesions at the injection sites were observed in all preclinical animal species. **Clinical Studies**: Injection site reactions occurred in 26% of SBS patients treated with teduglutide, compared to 5% of patients in the placebo arm. The reactions included injection site haematoma, injection site erythema, injection site pain, injection site swelling and injection site haemorrhage. The majority of reactions were moderate in severity and no occurrences led to drug discontinuation.
Characterisation of the risk	**Adult population**: In pre-clinical studies, severe granulomatous inflammations were found associated with the injection sites. A total of 73 cases of injection site reactions were reported for 36 subjects (18.9%, CI 13.6 to 25.3) with SBS in teduglutide Phase 2/3 studies. Injection site reactions occurred in 21% of SBS subjects treated with Revestive. The reactions appeared to be dose-dependent and occurred with similar frequency in subjects 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 subjects 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

Important Potential Risk: Local skin reactions

	erythema, injection site haematoma and injection site pain. **Paediatric Population:** In the Paediatric clinical studies, 19 events of injection site reaction were reported in 13 patients exposed to teduglutide (N=87, 14.9%, CI 7.0 to 21.0). None occurred in the SOC group. All of the events were non-serious and mild. The majority of the events (18/19) resolved. No AEs of injection site reactions were observed in infants in studies SHP633-301, SHP633-302 and SHP633-304.
Risk factors and risk groups	The SBS population is too small for stratified data analysis and the existence of risk groups is unknown.
Preventability	The subject should choose alternating injection sites in order to avoid repeated and permanent trigger of the same area of the skin.
Impact on the risk-benefit balance of the product	Events of local skin reactions will continue to be monitored through routine pharmacovigilance and routine risk minimisation measures. The risk-benefit balance remains positive in the overall SBS population. Such events would increase the burden of illness in an already ill patient.
Public health impact	None anticipated due to orphan drug status and an estimated SBS prevalence of 15 in 1 million.

AE=adverse event; ADR=adverse drug reaction; CI=confidence interval; GLP-2=glucagon-like peptide; HPN=home parenteral nutrition; MedDRA=Medical Dictionary for Regulatory Activities; PN=parenteral nutrition; PT=preferred term; SBS=short bowel syndrome, SOC=standard of care.
Note: Studies included: ALX0600-92001, CL0600-004 (Core study), CL0600-005 (extension study), CL0600-020 (Core study), and CL0600-021 (extension study), TED-C13-003 (paediatric study), and TED-C14-006 (paediatric study).

Important Potential Risk: Potential off-label use in patients with active Crohn's disease

Potential mechanisms	Not applicable.
Evidence source(s) and strength of evidence	Post marketing reports.
Characterisation of the risk	In the SBS development program, patients with active Crohn's disease were excluded from the safety and efficacy trials. With respect to commercial use, it is difficult to determine which patients just have active Crohn's without underlying SBS as not all physicians code SBS as an indication instead malnutrition ICD-9 codes may be used. Results from clinical studies with teduglutide in subjects with active Crohn's disease were published including a claim for a potential effect of teduglutide [35]. Although teduglutide may be used off-label to treat Crohn's disease, the risk profile for SBS subjects and active Crohn's disease subjects as determined in clinical trials is believed to be comparable, i.e., no increased clinical risk is expected in case of off label use of teduglutide in active Crohn's disease.

Important Potential Risk: Potential off-label use in patients with active Crohn's disease

Risk factors and risk groups	The Risk group might be patients with active Crohn's disease with concomitant SBS not adequately treated for Crohn's disease.
Preventability	Avoid use in Crohn's patients except those with SBS.
Impact on the risk-benefit balance of the product	Events off-label use in patients with active Crohn's disease will continue to be monitored through routine pharmacovigilance and routine risk minimization measures. The risk-benefit balance remains positive in the overall SBS population. It is unknown if any negative effects would arise in patients with Crohn's disease without SBS.
Public health impact	None anticipated due to orphan drug status and an estimated SBS prevalence of 15 in 1 million.

AE=adverse event; ADR=adverse drug reaction; CI=confidence interval; GLP-2=glucagon-like peptide; HPN=home parenteral nutrition; ICD-9=international classification of diseases-9; MedDRA=Medical Dictionary for Regulatory Activities; PN=parenteral nutrition; PT=preferred term; SBS=short bowel syndrome, SOC=standard of care.
Note: Studies included: ALX0600-92001, CL0600-004 (Core study), CL0600-005 (extension study), CL0600-020 (Core study), and CL0600-021 (extension study), TED-C13-003 (paediatric study), and TED-C14-006 (paediatric study).

Important Potential Risk - Medication errors

Potential mechanisms:	Not applicable.
Evidence source(s) and strength of evidence:	**Clinical Studies and Post Marketing**: Reports of accidental overdose were seen in clinical studies. Reports of medication errors are seen during the post-marketing period.
Characterisation of the risk:	**Adult population**: A total of 2 cases of medication errors (accidental overdoses) were reported for 2 patients in the 190 teduglutide exposed SBS patients and 59 placebo exposed patients in Phase 2/3 studies. One patient was on placebo and 1 patient was on teduglutide. **Paediatric population**: In the Paediatric study TED-C14-006, one subject received an approximate 6-fold overdose of study drug at the baseline visit. No AEs were associated with this accidental overdose. Minor rounding errors occurred in dosing of two subjects, which were not associated with AEs. Another subject received 0.025 mg/kg/day of teduglutide over a 7-day period instead of the originally assigned 0.05 mg/kg dose. The subject was not reported to have change in clinical status during this period. In the Paediatric study TED-C13-003, one subject who was allocated to 0.025 mg/kg/day received an incorrect dose of study medication at the baseline visit. This was deemed a minor protocol deviation and no AE was associated with the dosing error. In SHP633-301 infant study, and SHP633-304 study there were no medication errors reported. In study SHP633-302, Medication errors were reported in 1 infant.

Important Potential Risk - Medication errors

	The underdose was reported in infant (received a dose of 0.1mL instead of 0.13mL) due to human error. This infant experienced a ≥20% reduction in PS during the study. There was no associated AE observed in infant.
Risk factors and risk groups:	The SBS population is too small for stratified data analysis and the existence of risk groups is unknown.
Preventability:	Depending on nature of medication error, mainly ensuring readable and understandable SmPC and PL.
Impact on the risk-benefit balance of the product:	Events of medication errors will continue to be monitored through routine pharmacovigilance and routine risk minimisation measures. The risk-benefit balance remains positive in the overall SBS population. The impact on individual patients varies depending on the nature of the medication error but has the potential to lead to mild/moderate morbidity due to insufficient drug being delivered with exacerbation of gastrointestinal symptomatology.
Public health impact:	Low: drug exposure is limited to a relatively small patient population.

AE=adverse event; ADR=adverse drug reaction; CI=confidence interval; GLP-2=glucagon-like peptide; HPN=home parenteral nutrition; MedDRA=Medical Dictionary for Regulatory Activities; PL=package leaflet; PN=parenteral nutrition; PT=preferred term; SBS=short bowel syndrome, SOC=standard of care.
Note: Studies included: ALX0600-92001, CL0600-004 (Core study), CL0600-005 (extension study), CL0600-020 (Core study), and CL0600-021 (extension study), TED-C13-003 (paediatric study), and TED-C14-006 (paediatric study).

Important Potential Risk: Compromised nutritional status

Potential mechanisms	As with GLP-2, teduglutide has been shown to preserve mucosal integrity by promoting repair and normal growth of the intestine. Teduglutide increases villus height and crypt depth of the intestinal epithelium resulting in enhanced digestive absorptive capacity as demonstrated by greater absorption of fluids, electrolytes and nutrients and reduced faecal fluid loss. Teduglutide accelerates intestinal adaptation, increases nutrient transporter activity and enhances barrier function in the small intestine. Given the mechanism of action of teduglutide and the known biology of GLP-2, it is expected that patients with SBS who respond to teduglutide treatment would experience an increase in the amount of micronutrients/ minerals/vitamins absorbed from their GI tract, thereby reducing or eliminating the need to obtain PN. Thus, there is a theoretical rationale that subjects may become an imbalance of nutritional status for micronutrients/minerals/vitamins if not adequately compensated by nutrition.
Evidence source(s) and strength of evidence	Not applicable.
Characterisation of the risk	**Adult population:** In the phase 2/3 adult studies, 57 events were reported with the preferred terms of dehydration (24), electrolyte imbalance (1),

Important Potential Risk: Compromised nutritional status

	fluid overload (1), fluid retention (7), hyperkalaemia (3), hypertriglyceridaemia (3), hypervolaemia (1), hypokalaemia (8), hyponatraemia (1), malnutrition (2), and vitamin deficiency (6). The events were reported for 31 patients with SBS in the teduglutide exposed group (N=190; 16.3%, CI 11.4% to 22.4%). 10 events related to this risk were reported for 10 placebo patients (N=59, 16.9% CI 8.4% to 29.0 %). *Seriousness and Outcome* (% of total number of events [N=190]) Serious: 3(5.3%) Recovered: 44(77.2%) Recovering: 13(22.8%) Severity (% total number of subjects analysed [N=190]) Mild: 31(54.4%) Moderate: 22(38.6%) Severe: 4 (7.0%) **Paediatric population:** In the Paediatric clinical studies, 23 events related to this risk were reported in 14 patients exposed to teduglutide (N=87, 16.1%, CI 9.1 - to 25.5). These events included dehydration (16), hyperkalaemia (1), hypokalaemia (4), and hyponatraemia (1) and vitamin E deficiency (1). Seven of the events reported in the teduglutide exposed group were serious. The majority of the events resolved (22/23) and were mild or moderate (10 events were mild and 11 were moderate) in severity. One event of dehydration occurred in the SOC group (N=14; 7.1%; CI 0.2 – 33.9). In SHP633-301 study, there was one non-serious event of PT Iron deficiency anaemia in one subject was reported in teduglutide group and none in SOC. The event was assessed as not related to therapy and was not severe in nature. In SHP633-302 and SHP633-304, there were no events of compromised nutritional status observed in infants.
Risk factors and risk groups	The SBS population is too small for stratified data analysis and the existence of risk groups is unknown. Overall, all patients getting partially, or fully independent form PN/IV could be at risk for an imbalance of nutritional status.
Preventability	The current SmPC recommends optimising nutrition before starting therapy and evaluating treatment effects after 6 months. This includes nutritional status.
Impact on the risk-benefit balance of the product	Events of compromised nutritional status will continue to be monitored through routine pharmacovigilance and routine risk minimisation measures. The risk-benefit balance remains positive in the overall SBS population. Such events would increase the burden of illness in an already ill patient.

Important Potential Risk: Compromised nutritional status

Public health impact	None anticipated due to orphan drug status and an estimated SBS prevalence of 15 in 1 million.

AE=adverse event; ADR=adverse drug reaction; CI=confidence interval; GLP-2=glucagon-like peptide; HPN=home parenteral nutrition; MedDRA=Medical Dictionary for Regulatory Activities; PN=parenteral nutrition; PT=preferred term; SBS=short bowel syndrome, SOC=standard of care.
Note: Studies included: ALX0600-92001, CL0600-004 (Core study), CL0600-005 (extension study), CL0600-020 (Core study), and CL0600-021 (extension study), TED-C13-003 (paediatric study), and TED-C14-006 (paediatric study).

SVII.3.2. Presentation of the missing information

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

Evidence source	Not applicable.
Population in need of further characterization	Due to the exclusion criteria utilised in the clinical development program, subjects with a history or clinical manifestations of any clinically significant metabolic, haematological, pulmonary, GI, neurological, urological, renal, hepatic, cardiovascular or psychiatric disorder and a history of cancer within the last 5 years prior to studies start were not studied. It is possible that the pharmacological action of teduglutide may result in deterioration of these concomitant conditions.

Missing Information: Lack of experience in pregnant or lactating women

Evidence source	Not applicable.
Population in need of further characterization	No pregnant and/or lactating women have been included in the teduglutide clinical development program. There are no data from the use of teduglutide in pregnant women. It is unknown whether teduglutide is excreted in human milk.

Missing Information: Long-term safety in the paediatric population

Evidence source	Not applicable.
Population in need of further characterization	Potential long-term safety and efficacy issues in relation to paediatric use include the long-term risks of proliferations in the biliary tract and gastro-intestinal tract.

Missing Information: Limited long-term safety data over 1 year of exposure.

Evidence source	Not applicable.
Population in need of further characterization	Based on the results of the completed long-term studies (TED-C11-001, CL0600-021 and CL0600-004), the SAE profile for the subjects with long-term exposure is similar to the SAE profile seen

Missing Information: Limited long-term safety data over 1 year of exposure.

	with shorter exposures. No safety signals were identified so far with long-term use. Due to small number of patients studied and based on the potential long-term risk of proliferation in the biliary tract and the gastrointestinal tract, further data on the long-term use of Revestive in patients with SBS is warranted.

Missing Information: Lack of data in subjects with pre-existing severe hepatic impairment.

Evidence source	Not applicable.
Population in need of further characterization	Revestive has not been studied in subjects with severe hepatic impairment (Child Pugh grade B).

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Biliary AEs • Pancreatic AEs • Cardiovascular AEs associated with fluid overload • GI stenosis and obstruction • GI stoma complications • Intestinal Polyps • Benign neoplasia of the GI tract including the hepatobiliary system • Tumour promoting ability • Anxiety
Important potential risks	• AEs associated with increased absorption of oral concomitant medications • 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 • 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

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1. Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection include:

- **Targeted questionnaires**

Specific adverse reaction follow-up questionnaires for safety concerns:

Targeted questionnaires are implemented for Revestive to aid follow up on specific safety concerns as described below. The forms are provided in Annex 4 of the RMP.

Specific Adverse Drug Reaction Follow-up Forms

Safety Concern	Questionnaire
Biliary AEs such as cholecystitis and GI stenosis.	Gallbladder disorder/Cholecystitis questionnaire
Pancreatic AEs such as chronic and acute pancreatitis, pancreatic duct stenosis, pancreas infection and increased blood amylase and lipase.	Pancreatitis questionnaire
Cardiovascular AEs associated with fluid overload.	Fluid overload questionnaire
GI stenosis and obstruction.	GI Stenosis/intestinal obstruction questionnaire
Benign neoplasia of the GI tract including the hepatobiliary system.	Neoplasm questionnaire

Other forms of routine pharmacovigilance activities for safety concerns:

Obligatory expedited reporting independent of seriousness is implemented for the following safety concerns:

- Growth of pre-existing polyps of the colon
- Benign neoplasia of the gastrointestinal tract including the hepatobiliary system
- Tumour promoting ability

Respective case reports of the important identified and potential risks are presented separately in a special section of the periodic benefit-risk evaluation report (PBRER). Medication errors and off-label use are presented as listing in the PBRER.

III.2. Additional pharmacovigilance activities

The additional pharmacovigilance activities for Revestive aim to further characterise the safety concerns and collect further data on the missing information. These activities will potentially identify subjects or subject groups at increased risk.

Current ongoing additional pharmacovigilance activities include TED-R13-002 (Registry). The registry enables the acquisition of long-term safety information over 10 years, in addition to routine adverse event reporting from a representative teduglutide population of adults and children. It also

allows for the acquisition of comparison data from a control group who are not treated with teduglutide. The Registry will collect data on the occurrence of the primary safety outcome of colorectal cancer, and secondary safety outcomes such as other malignancies, benign neoplasia of the GI tract, hepatobiliary system and pancreas, colorectal polyps, intestinal obstruction, pancreatic and biliary disease, heart failure.

A tabulated summary of the ongoing and completed pharmacovigilance activities is presented below and is provide in Annex 2.

Protocols for ongoing studies in the pharmacovigilance plan are provided in Annex 3 of the RMP.

TED-R13-002 summary
Study short name and title: TED-R13-002.
Rationale and study objectives: 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. **Safety concerns to be addressed:** • Biliary AEs • Pancreatic AEs • Cardiovascular AEs associated with fluid overload • GI stenosis and obstruction • Intestinal polyps • Benign neoplasia of the GI tract including the hepatobiliary system • Tumour promoting ability • Adverse Events associated with increased absorption of oral concomitant medications • 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) • Lack of experience in pregnant or lactating women • 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
Study design: A prospective, multi-centre registry for patients with SBS.

TED-R13-002 summary
Study population: Male and female patients, of any age, with a diagnosis of SBS. Patients who have never received teduglutide treatment must be on PN/IV support for at least 6 months.
Milestones: • **Interim reports:** 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); • **Final study report:** Q2/2032.

III.3. Summary Table of additional Pharmacovigilance activities

Table Part III.1: On-going and planned additional pharmacovigilance activities

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
TED-R13-002 Ongoing	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.	• Biliary AEs. • Pancreatic AEs. • Cardiovascular AEs associated with fluid overload. • GI stenosis and obstruction. • Intestinal polyps • Benign neoplasia of the GI tract including the hepatobiliary system. • Tumour promoting ability. • Adverse Events associated with increased absorption of oral concomitant medications • Lack of	Interim reports	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).
			Final report	Q2/2032

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
		experience for administration of teduglutide in subjects with severe, clinically unstable concomitant diseases (e.g., cardiovascular, respiratory, renal, infectious, endocrine, hepatic, or CNS) • Lack of experience in pregnant or lactating women. • 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.		
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
NA	NA	NA	NA	NA
Category 3 - Required additional pharmacovigilance activities				
NA	NA	NA	NA	NA

Part IV: Plans for post-authorisation efficacy studies

Not applicable.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

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

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

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

[redacted]

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

Safety concern	Routine risk minimisation activities
	pancreas within the last 5 years). SmPC Section 4.4 "Special warnings and precautions for use" includes: - Precautionary language concerning gastrointestinal neoplasia including hepatobiliary tract; - Instructions for monitoring of small bowel, gallbladder and bile ducts, and pancreas, - Instructions for polyp surveillance prior to and during treatment, in adults as well as in children and adolescents. - Instructions to discontinue Revestive in case of malignancy SmPC Section 5.1 "Pharmacodynamic properties" describes the mechanism of action believed to be associated with the risk for the promotion of small intestinal and/or colonic neoplasia. PL section 2 includes: - GI and hepatobiliary cancer within the last 5 years or its suspicion as a contraindication. - Instructions for polyp surveillance prior to and during treatment, in adults as well as in children and adolescents. - Instructions to discontinue Revestive in case of malignancy. - Instructions for monitoring of small bowel, gallbladder and bile ducts, and pancreas. **Other routine risk minimisation measures beyond the Product Information:** Prescription only medicine. Use restricted to physicians in the treatment of SBS.
Anxiety	**Routine risk communication:** SmPC Section 4.8 Undesirable effects lists anxiety as a common undesirable effect. PL section 4 "Possible side effects" lists anxiety as common side effect. **Other routine risk minimisation measures beyond the Product Information:** Prescription only medicine. Use restricted to physicians in the treatment of SBS.
AEs associated with increased absorption of oral concomitant medications	**Routine risk communication:** SmPC Section 4.4 "Special warnings and precautions for use" recommends close monitoring of patients receiving oral concomitant medicinal products. SmPC Section 4.5 "Interaction with other medicinal products and other forms of interaction" informs prescribers on the potential for

Safety concern	Routine risk minimisation activities
	increased absorption of concomitant medicinal products. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** PL section 2 mentions regarding the potential effect on oral concomitant medications. **Other routine risk minimisation measures beyond the Product Information:** Prescription only medicine. Use restricted to physicians in the treatment of SBS.
Local skin reactions	**Routine risk communication:** SmPC Section 4.8 "Undesirable effects" lists Injection site reactions as very common adverse drug reactions. PL section 4 "Possible side effects" lists injection site reaction as very common side effect. **Other routine risk minimisation measures beyond the Product Information:** Prescription only medicine. Use restricted to physicians in the treatment of SBS.
Potential for off-label use in patients with active Crohn's disease	**Routine risk communication:** SmPC Section 4.1 "Therapeutic indications", Section 4.2 "Posology and method of administration". PL section 1 mentions the indication for use of Revestive. PL section 3 mentions the instructions to use Revestive. **Other routine risk minimisation measures beyond the Product Information:** Prescription only medicine. Use restricted to physicians in the treatment of SBS.
Medication errors	**Routine risk minimisation activities recommending specific clinical measures to address the risk:** Instructions for correct administration are provided in Sections 4.2 "Posology", Section 4.9 "Overdose" and Section 6.6 "Special precautions for disposal and other handling" of the SmPC. PL Section 3 mentions instructions for use and Section 5 mentions instructions for storage of Revestive. **Other routine risk minimisation measures beyond the Product Information:** Prescription only medicine. Use restricted to physicians in the treatment of SBS.

[redacted]

Safety concern	Routine risk minimisation activities
Compromised nutritional status	**Routine risk communication:** SmPC Section 4.2 "Posology and method of administration" recommends treatment to be initiated under the supervision of a medical professional with experience in the treatment of SBS. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.2 "Posology and method of administration" provides - Instructions to initiate treatment when it is reasonable to assume that a patient is stable following a period of intestinal adaptation. - Instructions for optimisation and stabilisation of IV fluid and nutrition support before initiation of treatment. PL section 2 mentions regular monitoring of body fluids and electrolytes. **Other routine risk minimisation measures beyond the Product Information:** Prescription only medicine. Use restricted to physicians in the treatment of SBS.
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	**Routine risk communication:** SmPC Section 4.4 Special warnings and precautions for use. PL section 2.
Lack of experience in pregnant or lactating women	**Routine risk communication:** SmPC Section 4.6 Fertility, pregnancy and lactation. PL Section 2.
Long-term safety in the paediatric population	**Routine risk communication:** SmPC Section 4.2 "Posology" and Section 4.8 "Undesirable Effects". PL Section 1 and Section 4.
Limited long-term safety data over 1 year of exposure	No risk minimisation activities are proposed at this time. Additional safety data will be available following completion of the NIS.

[redacted]

Safety concern	Routine risk minimisation activities
Lack of data in subjects with pre-existing severe hepatic impairment	**Routine risk communication:** SmPC Section 4.2 Posology. PL Section 2 mentions severely decreased liver function under "Warnings and Precautions".

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

Removal of additional risk minimisation activities:

Not applicable.

V.3. Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation activities	Pharmacovigilance activities
Biliary adverse events	**Routine risk minimisation measures:** SmPC Section 4.2, Section 4.4 and Section 4.8. PL Section 4. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** - Specific Adverse event follow up forms - Separate presentation of respective case reports in a special section of the PBRER. **Additional pharmacovigilance activities:** Registry TED-R13-002.
Pancreatic adverse events	**Routine risk minimisation measures:** SmPC Section 4.2, Section 4.4 and Section 4.8. PL Section 4. **Additional risk minimisation** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** - Specific Adverse event follow up forms - Separate presentation of respective case reports in a special section of the PBRER. **Additional pharmacovigilance activities:** Registry TED-R13-002.

[redacted]

Safety concern	Risk minimisation activities	Pharmacovigilance activities
Cardiovascular Adverse Events associated with fluid overload	**Routine risk minimisation measures:** SmPC Section 4.2, Section 4.4 and Section 4.8. PL Section 2 and Section 4. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Specific Adverse event follow up forms - Separate presentation of respective case reports in a special section of the PBRER. **Additional pharmacovigilance activities:** Registry TED-R13-002.
GI stenosis and obstruction	**Routine risk minimisation measures:** SmPC Section 4.2, Section 4.4 and Section 4.8. PL Section 4. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** - Specific Adverse event follow up forms - Separate presentation of respective case reports in a special section of the PBRER. **Additional pharmacovigilance activities:** Registry TED-R13-002.
GI stoma complications	**Routine risk minimisation measures:** SmPC Section 4.2 and Section 4.8. PL Section 4. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Intestinal polyps	**Routine risk minimisation measures:** SmPC Section 4.2, Section 4.3, Section 4.4 and Section 4.8. PL Section 2 and Section 4. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** - Obligatory expedited reporting independent of seriousness - Separate presentation of respective case reports in a special section of the PBRER.

Safety concern	Risk minimisation activities	Pharmacovigilance activities
		Additional pharmacovigilance activities: Registry TED-R13-002.
Benign neoplasia of the GI tract including the hepatobiliary system	**Routine risk minimisation measures:** SmPC Section 4.2, Section 4.3, Section 4.4, and Section 5.1. PL Section 2. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** - Specific Adverse event follow up forms - Obligatory expedited reporting independent of seriousness - Separate presentation of respective case reports in a special section of the PBRER **Additional pharmacovigilance activities:** Registry TED-R13-002.
Tumour promoting ability	**Routine risk minimisation measures:** SmPC Section 4.2, Section 4.3, Section 4.4, and Section 5.1. PL Section 2. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** - Specific Adverse event follow up forms - Obligatory expedited reporting independent of seriousness - Separate presentation of respective case reports in a special section of the PBRER **Additional pharmacovigilance activities:** Registry TED-R13-002.
Anxiety	**Routine risk minimisation measures:** SmPC Section 4.8. PL Section 4. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**Separate presentation of respective case reports in a special section of the PBRER **Additional pharmacovigilance activities:** None.
AEs associated with increased absorption of oral concomitant	**Routine risk minimisation measures:** SmPC Section 4.4 and Section	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal**

Safety concern	Risk minimisation activities	Pharmacovigilance activities
medications	4.5. PL Section 2 **Additional risk minimisation measures:** None.	**detection** Separate presentation of respective case reports in a special section of the PBRER. **Additional pharmacovigilance activities:** Registry TED-R13-002.
Local skin reactions	**Routine risk minimisation measures:** SmPC Section 4.8. PL Section 4. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Potential for off-label use in patients with active Crohn's disease	**Routine risk minimisation measures:** SmPC Section 4.1 and Section 4.2. PL Section 1 and Section 3. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Separate presentation of respective case reports in a special section of the PBRER **Additional pharmacovigilance activities:** None.
Medication errors	**Routine risk minimisation measures:** SmPC Section 4.2, Section 4.9 and Section 6.6. PL Section 3 and Section 5. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Separate presentation of respective case reports in a special section of the PBRER **Additional pharmacovigilance activities:** None.
Compromised nutritional status	**Routine risk minimisation measures:** SmPC Section 4.2. PL Section 2. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Separate presentation of respective case reports in a special section of the PBRER **Additional pharmacovigilance**

Safety concern	Risk minimisation activities	Pharmacovigilance activities
		activities: 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, or in patients with malignancies within the last 5 years	**Routine risk minimisation measures:** SmPC Section 4.4. PL Section 2. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** Registry TED-R13-002.
Lack of experience in pregnant or lactating women	**Routine risk minimisation measures:** SmPC Section 4.6. PL Section 2. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Documentation and reporting of pregnancy outcomes in accordance with documented company routine pharmacovigilance procedures. **Additional pharmacovigilance activities:** Registry TED-R13-002.
Long-term safety in the paediatric population	**Routine risk minimisation measures:** SmPC Section 4.2 and Section 4.8. PL Section 1 and Section 4. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** Registry TED-R13-002.
Limited long-term safety data over 1 year of exposure	No risk minimisation activities are proposed at this time. Additional safety data will be available following completion of the NIS.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:**

Safety concern	Risk minimisation activities	Pharmacovigilance activities
		Registry TED-R13-002.
Lack of data in subjects with pre-existing severe hepatic impairment	**Routine risk minimisation measures:** SmPC Section 4.2. PL Section 2. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** Registry TED-R13-002.

Part VI: Summary of the risk management plan

Summary of risk management plan for Revestive (Teduglutide)

This is a summary of the risk management plan (RMP) for Revestive. The RMP details important risks of Revestive, how these risks can be minimised, and how more information will be obtained about Revestive's risks and uncertainties (missing information).

Revestive's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Revestive should be used.

This summary of the RMP for Revestive should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Revestive's RMP.

I. The medicine and what it is used for

Revestive is authorised for the treatment of patients 1 year and above with Short Bowel Syndrome (SBS) (stable following a period of intestinal adaptation after surgery) (see SmPC for the full indication). The indication extension is being proposed in patients 4 months corrected gestational age and above. It contains teduglutide as the active substance and it is given by subcutaneous route.

Further information about the evaluation of Revestive's benefits can be found in Revestive's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/revestive.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Revestive, together with measures to minimise such risks and the proposed studies for learning more about Revestive's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Revestive is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Revestive are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Revestive. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety

of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	• Biliary AEs • Pancreatic AEs • Cardiovascular AEs associated with fluid overload • GI stenosis and obstruction • GI stoma complications • Intestinal Polyps • Benign neoplasia of the GI tract including the hepatobiliary system • Tumour promoting ability • Anxiety
Important potential risks	• AEs associated with increased absorption of oral concomitant medications • 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 • 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

II.B Summary of important risks

Important Identified Risk– Biliary adverse events

Evidence for linking the risk to the medicine	**Non-clinical**: Teduglutide-induced hyperplasia in the gallbladder and the biliary ducts were observed in nonclinical studies and may theoretically lead to concentration of the bile with increased risk for the occurrence of sludge and stones. **Clinical studies**: Biliary events like cholecystitis, cholangitis, and cholelithiasis have been observed in clinical trials. No obstruction of the bile ducts has been observed in clinical and nonclinical studies

[redacted]

Important Identified Risk– Biliary adverse events

	with teduglutide.
Risk factors and risk groups	The SBS population is too small for stratified data analysis and the existence of risk groups is unknown. Risk factors for cholecystitis mirror those for cholelithiasis. The overall incidence of gallbladder disease was about twice as high in women as in men, and it increased with age in both sexes without any evidence of an excess in the forties. Increase in weight and number of pregnancies were each associated with increased incidence. Additional risk factors include rapid weight loss and pregnancy (elevated progesterone levels during pregnancy may cause biliary stasis). Also, recent operation and consequences of previous intestinal surgery are associated with the occurrence of cholecystitis.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.2, Section 4.4 and Section 4.8. PL section 4. **Additional risk minimisation measures:** No risk minimisation activities.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Registry TED-R13-002 See Section II.C of this summary for an overview of the post-authorisation development plan.

Important Identified Risk – Pancreatic adverse events

Evidence for linking the risk to the medicine	**Non-clinical**: Teduglutide-induced hyperplasia in the gallbladder and the biliary ducts were observed in nonclinical studies and may theoretically lead to concentration of the bile with increased risk for the occurrence of sludge and stones. Also, hyperplasia of the pancreatic duct has been shown in nonclinical studies. **Clinical studies:** Pancreatic adverse events such as chronic and acute pancreatitis, pancreatic duct stenosis, pancreas infection and increased blood amylase and lipase have been reported in clinical studies.
Risk factors and risk groups	The SBS population is too small for stratified data analysis and the existence of risk groups is unknown. Pancreatitis is generally caused by toxic-metabolic events (e.g., alcohol, smoking, hyperlipidaemia), by duct obstruction and may also have a genetic, idiopathic or autoimmune aetiology. Thus, risk factors for pancreatitis partially mirror those for cholelithiasis and sludge. The overall incidence of gallbladder disease was about twice as high in women as in men, and it increased with age in both sexes without any evidence of an excess in the forties. Increase in weight and number of pregnancies were each associated with increased incidence. Also, the use of PN and the potential hyperlipidaemia

[redacted]

Important Identified Risk – Pancreatic adverse events

	might contribute to the occurrence of pancreatitis.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.2, Section 4.4 and Section 4.8. PL Section 4. **Additional risk minimisation measures:** No risk minimisation activities.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Registry TED-R13-002 See Section II.C of this summary for an overview of the post-authorisation development plan.

Important Identified Risk: Cardiovascular adverse events associated with fluid overload

Evidence for linking the risk to the medicine	**Clinical Trials**: Fluid overload and congestive heart failure have been observed in adults in clinical trials.
Risk factors and risk groups	The SBS population is too small for stratification.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.2, Section 4.4 and Section 4.8. PL Section 2 and Section 4. **Additional risk minimisation measures:** No risk minimisation activities.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Registry TED-R13-002 See Section II.C of this summary for an overview of the post-authorisation development plan.

Important Identified Risk: Gastrointestinal stenosis and obstruction

Evidence for linking the risk to the medicine	**Clinical Trials.** Cases of intestinal obstruction have been reported in adult clinical studies.
Risk factors and risk groups	The SBS population is too small for stratified data analysis.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.2, Section 4.4 and Section 4.8. PL section 4.

Important Identified Risk: Gastrointestinal stenosis and obstruction

	Additional risk minimisation measures: No risk minimisation activities.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Registry TED-R13-002 See Section II.C of this summary for an overview of the post-authorisation development plan.

Important Identified Risk: Gastrointestinal stoma complications

Evidence for linking the risk to the medicine	**Clinical Studies**: Stoma complications have been observed in clinical studies.
Risk factors and risk groups	The SBS population is too small for stratified data analysis and the existence of risk groups is unknown.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.2 and Section 4.8. PL section 4. **Additional risk minimisation measures:** No risk minimisation activities.

Important Identified Risk: Intestinal polyps

Evidence for linking the risk to the medicine	**Nonclinical:** Teduglutide bears the potential risk to enhance the growth of colon polyps. In the rat carcinogenicity study, benign tumours were found in the small bowel and the extrahepatic bile ducts. **Clinical:** Polyps were observed in adult patients in clinical studies.
Risk factors and risk groups	The SBS population is too small for stratified data analyses and the existence of risk groups is unknown. However, data from literature and from other populations indicate the following risk factors: **Age** Background prevalence between 23 and 41% in persons between ages of 50 and 82 years and between 7 and 40% for persons younger than 50 years of age. **Crohn's Disease / Ulcerative Colitis** The risk for colorectal cancer for subjects with active Crohn's disease/ulcerative colitis is approximately an 18-fold increase greater than for a person without chronic inflammatory bowel disease. **Presence of colon** Within the intestinal tract, colonic neoplasms are most frequent in men. Therefore, SBS subjects with colon may represent a subgroup

Important Identified Risk: Intestinal polyps

	with increased risk compared with subjects without colon.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.2, Section 4.3, Section 4.4 and Section 4.8. PL Section 2 and Section 4. **Additional risk minimisation measures:** No risk minimisation activities.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Registry TED-R13-002 See Section II.C of this summary for an overview of the post-authorisation development plan.

Important Identified Risk: Benign neoplasia of the gastrointestinal tract including the hepatobiliary system

Evidence for linking the risk to the medicine	**Nonclinical:** In the rat carcinogenicity study, benign tumours were found in the small bowel and the extrahepatic bile ducts. **Clinical**: These observations were not confirmed in clinical studies of more than one year duration.
Risk factors and risk groups	The SBS population is too small for stratified data analyses and the existence of risk factors or groups is unknown. However, data from literature and from other populations indicate the following risk factors and groups: Populations at risk of small bowel neoplasia include subjects with Crohn's disease, celiac disease, polyposis syndromes, or a history of small bowel-diverting surgeries and subjects elder than 50 years of age. Based on known risk factors for cholangiocarcinoma, it can be assumed that subjects with chronic inflammation of the biliary ducts or with liver cirrhosis of different origin are at increased risk for the occurrence of cholangiomas.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.2, Section 4.3, Section 4.4, and Section 5.1. PL Section 2. **Additional risk minimisation measures:** No risk minimisation activities.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Registry TED-R13-002 See Section II.C of this summary for an overview of the post-authorisation development plan.

Important Identified Risk: Tumour promoting ability

Evidence for linking the risk to the medicine	**Nonclinical**: Teduglutide was negative when tested in the standard battery of tests for genotoxicity. In a rat carcinogenicity study, treatment related benign neoplasms included tumours of the bile duct epithelium in males exposed to teduglutide plasma levels approximately 32- and 155-fold higher than obtained in patients administered the recommended daily dose (incidence of 1 out of 44 and 4 out of 48, respectively). Adenomas of the jejunal mucosa were observed in 1 out of 50 males and 5 out of 50 males exposed to teduglutide plasma levels approximately 10- and 155-fold higher than obtained in patients administered the recommended daily dose. In addition, a jejunal adenocarcinoma was observed in a male rat administered the lowest dose tested (animal:human plasma exposure margin of approximately 10-fold). **Clinical studies:** The clinical studies conducted could neither exclude nor confirm such an increased risk.
Risk factors and risk groups	The SBS population is too small for stratified data analyses and the existence of risk factors or groups is unknown. In general, risk groups are subjects with an increased risk for developing any kind of tumours such as an elderly population. In addition, certain subject characteristics like smoking, immune suppression therapy or previous cancers, which are known to be associated to a higher incidence / prevalence of neoplasias, are considered additional risk factors.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.2, Section 4.3, Section 4.4, and Section 5.1. PL Section 2. **Additional risk minimisation measures:** No risk minimisation activities.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Registry TED-R13-002 See Section II.C of this summary for an overview of the post-authorisation development plan.

Important Identified Risk: Anxiety

Evidence for linking the risk to the medicine	In the placebo-controlled studies CL0600-004 and CL0600-020, a higher reporting rate of subjects with anxiety has been observed in the teduglutide group compared with the placebo group. A potential mechanism for this observation is unknown. However, due to the facts that anxiety can have severe consequences and that no reports occurred in the placebo group, anxiety is considered an important identified risk.

Important Identified Risk: Anxiety

Risk factors and risk groups	The SBS population is too small for stratified data analysis and the existence of risk groups is unknown.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.8. PL Section 4. **Additional risk minimisation measures:** No risk minimisation activities.

Important Potential Risk: Adverse events associated with increased absorption of oral concomitant medications

Evidence for linking the risk to the medicine	**Clinical Trials:** Based upon the pharmacodynamic effect of teduglutide, there is a potential for increased absorption of concomitant medicinal products. No confirmed event of increased absorption of concomitant medications has occurred in the teduglutide development program.
Risk factors and risk groups	The SBS population is too small for stratified data analysis and the existence of risk groups is unknown.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.4 and Section 4.5. PL Section 2. **Additional risk minimisation measures:** No risk minimisation activities.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Registry TED-R13-002 See Section II.C of this summary for an overview of the post-authorisation development plan.

Important Potential Risk: Local skin reactions

Evidence for linking the risk to the medicine	**Non-Clinical**: Treatment-related inflammatory lesions at the injection sites were observed in all preclinical animal species. **Clinical Studies**: Injection site reactions occurred in 26% of SBS patients treated with teduglutide, compared to 5% of patients in the placebo arm. The reactions included injection site haematoma, injection site erythema, injection site pain, injection site swelling and injection site haemorrhage. The majority of reactions were moderate in severity and no occurrences led to drug discontinuation.
Risk factors and risk	The SBS population is too small for stratified data analysis and the

Important Potential Risk: Local skin reactions

groups	existence of risk groups is unknown.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.8. PL section 4. **Additional risk minimisation measures:** No risk minimisation activities.

Important Potential Risk: Potential off-label use in patients with active Crohn's disease

Evidence for linking the risk to the medicine	Post marketing reports
Risk factors and risk groups	The Risk group might be patients with active Crohn's disease with concomitant SBS not adequately treated for Crohn's disease.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.1 and Section 4.2. PL Section 1 and Section 3. **Additional risk minimisation measures:** No risk minimisation activities

Important Potential Risk: Medication errors

Evidence for linking the risk to the medicine	**Clinical Studies and Post Marketing**: Reports of accidental overdose were seen in clinical studies. Reports of medication errors are seen during the post-marketing period.
Risk factors and risk groups	The SBS population is too small for stratified data analysis and the existence of risk groups is unknown.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.2, Section 4.9 and Section 6.6. PL Section 3 and Section 5.

Important Potential Risk: Compromised nutritional status

Evidence for linking the risk to the medicine	Not applicable
Risk factors and risk groups	The SBS population is too small for stratified data analysis and the existence of risk groups is unknown. Overall, all patients getting partially, or fully independent form PN/IV could be at risk for an imbalance of nutritional status.

Important Potential Risk: Compromised nutritional status

Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.2. PL Section 2. **Additional risk minimisation measures:** No risk minimisation activities.

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

Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.4. PL Section 2. **Additional risk minimisation measures:** No risk minimisation activities.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Registry TED-R13-002 See Section II.C of this summary for an overview of the post-authorisation development plan.

Missing Information – Lack of experience in pregnant or lactating women

Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.6. PL Section 2. **Additional risk minimisation measures:** No risk minimisation activities.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Registry TED-R13-002 See Section II.C of this summary for an overview of the post-authorisation development plan.

Missing Information – Long-term safety in the paediatric population

Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.2 and Section 4.8. PL Section 1 and Section 4.

Missing Information – Long-term safety in the paediatric population

	Additional risk minimisation measures: No risk minimisation activities.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Registry TED-R13-002 See Section II.C of this summary for an overview of the post-authorisation development plan.

Missing Information – Limited long-term safety data over 1 year of exposure

Risk minimisation measures	No risk minimisation activities are proposed at this time. Additional safety data will be available following completion of the NIS.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Registry TED-R13-002 See Section II.C of this summary for an overview of the post-authorisation development plan.

Missing Information - Lack of data in subjects with pre-existing severe hepatic impairment

Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.2. PL Section 2. **Additional risk minimisation measures:** No risk minimisation activities.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Registry TED-R13-002 See Section II.C of this summary for an overview of the post-authorisation development plan.

II.C. Post-authorisation development plan

II.C.1. Studies which are conditions of the marketing authorisation

The following studies are conditions of the marketing authorisation:

Study name: Registry TED-R13-002: A Prospective, Multi-centre Registry for Patients with Short Bowel Syndrome

Purpose of the study:

Primary objective: 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 objective: To evaluate long-term clinical outcome in subjects with SBS.

II.C.2. Other studies in post-authorisation development plan

There are no studies required for Revestive.

[redacted]

Annex 4: Specific adverse drug reaction follow-up forms

Special questionnaires for follow-up for the following safety concerns:

- Biliary AEs such as cholecystitis and GI stenosis.
- 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.
- Benign neoplasia of the GI tract including the hepatobiliary system.

Pagination will differ in document appended as it has its own pagination.

[redacted]

Shire

Gallbladder disorder/Cholecystitis Questionnaire

SGSS# [case_num]: Shire Awareness Date (ddmmmyyyy): LDS Awareness Date (ddmmmyyyy):	**Send completed questionnaire by email (drugsafety@shire.com) or fax (1-484-595-8155)**

REPORTED ADVERSE EVENTS AND STATUS:

	Medical History and Adverse Event Details	**Response**
1.	Reported medical history: What is the patient's OTHER medical history and concurrent illnesses including history of Cholecystitis and/or Cholelithiasis (include dates and treatment)? What is the onset date and reason for Short bowel syndrome (SBS)?	
2.	What symptoms of the adverse event(s) did the patient have and what date did they first appear?	
3.	Was the patient hospitalized? If yes, dates of hospitalization: Date of discharge: What was the final hospital diagnosis?	☐Yes ☐No ☐Unknown
4.	If no, did the patient seek treatment at an emergency room or medical office? Please specify (include dates):	☐Yes ☐No ☐Unknown
5.	What treatment did the patient receive (i.e., surgery, medication for pain), if any?	
6.	Was a new diet prescribed? If yes, what is the new diet?	☐Yes ☐No ☐Unknown
7.	Does the patient have a family history of Cholecystitis and/or Cholelithiasis?	☐Yes ☐No ☐Unknown
8.	If yes, who in patient's family and what was the disorder?	
9.	Is the patient overweight and/or has his/her weight fluctuated?	☐Yes ☐No ☐Unknown
10.	If yes, describe weight issue (i.e., degree of obesity, duration, BMI) and/or fluctuations observed:	
11.	How long has the patient been Parenteral nutrition (PN) dependent?	
12.	Has the patient's PN been adjusted in response to the adverse event(s)? If yes, describe adjustment:	☐Yes ☐No ☐Unknown
13.	Provide the dates the patient used Revestive/Gattex and the most recent dose used:	
14.	Was Revestive/Gattex discontinued or was the dose adjusted in response to the adverse event(s): (if yes, please answer a – f)	☐Yes ☐No ☐Unknown
a.	Provide date it was discontinued (even if temporarily) OR Date dose was adjusted and the dose it was adjusted to:	

Shire

Gallbladder disorder/Cholecystitis Questionnaire

b.	Did the adverse event(s) recover or improve after Revestive/Gattex was discontinued / adjusted?	☐Yes ☐No ☐Unknown
c.	If Revestive/Gattex was discontinued, has the patient restarted use of Revestive/Gattex?	☐Yes ☐No ☐Unknown
d.	If yes, provide date of resumption of Revestive/Gattex:	
e.	Was Revestive/Gattex dose adjusted when it was resumed?	☐Yes ☐No ☐Unknown
f.	If Revestive/Gattex was resumed, did the adverse event(s) reappear?	☐Yes ☐No ☐Unknown

24. Reported concomitant medications:
What OTHER medications did the patient take at the time of or within 30 days prior to the adverse event?

Medication Name	Strength/Volume	Frequency	Indication

25. What diagnostic tests (i.e., ultrasound, ERCP, blood work, etc.) did the patient have, if any, and what were the results?

TEST(S)	DATE(S)	RESULT(S)

Signature Manifest

Document Number: RD FORM-0429 **Revision:** 01

Title: Gallbladder Disorder Questionnaire

All dates and times are in Eastern Standard Time.

RD SOP-0098 Questionnaire Forms

Final Approval and Release

Name/Signature	Title	Date	Meaning/Reason
[redacted]		10 Nov 2017, 11:33:28 AM	Approved
		10 Nov 2017, 11:35:12 AM	Approved

Shire

Pancreatitis Questionnaire

SGSS# [case_num]: Shire Awareness Date (ddmmmyyyy): LDS Awareness Date (ddmmmyyyy):		**Send completed questionnaire by email (drugsafety@shire.com) or fax (1-484-595-8155)**
REPORTED ADVERSE EVENT(S) AND STATUS:		***DATE(S) OF RECOVERY**
Medical History and Adverse Event Details		**Response**
1.	Reported medical history: What is the patient's OTHER medical history and concurrent illnesses including underlying condition precipitating Short Bowel Syndrome (SBS) and history of pancreatic disease (include dates and treatment)? What is the onset date for the patient's SBS?	
2.	If patient has a history of pancreatitis, is this episode a relapse?	☐Yes ☐No ☐Unknown
3.	Is the diagnosis acute or chronic pancreatitis?	
4.	Was the pancreatitis attributed to a procedure (i.e., post-ERCP pancreatitis)? Please specify (include dates):	☐Yes ☐No ☐Unknown
5.	What symptoms of this episode of pancreatitis did the patient have and what date did they first appear?	
6.	Since initially reported, have the adverse event(s) resolved? If yes, what were the dates of recovery for each?	*PLEASE INDICATE ABOVE
7.	Was the patient hospitalized for this episode of pancreatitis? If yes, dates of hospitalization:	☐Yes ☐No ☐Unknown
8.	If no, did the patient seek treatment at an emergency room or medical office? Please specify (include dates):	☐Yes ☐No ☐Unknown
9.	What treatment did the patient receive, if any?	
10.	Does the patient use alcohol? If yes, what kind?	☐Yes ☐No ☐Unknown
11.	How many drinks per week?	
12.	Is the patient prone to "binge" drinking? If yes, when was the most recent episode?	☐Yes ☐No ☐Unknown
13.	Was the patient advised to discontinue use of alcohol?	☐Yes ☐No ☐Unknown
14.	Was this episode associated with alcohol consumption?	☐Yes ☐No ☐Unknown
15.	Does the patient have a history of cigarette smoking? If yes, how many packs/day and for how long?	☐Yes ☐No ☐Unknown
16.	Has the patient been treated for, or do they have	☐Yes ☐No ☐Unknown

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Pancreatitis Questionnaire

	gallstones?	
17.	If yes, were gallstones removed?	☐Yes ☐No ☐Unknown
18.	If gallstones were not removed, when was the most recent follow-up?	
19.	Does the patient have elevated triglycerides?	☐Yes ☐No ☐Unknown
20.	If yes, is this a new condition?	☐Yes ☐No ☐Unknown
21.	If it is not a new elevation in triglycerides, describe the elevation, duration and treatment for the condition:	
22.	Is there a family history of pancreatitis? If yes, does the patient have hereditary pancreatitis?	☐Yes ☐No ☐Unknown ☐Yes ☐No ☐Unknown
23.	How long has the patient been Parenteral nutrition (PN) dependent?	
24	Has the patient's PN been adjusted in response to the adverse event(s)? If yes, describe adjustment:	☐Yes ☐No ☐Unknown
25.	Provide the dates the patient used Revestive/Gattex and the most recent dose used:	
26.	(Was Revestive/Gattex discontinued or was the dose adjusted in response to the adverse event(s): If yes, please answer a – f)	☐Yes ☐No ☐Unknown
a.	Provide date Revestive/Gattex was discontinued (even if temporarily) OR Date dose was adjusted and the dose it was adjusted to:	
b.	Did the adverse event recover or improve after Revestive/Gattex was discontinued/adjusted?	☐Yes ☐No ☐Unknown
c.	If Revestive/Gattex was discontinued, has the patient restarted use of Revestive/Gattex?	☐Yes ☐No ☐Unknown
d.	If yes, provide date of resumption of Revestive/Gattex:	
e.	Was Revestive/Gattex dose adjusted when it was resumed?	☐Yes ☐No ☐Unknown
f.	If Revestive/Gattex was resumed, did the adverse event reappear?	☐Yes ☐No ☐Unknown

27. Reported concomitant medications:
What OTHER medications did the patient take at the time of or within 30 days prior to the adverse event?

Medication Name	Strength/Volume	Frequency	Indication

28.	What diagnostic tests did the patient have, if any, and what were the results?

Shire

Pancreatitis Questionnaire

TEST(S)	DATE(S)	RESULT(S)

Signature Manifest

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Title: Pancreatitis Questionnaire

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Fluid Overload Questionnaire

SGSS# [case_num]: **Shire Awareness Date (ddmmmyyyy):** **LDS Awareness Date (ddmmmyyyy):**		**Send completed questionnaire by email (drugsafety@shire.com) or fax (1-484-595-8155)**
REPORTED ADVERSE EVENTS AND STATUS:		***DATE(S) OF RECOVERY**
Medical History and Adverse Event Details		**Response**
1.	Reported medical history: What is the patient's OTHER medical history and concurrent illnesses (including cardiovascular disease and type) and concurrent illnesses? What is the onset date and reason for Short bowel syndrome (SBS)?	
2.	Since initially reported, have the adverse event(s) resolved? If yes, what were the dates of recovery for each?	*PLEASE INDICATE ABOVE
3.	Was the patient hospitalized for the adverse event(s)? If yes, dates of hospitalization: Date of discharge: What was final hospital diagnosis(es):	☐Yes ☐No ☐Unknown
4.	If no, did the patient seek treatment at an emergency room or medical office? Please specify:	☐Yes ☐No ☐Unknown
5.	What treatment did the patient receive, if any?	
6.	How long has the patient been Parenteral nutrition (PN) dependent?	
7.	Has the patient's PN been adjusted in response to the adverse event(s)? If yes, describe adjustment:	☐Yes ☐No ☐Unknown
8.	Provide the dates the patient used Revestive/Gattex and the most recent dose used:	
9.	Was Revestive/Gattex discontinued or was the dose adjusted in response to the adverse event(s): (if yes, please answer a – f)	☐Yes ☐No ☐Unknown
a.	Provide date it was discontinued (even if temporarily) OR Date dose was adjusted and the dose it was adjusted to:	
b.	Did the adverse event(s) recover or improve after Revestive/Gattex was discontinued / adjusted?	☐Yes ☐No ☐Unknown
c.	If Revestive/Gattex was discontinued, has the patient restarted use of Revestive/Gattex?	☐Yes ☐No ☐Unknown
d.	If yes, provide date of resumption of Revestive/Gattex:	

Fluid Overload Questionnaire

e.	Was Revestive/Gattex dose adjusted when it was resumed?	☐Yes ☐No ☐Unknown
f.	If Revestive/Gattex was resumed, did the adverse event(s) reappear?	☐Yes ☐No ☐Unknown

10. Reported concomitant medications:
What OTHER medications did the patient take at the time of or within 30 days prior to the adverse event?

Medication Name	Strength/Volume	Frequency	Indication

11. What diagnostic tests did the patient have, if any, and what were the results?

TEST(S)	DATE(S)	RESULT(S)

Signature Manifest

Document Number: RD FORM-0428 **Revision:** 01

Title: Fluid Overload Questionnaire

All dates and times are in Eastern Standard Time.

RD SOP-0098 Questionnaire Forms

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[redacted]		10 Nov 2017, 11:33:28 AM	Approved
		10 Nov 2017, 11:35:12 AM	Approved

GI Stenosis/Intestinal obstruction Questionnaire

SGSS# [case_num]: Shire Awareness Date (ddmmmyyyy): LDS Awareness Date (ddmmmyyyy):		**Send completed questionnaire by email (drugsafety@shire.com) or fax (1-484-595-8155)**
REPORTED ADVERSE EVENTS AND STATUS:		***DATE(S) OF RECOVERY**
Medical History and Adverse Event Details		**Response**
1.	Reported medical history: What is the patient's OTHER medical history and concurrent illnesses including Crohn's disease and GI obstruction, onset date and reason for Short bowel syndrome (SBS)?	
2.	In addition to above, does the patient have a history of abdominal cancer treated with radiation?	
3.	How many abdominal surgeries has the patient had to date?	
4.	Does the patient have a stoma?	☐Yes ☐No ☐Unknown
5.	What symptoms of the adverse event(s) did the patient have and when did they first appear?	
6.	Since initially reported, have the adverse event(s) resolved? If yes, what were the dates of recovery for each?	*PLEASE INDICATE ABOVE
7.	Was the patient hospitalized for the adverse event(s)? If yes, dates of hospitalization: Date of discharge: What was the final hospital diagnosis?	☐Yes ☐No ☐Unknown
8.	If no, did the patient seek treatment at an emergency room or medical office? Please specify (include dates):	☐Yes ☐No ☐Unknown
9.	What treatment did the patient receive, if any?	
10.	How long has the patient been Parenteral nutrition (PN) dependent?	
11.	Has the patient's PN been adjusted in response to the adverse event(s)? If yes, describe adjustment:	☐Yes ☐No ☐Unknown
12.	Provide the dates the patient used Revestive/Gattex and the most recent dose used:	
13.	Was Revestive/Gattex discontinued or was the dose adjusted in response to the adverse event(s): (if yes, please answer a – f)	☐Yes ☐No ☐Unknown
a.	Provide date it was discontinued (even if temporarily) OR Date dose was adjusted and the dose it was adjusted to:	

GI Stenosis/Intestinal obstruction Questionnaire

b.	Did the adverse event(s) recover or improve after Revestive/Gattex was discontinued / adjusted?	☐Yes ☐No ☐Unknown
c.	If Revestive/Gattex was discontinued, has the patient restarted use of Revestive/Gattex?	☐Yes ☐No ☐Unknown
d.	If yes, provide date of resumption of Revestive/Gattex:	
e.	Was Revestive/Gattex dose adjusted when it was resumed?	☐Yes ☐No ☐Unknown
f.	If Revestive/Gattex was resumed, did the adverse event(s) reappear?	☐Yes ☐No ☐Unknown

14. Reported concomitant medications:
What OTHER medications did the patient take at the time of or within 30 days prior to the adverse event?

Medication Name	Strength/Volume	Frequency	Indication

15. What diagnostic tests did the patient have, if any, and what were the results?

TEST(S)	DATE(S)	RESULT(S)

Signature Manifest

Document Number: RD FORM-0430 **Revision:** 01

Title: GI Stenosis / Intestinal Obstruction Questionnaire

All dates and times are in Eastern Standard Time.

RD SOP-0098 Questionnaire Forms

Final Approval and Release

Name/Signature	Title	Date	Meaning/Reason
[redacted]		10 Nov 2017, 11:33:28 AM	Approved
		10 Nov 2017, 11:35:12 AM	Approved

Shire

Neoplasm Questionnaire

SGSS# [case_num]: **Shire Awareness Date (ddmmmyyyy):** **LDS Awareness Date (ddmmmyyyy):**		**Send completed questionnaire by email (drugsafety@shire.com) or fax (1-484-595-8155)**
REPORTED ADVERSE EVENT(S) AND STATUS OF THE EVENT(S): **EVENT TERM(S) [Please record here]:**		***DATE(S) OF RECOVERY**
Medical History and Adverse Event Details		**Response**
1.	Reported medical history: What is the patient's OTHER medical history and concurrent illnesses including history of neoplasm/cancer (include dates and treatment)? What is the onset date (dd/mmm/yyyy) for the patient's Short Bowel Syndrome (SBS)?	
2.	If patient has a history of cancer, provide date(s), type of cancer, site, treatment and if it metastasized:	
3.	Does the patient have a family history of cancer?	☐Yes ☐No ☐Unknown
4.	If yes, who in the family, what type of cancer, how it was treated and the outcome, if known?	
5.	If diagnosed with cancer, what other risk factors are present in the patient's profile that may have contributed to the development of this type of cancer?	
For gastrointestinal neoplasm: please answer a – j		
a.	Does the patient have a history of polyps?	☐Yes ☐No ☐Unknown
b.	If yes, provide date(s), site and treatment (ddmmmyyyy):	
c.	Prior to starting Revestive/Gattex, did the patient have a colonoscopy?	☐Yes ☐No ☐Unknown
d.	If yes, provide the date (ddmmmyyyy) of the colonoscopy:	
e.	Was a complete colonoscopy performed?	☐Yes ☐No ☐Unknown
f.	Was the prep for the colonoscopy done satisfactorily?	☐Yes ☐No ☐Unknown
g.	Were any abnormalities noted, such as polyps?	☐Yes ☐No ☐Unknown
h.	Were the abnormalities addressed (e.g., the polyps were removed)?	☐Yes ☐No ☐Unknown
i.	What was the pathology result, if applicable, including: • Size of polyp(s) • Location of the polyp(s)	
j.	When is the patient to return for an additional colonoscopy?	

Shire

Shire

Neoplasm Questionnaire

SGSS# [case_num]: **Shire Awareness Date (ddmmmyyyy):** **LDS Awareness Date (ddmmmyyyy):**		**Send completed questionnaire by email (drugsafety@shire.com) or fax (1-484-595-8155)**
6.	Since initially reported, have the adverse event(s) resolved? If yes, what were the dates of recovery for each?	*PLEASE INDICATE ABOVE
7.	Was the patient hospitalized for the adverse event(s)?	☐Yes ☐No ☐Unknown
8.	If yes, dates (ddmmmyyyy) of hospitalization and final diagnosis for the adverse event(s): Date (ddmmmyyyy) of discharge:	
9.	If no, did the patient seek treatment at an emergency room or medical office? Please specify (include dates):	☐Yes ☐No ☐Unknown
10.	What treatments did the patient receive, if any?	
11.	How long has the patient been Parenteral nutrition (PN) dependent?	
12.	Has the patient's PN been adjusted in response to the adverse event(s)? If yes, describe adjustment:	☐Yes ☐No ☐Unknown
13.	Provide the dates the patient used Revestive/Gattex and the most recent dose used:	
14.	Was Revestive/Gattex discontinued or was the dose adjusted in response to the adverse event(s): (if yes, please answer k - p)	☐Yes ☐No ☐Unknown
k.	Provide date (ddmmmyyyy) it was discontinued (even if temporarily) OR Date (ddmmmyyyy) dose was adjusted and the dose it was adjusted to:	
l.	Did the adverse event(s) recover or improve after Revestive/Gattex was discontinued / adjusted?	☐Yes ☐No ☐Unknown
m.	If Revestive/Gattex was discontinued, has the patient restarted use of Revestive/Gattex?	☐Yes ☐No ☐Unknown
n.	If yes, provide date (ddmmmyyyy) of resumption of Revestive/Gattex:	
o.	Was Revestive/Gattex dose adjusted when it was resumed?	☐Yes ☐No ☐Unknown
p.	If Revestive/Gattex was resumed, did the adverse event(s) reappear?	☐Yes ☐No ☐Unknown

Shire

Shire

Neoplasm Questionnaire

SGSS# [case_num]: Shire Awareness Date (ddmmmyyyy): LDS Awareness Date (ddmmmyyyy):	Send completed questionnaire by email (drugsafety@shire.com) or fax (1-484-595-8155)

15. Reported concomitant medications:
What OTHER medications did the patient take at the time of or within 30 days prior to the adverse event?

Medication Name	Strength/Volume	Frequency	Indication

16. What diagnostic tests did the patient have, if any, and what were the results (including benign, malignant, stage, size, etc.)?

TEST(S)	DATE(S) (ddmmmyyyy)	RESULT(S)

QUESTIONNAIRE COMPLETED BY			
	Printed Name:		Today's Date (ddmmmyyyy):
	Signature:		
	Address:		
	Contact Number:		Email:

Shire

Signature Manifest

Document Number: RD FORM-0434 **Revision:** 01

Title: Neoplasm Questionnaire

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RD SOP-0098 Questionnaire Forms

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		10 Nov 2017, 11:35:12 AM	Approved

Annex 6: Details of proposed additional risk minimisation activities (if applicable)

Not applicable.

[redacted]