7 August 2012
EMA/CHMP/525255/2012

Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Revestive

teduglutide

Procedure No.: EMEA/H/C/002345/

Note

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 Facsimile +44 (0)20 7418 8613
E-mail info@ema.europa.eu Website www.ema.europa.eu

Table of contents

1. Background information on the procedure....5
1.1. Submission of the dossier....5
1.2. Steps taken for the assessment of the product....6
2. Scientific discussion....8
2.1. Introduction....8
2.2. Quality aspects....11
2.2.1. Introduction....11
2.2.2. Active Substance....11
2.2.3. Finished Medicinal Product....13
2.2.4. Discussion on chemical, pharmaceutical and biological aspects....15
2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects....15
2.3. Non-clinical aspects....16
2.3.1. Introduction....16
2.3.2. Pharmacology....16
2.3.3. Pharmacokinetics....18
2.3.4. Toxicology....21
2.3.5. Ecotoxicity/environmental risk assessment....26
2.3.6. Discussion on non-clinical aspects....26
2.3.7. Conclusion on the non-clinical aspects....27
2.4. Clinical aspects....29
2.4.1. Introduction....29
2.4.2. Pharmacokinetics....31
2.4.3. Pharmacodynamics (PD)....35
2.4.4. Discussion on clinical pharmacology....36
2.4.5. Conclusions on clinical pharmacology....37
2.5. Clinical efficacy....37
2.5.1. Dose response study(ies)....37
2.5.2. Main studies....40
Supportive study(ies)....71
2.5.3. Discussion on clinical efficacy....77
2.5.4. Conclusions on the clinical efficacy....81
2.6. Clinical safety....81
2.6.1. Discussion on clinical safety....90
2.6.2. Conclusions on the clinical safety....92
2.7. Pharmacovigilance....93
2.8. User consultation....100
3. Benefit-Risk Balance....101
4. Recommendations....104

List of abbreviations

A4F	Asymmetrical-flow-field-flow-fractionation
ALAG	Lagtime of absorption
ASAT	Aspartate AminoTransferase
AUC	Area Under the Curve
BI	Boehringher Ingelheim
BID	Bis In Die
CD	Circular Dicroism
CHMP	Committee for Medicinal Products for Human Use
Cl_{cr}	Creatinine Clearance
C_{max}	maximum (or peak) concentration
CMH	Cochran-Mantel-Haenszel (test)
CNS	Central Nervous System
CRBSI	Catheter Related Blood Stream Infections
CSF	CerebroSpinal Fluid
DDIs	Drug-Drug-Interactions
DLS	Dynamic Light Scattering
DPP-IV	DiPeptidyl petidase-IV
DP	Drug Product
DS	Drug Substance
ECP	E. Coli Protein
EC50	Half Maximal Effective Concentration
EDTA	EthyleneDiamineTetraacetic Acid
EGF	Epidermal Growth Factor
ELISA	Enzyme-Linked ImmunoSorbent Assay
EMA	European Medicines Agency
ESRD	End Stage Renal Disease
FTIR	Fourier transform Infrared Spectroscopy
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GI	GastroIntestinal
GMP	Good Manufacturing Practice
GLP	Good Laboratory Practice
GLP-2	Glucagon-Like Peptide 2
GLP-2R	Glucagone-Like Peptide 2 Receptor
[gly]-hGLP-2	Teduglutide
hERG	human Ether-a-go-go Related Gene
HPLC	High Performance Liquid Chromatography
IC50	Half Maximal Inhibitory Concentration
ICH	International Conference on Harmonisation
IEF	Isoelectric Focusing
IGF-1	Insulin-Like Growth Factor 1
IPC	Integrated Process Control
IPTG	Isopropyl-β-D-Thiogalactoside
ITT	Intention To Treat (population)
i.v.	intravenous
KGF	Keratinocyte Growth Factor
LC-MS/MS	Liquid Chromatography method with tamdem Mass Spectrometry
LLOQ	Lower Level of Quantification
NCA	Non-Compartmental Analysis
NOAEL	Non Observable Adverse Effect Level
NPS	Natural Product Sciences
NZW	New Zeland White
PA	Protocol Assistance
PAGE	Polyacryl Amide Gel Electrphoresis
PFS	PreFilled Syringe
pI	Isoelectric point
PIP	Paediatric Investigational Plan
PK	PharmacoKinetic
PN	Parenteral Nutrition

PopPK	Population Pharmacokinetics
PP	Per Protocol (population)
QD	Quaque Die
RP-HPLC	Reverse Phase High Performance Liquid Chromatography
SBS	Short Bowel Syndrome
s.c.	subcutaneous
SDS-PAGE	Sodium Dodecyl Sulfphate Polyacryl Amide Gel Electrphoresis
SEC	Size Exclusion Chromatography
SGLT	Sodium-dependent GLucose coTransporters
SGS	Société Générale de Surveillance
SmPC	Summary of Product Characteristics
SOCs	System Organ Classes
SOP	Standard Operating Procedure
sWfI	sterile Water For Injection
$t_{1/2}$	Half Life
TAMC	Total Aerobic Microbial Count
TAMV	Time Averaged Maximal Velocity
TEAEs	Treatment Emergent Adverse Events
TESAEs	treatment Emergent Serious Adverse Events
T_{max}	time for C_{max}
TPN	Total Parenteral Nutrition
TSE	Transmissible Spongiform Encephalopathy
TYMC	Total Yeasts Moulds Count
V_d	Volume of distribution
WBC	White Blood Cells
WCB	Working Cell Bank

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Nycomed Danmark ApS submitted on 3 March 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Revestive, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 26 May 2010.

Revestive, was designated as an orphan medicinal product EU/3/01/077 on 11 December 2001. Revestive was designated as an orphan medicinal product in the following indication: Treatment of Short Bowel Syndrome.

The applicant applied for the following indication: Treatment of Short Bowel Syndrome.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/238/2010 on the agreement of a paediatric investigation plan (PIP). At the time of the submission of the application, the PIP (EMEA-000482-PIP0108) was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

The application did not contain a critical report pursuant to article 8 of Regulation (EC) No 141/2000 and Article 3 of the Commission Regulation (EC) No 847/2000, addressing the possible similarity with authorised orphan medicinal products.

Derogation from market exclusivity

Not applicable

Applicant's request for consideration

Conditional Marketing Authorisation

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14(7) of the Regulation 726/2004 based on the following claims: Nycomed wishes to apply for a conditional marketing authorisation for Teduglutide for the treatment of adult patients with short bowel syndrome (SBS). Nycomed request consists of justifications to show that Teduglutide falls within the scope of the conditional marketing authorisation regulation (Article 2 of EC Regulation N°507/2006). Indeed, given its EU orphan drug designation (EU/3/01/077), Teduglutide falls into the Article 2(3) of EC Regulation N°507/2006 that qualifies for a conditional marketing authorisation. Moreover, Nycomed claims that the requirements for conditional marketing authorisation are fulfilled (Article 4 of EC Regulation N°507/2006), together with Nycomed's proposal for completion of complementary ongoing studies.

New active Substance status

The applicant requested the active substance Teduglutide contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Protocol Assistance

The applicant received Protocol assistance in July 2003 (EMEA/CPMP/SAWG/3829/03), procedure no EMEA/H/SA/420/1/2003/PA) and Follow-up protocol assistance in June 2007 (EMEA/CHMP/SAWP/257466/2007, procedure No EMEA/H/SA/420/1/FU/1/2007/PA/II). The protocol assistance and the follow-up protocol assistance pertained to clinical development of the dossier. Furthermore, the applicant received protocol assistance in June 2010 (EMA/CHMP/SAWP/359238/2010, procedure No EMEA/H/SA/430/3/2010/PA/PED/III). The protocol assistance pertained to paediatric development of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jens Ersbøll Co-Rapporteur: Harald Enzmann

- The application was received by the EMA on 3 March 2011.
- The procedure started on 23 March 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 14 June 2011. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 10 June 2011.
- During the meeting on 18-21 July 2011 the CHMP adopted the report from the Biologics Working Party.

- During the meeting on 18-21 July 2011, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 22 July 2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 9 January 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 24 February 2012.
- During the meeting on 12-15 March 2012 the CHMP adopted the report from the Biologics Working Party.
- During the CHMP meeting on 12-15 March 2012, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 23 April 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 7 May 2012.
- During a meeting of an Expert group on 8 May 2012, experts were convened to address questions raised by the CHMP.
- During the CHMP meeting on 21-24 May 2012, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 21-24 May 2012 the CHMP adopted the report from the Biologics Working Party.
- During the CHMP meeting on 21-24 May 2012, the CHMP agreed on a second list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the second CHMP List of Outstanding Issues on 30 May 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 8 June 2012.
- The Rapporteurs circulated the updated Joint Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 15 June 2012.
- During the meeting on 18-21 June 2012, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Revestive on 21 June 2012.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Revestive as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website ema.europa.eu/Find medicine/Rare disease designations.

2. Scientific discussion

2.1. Introduction

Problem Statement

Short bowel syndrome (SBS) is a serious, disabling, socially incapacitating and potentially life-threatening condition (Nightingale and Woodward, 2006). SBS results from surgical resection, congenital defect, or disease-associated loss of intestinal absorption and is characterised by the inability to maintain protein-energy, fluid, electrolyte, or micronutrient balances when on a conventionally accepted, normal diet (O'Keefe et al., 2006).

SBS is characterised by large heterogeneity, where some patients are able to compensate for their malabsorption of fluids, electrolytes, trace elements, vitamins or nutrients by increasing oral intake and adapt metabolically (Messing et al., 1991, Jeppesen et al., 2000), whereas other patients depend on parenteral infusions (Fleming and Remington, 1981, O'Keefe et al., 2006, Buchman et al., 2003). A large part of this heterogeneity is explained by differences in remnant bowel anatomy (Nightingale and Lennard-Jones, 1993).

Although frequently life saving in Parenteral Nutrition (PN)-dependent SBS patients, the parenteral administration of fluids, electrolytes, trace elements, vitamins and nutrients may be associated with rare, but potentially life-threatening, complications. Poor catheter care technique and insertion site, tunnel and catheter related blood stream infections (CRBSI) may lead to bacteraemia and even septicaemia, and the presence of a central catheter may lead to central venous thrombosis and even embolism (Buchman et al., 2003). In addition, parenteral constituents and chronic dehydration may contribute to PN associated liver and renal disease and even eventually organ failure (Goulet et al., 2009 Lauverjat et al., 2006). Mutually, the symptoms of SBS and the inconveniences and complications in relation to parenteral support may cause potential restrictions in the lifestyle of these patients and may lead to significant impairment of their quality of life (Jeppesen et al., 1999, Baxter et al., 2006).

Factors associated with the prognosis of SBS include length of residual small intestine, presence of residual underlying disease, the presence or absence of the terminal ileum, ileocecal valve and a colon in continuity, the nature of the primary disorder, and the degree to which intestinal adaptation takes place following resection and/or intestinal injury (O'Keefe et al., 2006).

Intestinal adaptation is a process where the remaining intestine increases its absorptive capacity to compensate for the resected part. In adults, this occurs during the first 1-2 years after resection/injury, and is characterized by increase in crypt depth and villus height, mucosal hyperplasia, increased mucosal blood flow, improved segmental absorption and increased hepatobiliary secretions (O'Keefe et al., 2006).

There are no established pharmacological treatments available for the SBS condition, which receives only supportive symptoms related drug care. None the less, in recent years, the hormonal stimulation to augment remnant bowel adaptation has been suggested, with glucagon-like peptide 2 (GLP-2), a peptide which is secreted from the intestinal L-cells following meal ingestion, as a key factor in this respect.

About the product

Teduglutide is a novel recombinant analogue for GLP-2, a natural occurring peptide which is secreted primarily by the lower gastrointestinal tract. Teduglutide differs from GLP-2 due to an Alanine to

Glycine substitution in the N-Terminus of the 33 aminoacid chain constituting the molecule. The aminoacid changing confers to Teduglutide a longer half life of 2 hours compared to its naturally occurring analogue. The longer half life is due to a resistance of Teduglutide to the in vivo degradation carried out by the enzyme dipeptidyl peptidase IV.

Teduglutide naturally compares to GLP-2 in its mechanism of action. In vitro activation of G-Protein coupled GLP-2 receptors is the proof of concept.

Teduglutide (Revestive) is claimed for the following indication: Revestive is indicated for the treatment of adult patients with Short Bowel Syndrome. Patients should be stable following a period of intestinal adaptation after surgery.

Teduglutide is provided as powder and solvent for subcutaneous injection in strength of 5 mg. This is reconstituted with 0.5 ml of sterilised water for injection, i.e. after reconstitution a nominal 10 mg/ml solution is obtained. The reconstituted product containing a nominal 10 mg/ml Teduglutide solution is administrated subcutaneously with a recommended daily dose of 0.05 mg/kg body weight.

Type of application and aspects on development

This application is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

A deferral of the paediatric studies included in the approved paediatric investigation plan has been granted (PIP procedure No EMEA-000482-PIP0108, PIP decision number P/238/2010).

There is no specific regulatory guideline for the clinical development of medicinal products for the treatment of short bowel syndrome.

Protocol assistance on clinical development was given in July 2003 (EMEA/CPMP/SAWG/3829/03, procedure no EMEA/H/SA/420/1/2003/PA) and Follow-up Protocol assistance in June 2007 (EMEA/CHMP/SAWP/257466/2007, procedure No EMEA/H/SA/420/1/FU/1/2007/PA/II). Furthermore, Protocol assistance was given in June 2010 on the paediatric development (EMA/CHMP/SAWP/359238/2010, procedure No EMEA/H/SA/430/3/2010/PA/PED/III)

During the PA procedure 2003 the issues discussed were the selection of the patient population, the stabilization procedure to optimize patients' PN and i.v. fluid requirements and the PN/fluid reduction algorithm, the statistical methodology and the handling of the "functional unblinding" of patients, as they might become aware if receiving active treatment. Further, the appropriateness of the proposed 2 doses 0.05mg/kg/d and 0.10mg/kg/d and the inclusion of a placebo group were discussed and accepted by CHMP. Also the proposed primary endpoint, the percentage of patients who reduce their PN/fluid requirement by a minimum of 20% of their optimized baseline value was discussed. This was accepted by CHMP, however, it was also mentioned that the clinical significance of this variable should not be overemphasized. For instance, if patients adhere to a low frequency of infusions, a 20% reduction would not make an important difference. It was also stressed that total weaning from PN would be very significant. Furthermore, rather time of infusion than fluid volume is relevant for patients' daily life and in this regard the evaluation of quality of life would be important.

The follow-up protocol assistance was requested to get advice on the change of the primary endpoint (changed from the dichotomous response criterion to an ordered categorical criterion that accounts for both duration (weeks 16-20 as well as weeks 20-24) and intensity of response (20%-100% clinical improvement)). CHMP did not agree on the change of primary endpoint and advised the company to evaluate the primary variable as stated in the original study protocol. The changed variable could be

included as an additional secondary endpoint. Also reduction of PN in days should be included as secondary endpoint.

The protocol assistance procedure of June 2010 related exclusively to the paediatric development.

In the initial submission the applicant requested the application considered under article 14 (7) of Regulation 726/2004, i.e. a Conditional Marketing Authorisation. The pivotal basis for the application was study CL0600-004; it was proposed to submit study results from a complementary clinical phase 3 study (CL0600-20) and its ongoing safety follow-up study (CL0600-021) in post-authorisation phase. However, in order to satisfactorily address the questions raised by the CHMP, the applicant has provided the completed study CL0600-020 as well as an interim report (data cut-off date: June 30, 2011) of the ongoing study CL0600-021 including the available safety data during the assessment procedure. Consequently, the basis for the request for a Conditional Marketing Authorisation was no longer valid.

Bibliography

Baxter J.P., Fayers P.M., McKinlay A.W.. *A review of the quality of life of adult patients treated with long-term parenteral nutrition*. Clinical Nutrition (2006) 25, 543–553

Buchman A.L., Scolapio J., Fryer J.. *AGA Technical Review on Short Bowel Syndrome and Intestinal Transplantation*. Gastroenterology (2003) 124, 1111–1134

Fleming C.R., Remington M.. *Intestinal Failure. From "Clinical Surgery International. Chapter 2: Nutrition and surgical patient*. Ed. Churchill Livingstone. Edinbourgh, London Melburne, New York, 1981

Goulet O., Joly F., Corriol O., Colomb-Jung V.. *Some new insights in intestinal failure-associated liver disease*. Current Opinion in Organ Transplantation (2009) 14, 256–261

Jeppesen P.B., Langholz E., Mortensen P.B.. *Quality of life in patients receiving home parenteral nutrition*. Gut (1999) 44, 844-852

Jeppesen P.B., Hartmann B., Thulesen J., Hansen B.S., Holst J.J., Poulsen S.S., Mortensen P.B.. *Elevated plasma glucagon-like peptide 1 and 2 concentrations in ileum resected short bowel patients with a preserved colon*. (Gut 2000) 47, 370-376

Lauverjat M., Aissa A.H., Vanhems P., Bouletreau P., Fouque D., Chambrier C.. *Chronic dehydration may impair renal function in patients with chronic intestinal failure on long-term parenteral nutrition*. Clinical Nutrition (2006) 25, 75–81.

Messing B., Pigot F., Rongier M., Morin M.C., Ndeindoum U., Rambaud J.C.. *Intestinal absorption of free oral hyperalimentation in the very short bowel syndrome*. Gastroenterology, (1991) 100, 1502-1508.

Nightingale J.M.D., Lennard-Jones J.E.. *The Short Bowel Syndrome: What's new and old*. Dig Dis (1993) 11, 12-31

Nightingale J., Woodward J.M.. *Guidelines for management of patients with a short bowel*. Gut (2006) 55(Suppl IV), iv1–iv12.

O'Keefe S.J.D., Buchman A.L., Fishbein T.M., Jeejeebhoy K.N., Jeppensen P.B., Shaffer J.. *Short Bowel Syndrome and Intestinal Failure: Consensus definitions and overview*. Clinical Gastroenterology and Hepathology (2006) 4, 6–10

2.2. Quality aspects

2.2.1. Introduction

Teduglutide, [gly2]-hGLP-2, is a novel recombinant analogue of the human glucagon-like peptide-2 (GLP-2) a peptide that is secreted primarily from the lower gastrointestinal tract. Teduglutide is a 33 amino acid peptide that differs from GLP-2 in the substitution of alanine by glycine at the second position at the N-terminus. The single amino acid substitution relative to naturally occurring GLP-2 results in resistance to in vivo degradation by the enzyme dipeptidyl peptidase-IV (DPP-IV). In consequence, the extended half-life ($t_{1/2}$) of approximately 2 hours for teduglutide prolongs the biological activity compared to the native peptide which present with a $t_{1/2}$ of 7 minutes.

Due to the high analogy between the two molecules and based on the activation of the G-protein coupled GLP-2 receptor as an in vitro proof of concept, Teduglutide is deemed to have the same effects described for GLP-2. GLP-2 activation is thought to result in the release of several growth factors such as IGF-1, EGF and KGF. Native GLP-2 reduces gastric motility, inhibits gastric acid secretion, increases intestinal blood flow, and enhances the transport, absorption and utilization of nutrients. In addition, it is involved in regulating maintenance and adaptive growth of the small intestinal mucosa.

Teduglutide is provided as powder and solvent for subcutaneous injection in a strength of 5 mg. This is reconstituted with 0.5 mL of sterilised water for injection, i.e. after reconstitution a nominal 10 mg/mL solution is obtained.

2.2.2. Active Substance

Teduglutide is a single-chain polypeptide with a mass of 3750.5 Da. It has no disulfide bonds, no glycosylation sites, and no post-translational modifications. Structural investigations of teduglutide show that the peptide contains varying amounts of α-helix and β-sheet secondary structures, depending on the peptide concentration and surrounding conditions.

The biological activity of teduglutide is measured in a cell-based bioassay, where teduglutide samples are measured against a reference standard. Both teduglutide and native human GLP-2 have been demonstrated to be fully active in the bioassay.

Manufacture

Description of manufacturing process and process controls

Teduglutide is expressed by a genetically modified strain of E.coli. The cell culture process is a conventional process starting from thaw of Working Cell Bank (WCB) with inoculum build-up and a main fermentation with induction. Tetracycline is added to the fermentation medium to maintain selective pressure. Teduglutide is secreted to the medium, recovered and purified downstream by four consecutive chromatography purification steps and one final desalting step. The pool is filtered through a 0.2 µm filter, aliquoted, frozen and stored in buffer.

Control of materials

The information given on raw materials used in the teduglutide drug substance manufacturing process was considered sufficient. Information on origin, sourcing and history of the teduglutide expressing E.Coli cell line were given together with the full nucleotide sequence of the plasmid. Generation and testing of Master- and Working cell bank is acceptably performed. The procedure for generation of future WCBs was described. The genetic stability of the production strain was demonstrated.

Control of critical steps and intermediates

The number of critical steps in the teduglutide drug substance manufacturing process is limited, which reflects the relative simplicity of the teduglutide molecule and of the manufacturing process. Bioburden is controlled in the downstream process. The stability of the process intermediates has been demonstrated.

Process Validation

The process validation followed a traditional approach. Three consecutive batches were manufactured according to the pre-determined operational parameters. Overall the process validation is considered acceptable and all data presented are consistently within the acceptance criteria established for the validation as well as the in-process limits and drug substance specification. In general, the established acceptance criteria for process parameters are considered narrow and expected to support a consistent manufacturing process and thereby a consistent and acceptable quality of teduglutide drug substance. Depletion of process-derived impurities was monitored throughout the three validation runs, and found to be able to reduce these impurities to acceptably low levels.

Manufacturing process development

Three manufacturing scales and sites have been used during development of teduglutide drug substance. A side-by-side comparison of batches from the commercial site and the site manufacturing the product at the previous scale, including release testing, additional physicochemical characterisation, comparison of host-derived impurities as well as stability data have been presented. All release- and physicochemical data presented confirmed comparability of teduglutide manufactured at the two sites.

Side-by-side comparison in relation to product related impurities included batches from all three sites. Overall comparable levels of impurities have been demonstrated across the three sites and batch scales.

Given the molecular structure of teduglutide and the homology of teduglutide with the naturally occurring GLP-2, immunogenicity has been considered with respect to aggregates, E.Coli protein (ECP) and purity. The immunological events described indicated that Anti ECP antibodies developed in more than 1 out 3 patients but no effect on safety have been demonstrated.

Specification

Characterization

The characterisation was performed on drug substance batches representative for the proposed commercial process. The following techniques were employed for structure elucidation: electrospray ionization mass spectrometry, SDS-PAGE, isoelectric focusing (IEF), amino acid sequence by N-terminal sequencing, amino acid analysis, peptide mapping, CD spectroscopy polyacrylamide gel electrophoresis analysis, dynamic light scattering (DLS) and asymmetrical-flow-field-flow-fractionation. A bioassay was used to determine the biological activity.

The primary structure of teduglutide was confirmed. The level of α-helix and β-sheet was determined. Teduglutide does not exhibit a substantial amount of tertiary structure (i.e. the protein is unfolded).

Impurities

Process-related impurities are separated into host organism-derived impurities and process material-derived impurities. ECP and endotoxins are routinely measured as part of drug substance batch release testing.

Characterization of teduglutide product-related impurities was performed using several RP-HPLC methods. Most of the remaining impurities identified represent fragments of teduglutide. The identity of all significant impurities in teduglutide drug substance was evaluated by HPLC, mass spectrometry, N-terminal sequencing, and peptide mapping.

The biological activity of some of the identified impurities and potential degradation products of teduglutide was determined.

During various studies it has been demonstrated that teduglutide may form aggregates, including subvisible and visible particles. Aggregates were, however, only formed under stressed conditions and were not formed either under the manufacture or storage conditions.

Control of Drug Substance (DS)

The drug substance specification included the following parameters: appearance, identity by RP-HPLC, identity by peptide map, concentration by RP-HPLC, bioactivity, purity and impurities by RP-HPLC, Teduglutide Impurity (1-30) by RP-HPLC, ECP, pH, endotoxins, (Total Aerobic Microbial Count) TAMC and (Total Yeasts Moulds Count) TYMC. The methods were sufficiently described and validated. The bioassay setup was improved which led also to an improved precision. Analytical results from release specification testing of the presented teduglutide drug substance batches, manufactured at the commercial site and scale were within the specification.

Reference standards or materials

There is no international reference standard for teduglutide. The reference standards (teduglutide and synthetic 1-30) have been well characterised and their replacement as well as the qualification of new reference standards has been acceptably described.

Container closure system

Container closure system for storage of teduglutide drug substance was sufficiently described.

Stability

Teduglutide is a rather stable molecule which only degrades under harsh storage conditions (high temperature, low or high pH or oxidative stress). Degradation product generated under these stress conditions have not been seen under the proposed storage conditions. All data have been within the specifications and there was no trend indicating degradation or loss of activity. All data support the proposed storage of 60 months at -20°C.

2.2.3. Finished Medicinal Product

Teduglutide drug product (Revestive) is supplied in 3 ml single-use type I glass vials with bromobutyl stoppers containing 5 mg teduglutide as a lyophilised powder. The lyophilised powder is intended for reconstitution with 0.5 ml sterile water for injections immediately before self-administration by subcutaneous injection (0.05 mg/kg/day). 0.5 ml sterilised water for injections is supplied in a prefilled 1.5 ml glass syringe. Teduglutide powder vials and prefilled sWfI syringes are packed together in a carton box.

The proposed formulation contains well known excipients for peptide/protein lyophilised formulations.

Pharmaceutical Development

Numerous drug product (DP) batches have been used throughout pre-clinical and clinical development but the formulation changes have been modest.

DP batch analysis data were provided for all batches used throughout clinical development.

Manufacture of the product

Manufacturing and primary packaging, as well as part of the release testing of teduglutide drug product for commercial supply takes place at Patheon Italia S.p.a, Monza, Italy. Nycomed Danmark ApS, Roskilde, Denmark is responsible for batch release of the teduglutide drug product.

The manufacturing of teduglutide drug product comprises buffer solution preparation, drug substance thawing, compounding, prefiltration, sterilising filtration, filling/stopper placement, lyophilisation/stoppering, crimping, and visual inspection. Three consecutive validation batches were manufactured, monitored and tested at Patheon. All manufacturing steps were validated.

Container closure integrity has been demonstrated.

Product specification

Control of excipients

All excipients are compendial and no excipients are of human/animal origin.

Control of drug product

Release and shelf-life specifications for the lyophilised vial contains methods such as: Appearance, Identity and content by RP-HPLC, bioactivity, purity and impurity by RP-HPLC, rate of dissolution, water content, endotoxin, sterility.

The results of the clinical batches comply with specifications in use at the particular time of manufacture.

Container closure system

The primary packaging material was considered to be adequate to support the quality and stability of teduglutide drug product.

Extractable studies were provided. Leach studies were not considered necessary based on the toxicological assessment.

Solvent: Water for injection in PreFilled Syringe (PFS)

The information presented on pharmaceutical development as well as on manufacturers, batch formula and manufacturing process of sterilized Water for Injection (sWfI) in pre-filled syringes (PFS) was considered sufficient. Operating parameters as well as process controls and critical controls were indicated. For sterilisation, a standard procedure is used.

The manufacturing process and the IPC performed are considered appropriately described. Thorough and adequate process validation was performed.

The specification for sWfI was set according to the European Pharmacopoeia. The batch analysis data presented confirmed that the defined process will assure batch to batch reproducibility for the 0.50 ml fill volume.

The stability studies have been carried out in accordance with the current ICH/CHMP guidelines. The stability data submitted support the shelf-life of 48 months for the 0.5 mL sWfI pre-filled syringes when stored at 2-30°C.

Stability of the product

The analytical methods used for the stability studies were the same as those used for testing at release.

In general, the results support the shelf life of 36 months and the storage conditions as defined in the SmPC.

The reconstituted drug product should be used immediately as described in the SmPC.

Adventitious agents

Based on the fact that teduglutide is expressed in E.coli and that all raw material of biological origin used in the production are controlled and do not pose any risk of adventitious agents contamination risk, the overall adventitious agents safety is considered assured for teduglutide.

The materials used are unlikely to present any Transmissible Spongiform Encephalopathy (TSE) risk and are therefore considered to comply with the TSE note for guidance.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

No major objections were raised during the assessment of the quality part of the dossier.

During the evaluation process, the Applicant was requested to clarify a number of other quality concerns on the manufacturing process and the control of the drug substance and the drug product. These issues included the level of aggregate formation, acceptance criteria in specifications and the pooling of data across drug substance and drug product to establish specifications.

All these issues were satisfactorily addressed by the Applicant.

In conclusion, information on development, manufacture and control of the drug substances and drug product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

The overall Quality of Revestive is considered acceptable.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Based on the review of the data on quality, the manufacture and control of the teduglutide drug substance and the Revestive drug product are considered acceptable.

The Quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in satisfactory way.

Data has been presented to give reassurance on viral/TSE safety.

2.3. Non-clinical aspects

2.3.1. Introduction

The nonclinical safety evaluation of teduglutide was conducted in accordance with the ICH guideline S6 and its recent addendum S6(R1), and all pivotal safety studies were conducted according to Good Laboratory Practice (GLP).

2.3.2. Pharmacology

Human Glucagon-like peptide-2(GLP-2) is a peptide primarily secreted by the lower gastrointestinal tract and its activity is mediated through the G protein coupled receptor GLP-2R. It is implicated in reduction of gastric motility, inhibits gastric acid secretion, increases intestinal blood flow and enhances the transport, absorption and utilization of nutrients. In addition, it is involved in regulating maintenance and adaptive growth of the small intestinal mucosa (Estall & Drucker, 2006).

Native GLP-2 is secreted in response to luminal nutrients by the endocrine L-cell which is primarily located in the intestinal tract (Xiao et al., 1999; Estall & Drucker, 2006). The biological half life of circulating GLP-2 is relatively short (approximately 7 minutes in humans) due to extensive renal clearance and rapid degradation by the proteolytic enzyme DPP-IV (Hartmann et al., 2000; Tavares et al., 2000). The biological actions of GLP-2 may be further limited by competition at the GLP-2 receptor with its own main metabolite, GLP-2(3-33), that is produced as a result of DPP-IV cleavage. (Thulesen et al., 2002: Estall & Drucker, 2006).

Primary pharmacodynamic studies

Teduglutide was shown to increase cAMP accumulation in human embryonic kidney 293 (HEK293) cells expressing rat or human GLP-2 receptor (GLP-2R) with EC50 values (2.0 ± 0.2nM or 0.5 ± 0.1nM, respectively) comparable to native human GLP-2 (1.3 ± 0.2 nM or 0.7 ± 0.2 nM, respectively).

The primary effect of native GLP-2 is mucosal expansion of the small bowel due to the stimulation of cell proliferation in the crypt compartment and the inhibition of enterocyte apoptosis. In all species tested (mouse, rat, ferret, piglet, dog and monkey), teduglutide treatment resulted in increased small intestine weight while variable effects were seen on large intestinal weight and intestinal length. Morphologically, teduglutide (and GLP-2) treatment caused an increase in villus height as well as in crypt depth.

Two studies addressed the dose-response relationship for the pharmacological effects of teduglutide. A steep sigmoidal dose-response curve for small intestinal weight was observed when evaluated following 14 days s.c. treatment of CD-1 mice with teduglutide. The plateau phase of the dose-response curve was reached at 0.1 mg/kg/day. The ED50 was 0.065 mg/kg/day for a BID treatment

regimen and 0.05 mg/kg/day for a QD treatment regimen, respectively. Furthermore, the effects were generally reversible. In rats administered with a continuous s.c. infusion of 0.5, 2.0 and 10 mg/kg teduglutide, small intestinal weight, small intestinal length, and mucosal hyperplasia were increased to a similar extent in all the teduglutide treated rats. Hence, the plateau phase of the dose-response curve was reached already at the lowest dose level. The intestinotrophic effects in rats occurred at clinically relevant teduglutide exposure levels.

In rat models of total parenteral nutrition (TPN)-induced hypoplasia, i.v. teduglutide treatment increased small intestinal weight, protein content and villus height relative to rats only receiving TPN. No consistent treatment-effect was observed on colon weight. In a rat model of surgically induced short bowel syndrome, increased luminal diameter, increased total intestinal and mucosal weight as well as increased villus height and increased sucrase activity were observed in the proximal jejunum of teduglutide-treated resected rats (0.1 mg/kg s.c. BID) relative to vehicle treated resected rats. No treatment-effect was observed on the distal ileum. However, in a study of similar design, teduglutide treatment had no effect on any of the evaluated parameters. The applicant ascribes the lack of treatment-effect to the analyzed segments being collected from sites immediately adjacent to the resection. At these sites, the morphological adaptation is considered to be greatest, leading to less obvious treatment-related effects. The position is supported, since the conducted rat studies included evaluations within 21 days following resection during which the adaptive response was still ongoing.

In ferrets s.c. administration of teduglutide for 10 and 20 days resulted in dose-related increases in intestinal weight of this non-rodent species. Administration of teduglutide (0.3 or 1.0 mg/kg/day s.c.) for 10 days to female beagle dogs resulted in mostly dose-dependent intestinotrophic responses. In 80 % jejuno-ileal resected neonatal piglets, teduglutide treatment (1 mg/kg/day i.v. for up to 7 days) resulted in increased ileal and colonic weight, increased mucosal mass in the jejunum and ileum and increased small intestinal villus height.

Teduglutide (0.1 to 100 µg intra-arterially) caused dose-dependent stimulatory and inhibitory effects on the peristaltic reflex in the antrum, jejunum and ileum of anaesthetized dogs. Moreover, teduglutide and GLP-2 inhibited contractility in segments of rat colon with a similar IC_{50} values (5 and 13.5 nM, respectively).

Overall, the studies conducted in animal models of short-bowel syndrome support that teduglutide may have a beneficial effect in the proposed patient population.

Secondary pharmacodynamic studies

At concentrations considerably higher than the one which will be achieved clinically, teduglutide displayed no significant activity against a panel of G-protein coupled receptors composed of serontonin receptors, dopamine receptors, α1-adrenergic and muscarinic receptors and the human GLP-1 receptor.

The GLP-2R is expressed by rat and human pancreatic alpha cells and GLP-2 (10 nM) increases glucagon secretion in perfused rat pancreas as well as in humans (deHeer et al. 2007; Christensen et al. 2010). Furthermore, recent data demonstrate that GLP-2 modulate the intestinal glucose/ Na^+ transporter SGLT1 (Shirazi-Beechey et al. 2011). Hence, based on the literature data, a treatment effect on plasma glucose cannot be excluded. However, no effect on plasma glucose levels was observed in the repeat-dose toxicity studies. No consistent effect on plasma glucose was observed in the clinical studies.

Furthermore, GLP-2R mRNA has been detected at various sites within the rat brain. In vitro studies suggest that GLP-2R protein is expressed in rodent brain since functional effects of GLP-2 treatment

were observed in murine hippocampal and cortical cell cultures as well as in cultured rat astrocytes. At present, it remains to be determined whether or not GLP-2R is expressed in human brain. Brain GLP-2 has been associated with an effect on feeding behavior. Indeed, intracerebrovascularly administered GLP-2 has been shown to reduce food intake in rats (Tang-Christensen et al. 2000, 2001) whereas peripherally administered GLP-2 had no effect on appetite or energy intake in healthy volunteers (Sorensen et al. 2003). Pharmacokinetic data from rats shows that the passage of plasma teduglutide into the cerebrospinal fluid is negligible (2-5% of C_{max}). No decrease in food intake was observed in the toxicity studies conducted with teduglutide. An increase in food intake and body weight was observed in the repeat-dose toxicity studies performed in mice while this finding was neither confirmed in rats nor in Cynomolgus monkeys. Moreover, no effects were observed in the rat CNS safety pharmacology study at doses up to 25 mg/kg (80-fold the human dose on a mg/ m^2 basis). To conclude, it is considered unlikely that teduglutide should exert an effect on feeding behavior in patients.

Safety pharmacology programme

The conducted safety pharmacology studies (see table below) did not identify any risk for effects on the cardiovascular, respiratory and central nervous system (CNS). The s.c. CNS study and the i.v. cardiovascular/respiratory study applied doses 80- and 100-fold higher than what is applied clinically, respectively, when based on allometric scaling (mg/m2). Although not required for biotech products, hERG and Purkinje fiber assays were conducted. As could be expected, no treatment-related findings were made in these studies.

The results from the safety pharmacology studies are summarized in the following table.

Study type GLP status	**Species or cell type N/group**	**Route**	**Dose (mg/kg) or concentration**	**Major findings**	**Study number**
hERG channel GLP	HEK cells 3/group	*In vitro*	0.05 to 50 ng/mL	Max inhibition of 4.4%	031203.OQQ
hERG channel GLP	HEK cells 3/group	*In vitro*	30, 300 µg/mL	Max inhibition of 0.6%	070320.OQQ
Purkinje fiber GLP	Beagle dog 4/group	*In vitro*	0.05 to 5 ng/mL	Max prolongation of 8.4%	031202.OQQ
Cardiovascular and respiratory safety *in vivo* GLP	Anaesthetized Beagle dog 4/group	IV	0.1-10 mg/kg	No treatment-related findings.	1621-009-D6146
CNS safety GLP	SD rats 10/males/ Group	SC	1, 5, 25 mg/kg	No treatment-related Findings	0200RN12-001

Pharmacodynamic drug interactions

No formal studies on pharmacodynamic drug interactions have been conducted, since no such interactions are expected. The lack of non-clinical pharmacodynamic drug interaction studies is considered acceptable.

2.3.3. Pharmacokinetics

METHOD OF ANALYSIS

An enzyme-linked immunosorbent assay (ELISA) method was used to support the toxicity studies with the exception of the 90 day juvenile minipig toxicity study for which an LC-MS/MS method was applied. Overall, the methods of analysis are considered sufficiently validated.

ABSORPTION, DISTRIBUTION, METABOLISM and EXCRETION

The below tables summarises the Pharmacokinetic parameters after single dose administration of teduglutide in mouse, rat, rabbit minipig and monkey, as demonstrated across studies.

Similar pharmacokinetic properties were observed following single and repeated teduglutide dosing. Teduglutide was rapidly absorbed following s.c. dosing with peak concentrations attained in less than 1 hour in CD-1 mice and Sprague-Dawley/Wistar rats, in 0.5 to 1.5 hours in pregnant NZW rabbits, within 2 hours in Goettingen minipigs and Cynomolgus monkeys and around 4 hours in humans. The bioavailability following s.c. dosing was higher than 75% in mice, rats, rabbits, minipigs and monkeys. In mice and rats, there was an excellent relationship between dose level and plasma exposure, especially based on the AUC values. In rabbits, minipigs and monkeys, the exposure to teduglutide generally increased in a dose-proportional manner. Teduglutide plasma exposure (AUC and C_{max}) was generally lower in female mice and rats than in males while a similar trend was not observed in rabbits, minipigs or monkeys. The half-life ranged from 0.4 to 0.7 hours in mice and rats and from 0.8 to 2.0 hours in rabbits, minipigs and monkeys and was around 2 hours in humans. Teduglutide was predominantly confined to the blood compartment since the volume of distribution approximately corresponded to the blood volume in mice, monkeys and humans whereas it was higher than the blood volume in rats. The clearance of teduglutide was 163 to 744 ml/hr/kg in all species studied. Altogether, teduglutide displayed similar pharmacokinetic characteristics in the animals used for toxicity testing and in humans.

The studies investigating the distribution of teduglutide are limited. The calculated apparent volume of distribution indicated that teduglutide was mainly distributed in the plasma compartment. Conventional radiographic assays to investigate the accumulation of the test substance in the different tissues were not performed.

In order to determine whether teduglutide penetrates the blood-brain barrier, samples of cerebrospinal fluid (CSF) and plasma were collected from rats administered teduglutide s.c. at a single dose of 3 or 10 mg/kg. The CSF teduglutide concentration did not exceed 5% of the peak concentrations in plasma. The results indicated that teduglutide did not readily penetrate the blood-brain barrier.

The extent of placental transfer of teduglutide after s.c. administration to pregnant rabbits and lacteal excretion in lactating rats were investigated. Only 0.1% of the dams' plasma level was detected in foetal rabbits and did not differ from background estimates (ELISA). Hence, the transfer of teduglutide across the rabbit placenta is minimal to nonexistent. In rats, the mean milk concentration was 0.9% and 2.9% of the corresponding mean maternal plasma concentration at 1.5 and 4 hrs, respectively. Therefore, the excretion of teduglutide into rat milk is expected to be very low.

Specific studies to investigate metabolism of teduglutide are not presented. It is known, that the native GLP-2 peptide is rapidly cleaved by the serine protease DPP-IV resulting in a peptide with a significant lower activity. Teduglutide is more resistant to protease degradation when compared to GLP-2. It is expected that the teduglutide will be cleaved into small peptides and that this small degradation products will undergo the physiological metabolism of peptides and amino acids.

The excretion of teduglutide was not investigated in detail. Publications show (Tavares et al, 2000; Marier et al, 2008), that the peptide and its break down products will likely be eliminated by the kidney. Experimentally, it has been demonstrated that the kidney plays a significant role in the clearance of teduglutide.

Table. Pharmacokinetic parameters after single dose administration of teduglutide in mouse, rat, rabbit minipig and monkey:

Study ID	Species	N (group)	Dose (mg/kg)	Route	Cmax (µg/ml)		Tmax (hr)		AUC (µg hr/ml)	
					♂	♀	♂	♀	♂	♀
7203-107	Mouse (CD-1)	50 ♂/ 50 ♀	1 25	i.v.	11.0 271	7.6 207	0.08 0.08	0.08 0.08	3.52 89.5	2.27 63.7
7203-107	Mouse (CD-1)	50 ♂ /50 ♀	1 25	s.c.	2.83 46.3	2.16 31.4	0.33 0.33	0.33 0.33	2.91 69.9	1.91 49.2
ALX0600-10101-R	Rat (SD)	5 ♂/5 ♀ (1 mg/kg)	0.1 1 3 10	i.v.						
ALX0600-10101-R	Rat (SD)	5 ♂	1	s.c.	0.657		0.7			
800759	Rat (SD) Rat (WH) Rat (WH)	9 ♂/9 ♀	15 1.5 15	s.c.	5.48 0.633 5.38	5.15 0.751 5.81	0.5 0.5 0.5	0.25 0.5 0.5	12.8 0.768 7.88	8.46 0.691 7.41
7203-105	Rabbit (NZW)	12 ♂/ 12 ♀	1 25 1 25	i.v i.v. s.c. s.c.	6.5 164 1.17 9.06	5.86 174 0.738 8.57	0.08 0.08 0.5 1	0.08 0.08 0.5 1	1.95 53.5 1,82 44,5	1.92 57.3 1.53 56.9
51170	Minipig (Göttingen)	3 ♂/3 ♀	0.5 12.5 0,5 12,5	i.v. i.v. s.c. s.c..	2.00 51.6 0.639 9.44	1.78 50.0 0.640 7.96	0.3 0.3 0.8 0.9	0,3 0.3 0.8 1,6	1.70 44.3 1.38 33.3	1.44 42.66 1.16 32.5
7203-106	Monkey (cynomolgus)	3 ♂/3 ♀	0.5 12.5 0.5 12.5	i.v. i.v. s.c. s.c.	7.11 157 0.754 12.9	6.36 139 0.814 9.26	0.08 0.08 0.83 2,7	0.08 0.08 1.3 2.7	3.18 64.1 2.45 75.3	3.16 62.7 2.65 50.4

Table. Pharmacokinetic parameters after single dose administration of teduglutide in mouse, rat, rabbit minipig and monkey:

Study ID	Species	N	Dose (mg/kg)	Route	t½. el (hr)		Vd (ml/kg)		Clt (ml/hr/kg)	
					♂	♀	♂	♀	♂	♀
7203-107	Mouse (CD-1)	50 ♂/ 50 ♀	1 25	i.v.	0.39 0.92	0.41 1.1	159 371	262 628	284 279	441 392
7203-107	Mouse (CD-1)	50 ♂ /50 ♀	1 25	s.c.	0.37 0.57	0.42 0.58	- -	- -	- -	
ALX0600-10101-R	Rat (SD)	5 ♂/5 ♀ (1mg/kg)	0.1 1 3 10	i.v.	0.37 0.67 0.53 0.60	- 0.72 - -	- - - -	- - - -	419 666 521 435	- 464 - -
ALX0600-10101-R	Rat (SD)	5 ♂	1	s.c.	1.30	0.89	-			
800759	Rat (SD) Rat (WH) Rat (WH)	9 ♂/9 ♀	15 1.5 15	s.c.	0.64 0.41 0.67	0.67 0.36 0.61	- - -	- - -	- - -	- - -
7203-105	Rabbit (NZW)	12 ♂/ 12 ♀	1 25 1 25	i.v i.v. s.c. s.c.	- - - 1.6	- - 0.87 1.7	- - - -	- - - -	- - - -	- - - -
51170	Minipig (Göttingen)	3 ♂/3 ♀	0.5 12.5 0.5 12.5	i.v. i.v. s.c. s.c..	0.81 0.96 0.80 1.59	0.90 0.92 0.83 1.97	692 828 - -	996 810 - -	584 604 - -	744 616 - -
7203-106	Monkey (cynomolgus)	3 ♂/3 ♀	0.5 12.5 0.5 12.5	i.v. i.v. s.c. s.c.	1.1 3.1 1.4 1.9	1.1 2.8 1.3 1.9	252 978 - -	269 829 - -	164 217 - -	163 208 - -

2.3.4. Toxicology

To support the safety of teduglutide, a complete toxicology assessment was conducted, including single-dose toxicity, repeat-dose toxicity, genetic toxicity, carcinogenicity, reproductive and developmental toxicity, and other toxicity studies using mice, rats, cynomolgus monkeys, minipigs, and rabbits. The provided non-clinical documentation on toxicity was in accordance with the requirements laid forward in ICH S6 guideline and the ICH S6 Addendum.

Single dose toxicity

Teduglutide was evaluated for acute toxicity following 2 s.c. injections administered 8 hours apart on a single day in a mouse study (88614). The mice received a total dose of 200 mg/kg and no teduglutide-related findings were noted. The maximum tolerated dose in mice is therefore considered to be above 200 mg/kg.

The maximum s.c. dose administered in non-rodents was 50 mg/kg (25 mg/kg BID) for 13 days in pregnant rabbits (487001) and 50 mg/kg (25 mg/kg BID) for 3 days in Cynomolgus monkeys (88616) and did not produce any acute toxicity. The maximum tolerated dose in non-rodents is therefore above 50 mg/kg.

The lack of a dedicated single-dose toxicity studies is acceptable and in accordance with the current recommendations from EMA (CHMP/SWP/302413/08 and EMA/CHMP/SWP/81714/2010). The acute

toxic potential of teduglutide appears low as s.c. doses more than 50-fold higher than the recommended human daily dose were well-tolerated in mice, monkeys and pregnant rabbits.

Repeat dose toxicity

The repeat-dose studies were conducted in CD-1 mice (up to 26-weeks) and in Cynomolgus monkeys (up to 52-weeks). Mice and monkeys were chosen because both have demonstrated the expected intestinotrophic effect upon teduglutide administration. All dose levels applied in the repeat dose toxicity studies, including the lowest dose level of 0.2 mg/kg/day produced an intestinotrophic effect in mice, monkeys and rats. The upper dose level (25 mg/kg/day in monkeys and 50 mg/kg/day in rodents) was considered the highest feasible dose.

The pattern of toxicity was consistent amongst the various species studied, with the majority of the findings being associated with the pharmacodynamic action of teduglutide: Hypertrophy and hyperplasia of the intestinal mucosa and increases of food consumption and body weight compared to control. Effects on intestinal mucosa were described as increased length of intestinal villi and enlarged crypts. The exaggerated pharmacodynamic activity of teduglutide included a stimulation of cell proliferation which gave rise to hyperplasia of bile- and pancreatic duct epithelium. The inflammation observed in bile- or pancreatic ducts was most likely secondary changes related to hyperplasia-induced dysfunctions of the epithelium. These findings either partially or completely resolved during the recovery period. The hyperplasia was observed in mice and monkeys at clinical relevant exposures.

Other findings included an elevation of the transaminase enzymes, injection site reactions and signs of a response of the haematopoietic system.

The observed elevation of the transaminase enzymes was less than 2-fold in the high dose groups and neither dose-related nor associated with liver cell degeneration. The elevated ASAT values could be associated with the injection site irritation.

At the injection site, chronic inflammation was a common finding. The inflammation exhibited dose-response relationship and was most pronounced in monkeys (mild to severe) and less severe in mice (minimal to mild) and rats (minimal to moderate). At least partial recovery of the local toxicity was noted following a non-treatment period of several weeks duration.

Effects on the haematopoietic system included increased white blood cell parameters, splenic extramedullary haematopoiesis, and myeloid hyperplasia. Nevertheless, an assessment of the haemolytic potential or the plasma compatibility of teduglutide in whole blood or plasma from mouse, rat, cynomolgus monkey and human showed that teduglutide neither caused haemolysis nor precipitation at blood or plasma concentrations of 0.1, 1.0 or 10.0 mg/ml.

The applicant evaluated the effects of exaggerated pharmacology in the non-clinical species as non-adverse. Hence, the NOAEL in the pivotal chronic toxicity study in mice was 50 mg/kg/day in mice, i.e. the highest dose tested, corresponding to a mean safety margin of exposure (AUC) of more than 178-fold compared to the mean exposure level in patients treated with 0.05 mg/kg/day. The established NOAEL of 5 mg/kg/day in monkeys was based on the severity of injection site reactions at higher doses and correlated with a mean safety margin of exposure (AUC) of 54-fold. However, clinical adverse effects related to biliary and pancreatic system and clinical findings related to injection site reactions to teduglutide such as pain reactions and erythema have been recorded.

Genotoxicity

Teduglutide was negative in standard in vitro and in vivo genotoxicity studies. According to the ICH Guidance for industry S6, proteins are considered to be non-genotoxic.

Carcinogenicity

The carcinogenic potential of teduglutide and its associated risk in humans was evaluated according to the ICH Guidance for industry S6, in association with its recent addendum S6(R1). Since standard carcinogenicity bioassays are generally inappropriate for biotechnology-derived pharmaceuticals such as teduglutide, a product-specific assessment was performed, based on a 2-year rat carcinogenicity study with teduglutide and literature published on the in vitro and in vivo activity of other Gly2-GLP-2 peptides.

An overview of the conducted long-term rat carcinogenicity study is given in the table below

Study ID /GLP	**Dose/Route**	**Exposure (AUC ♂/♀)**	**Species/No. of animals**	**Major findings**
SR800070/ GLP	3, 10, 35 mg/kg/SC	2.3/2.2, 7.5/4.9, 36.5/22.9 µg*hr/ml	Rat Wistar Han IGS/50/group/sex	Cholangioma/intestinal adenoma

In a Wistar rat carcinogenicity study, treatment related benign neoplasms included tumours of the bile duct epithelium seen in males treated at 10 and 35 mg/kg/day (at an incidence of 1/44 and 4/48, respectively) and adenomas of the jejunal mucosa was seen in 1/50 males at 3 mg/kg and 5/50 males treated at 35 mg/kg/day. In addition a jejunal adenocarcinoma was observed in a male rat administered 3 mg/kg. Since a dose-response effect is present for bile duct hyperplasia and no cholangiomas are observed at 3 mg/kg, 3 mg/kg is the NOAEL for bile duct cholangiomas. However, at the terminal sacrifice, all evaluated males displayed jejunal hyperplasia, indicating that a plateau effect was obtained already at the lowest dose level (3 mg/kg). Hence, it cannot be excluded that the single cases of jejunal adenoma and jejunal adenocarcinoma observed at 3 mg/kg are related to treatment. This conclusion is supported by the finding that jejunal adenomas and carcinomas were not observed in 532 Wistar male control rats included in five carcinogenicity studies conducted within the same time frame and at the same contract research organization as the teduglutide rat carcinogenicity study. The jejunal neoplatic findings were made at plasma exposure levels ≥ 8-fold higher than is observed in patients administered the recommended daily dose.

Based on tumour initiation studies in mice, teduglutide may exert a tumour-promoting effect. Teduglutide does not have a direct growth promoting effect on isolated tumour cells thus it most likely acts indirectly via induction of release of growth mediators. Considering that teduglutide and GLP-2 induce intestinotrophic effects, it is not unexpected that intestinal neoplasms may occur following life-long treatment of rats. Hence, it cannot be excluded that teduglutide may have a tumour-promoting effect in patients undergoing long-term treatment. However, in line with the ICH S6 addendum, growth factors pose a potential carcinogenic risk which can best be evaluated by post-marketing clinical surveillance rather than further nonclinical studies. To this purpose an International Short Bowel Syndrome Registry, including reports of malignancies in patients treated with Teduglutide has been requested as post authorisation obligation. Moreover, even though the preclinical observation have not been confirmed in clinical studies, based on these data it is contraindicated for patients with a history of gastrointestinal malignancies to be treated with Teduglutide. Special warning of polyps removal is suggested before teduglutide treatment starts and an enhanced gastrointestinal survelliance for malignancies, scheduled based on the patient characteristics, should be performed. Revestive therapy should be suspended in case of active or suspected malignancy.

Reproduction Toxicity

The results from the reproductive toxicity studies conducted with teduglutide are summarized in the table below.

Study type/ Study ID / GLP	Species; Number Female/ group	Route & dose[a]	Dosing period	Major findings	NOAEL (mg/kg &AUC)
Segment I Male and female fertility/98357/ GLP	Sprague Dawley rat/22/sex/group	0, 2, 10, 50 mg/kg SC	Pre-mating/ Mating/ GD 1-7	None	50 mg/kg
Segment II Embryo-fœtal development/7203-117/GLP	Sprague Dawley rat/25♀/group	0, 2, 10, 50 mg/kg SC	GD 6-17	≥ 2: Incomplete ossification of skull/ribs	F0/F1 50 mg/kg AUC=39.2 µg*h/ml
Segment II Embryo-fœtal development/WIL-487001/GLP	NZW Rabbit/22 ♀/group	0, 2, 10, 50 mg/kg SC	GD 7-29	None	F0/F1 50 mg/kg AUC=49.6 µg*h/ml
Segment III Pre-/Post natal development/XGW 00008/GLP	Sprague Dawley rat/22♀/group	0, 2, 10, 50 mg/kg SC	GD 7-LD 20	None	F0/F1/F2 50 mg/kg AUC=39.2 µg*h/ml

[a]=dose administrated as 2 daily injections approximately 8 hours apart

Based on studies of placental transfer and milk excretion of teduglutide only limited exposure of the embryos/foetuses and pups are expected. Hence, treatment related findings were unlikely to be recorded in the reproductive toxicology studies. Indeed, no adverse effects were recorded on fertility or embryo-foetal development. The observed increased incidences of incomplete ossification of foetal skull or ribs in rat foetuses were not dose related. These changes are not uncommon in the applied strain of rats and the recorded incidences were within the range of historical background data. The reproductive development as well as viability, growth, behaviour and learning capability of the F1 generation were unaffected by treatment.

Juvenile toxicity studies were conducted in 7-day old mini-pigs and 5-day old rabbits with SC teduglutide dosing for 90 and 14-days, respectively. Similar treatment-effects as well as pharmacokinetics were observed in the juvenile and adult animals thus teduglutide treatment did not cause adverse effects on the developing gastrointestinal tract.

Local Tolerance

The results from the local tolerance studies are given in the table below:

Study type/ Study ID / GLP	Species; Number Female/ group	Route & dose (mg)	Dosing period	Major findings
14 days SC Local tolerance/ 6852-175/ GLP	Goettingen mini-pig/ 4/♀/group	SC Inj.sites: 1: 0[a,1] 2: 0[a,2] 3: 20[a,1] 4: 30[a,2] 5: 50[a,2] 6: 30[b,2]	Gr.1: Once daily Gr.2: every 4. day	**Histopathology**: Gr.1: ≥20 adverse local irritation Gr.2: ≤ 30 non-adverse local irritation; 50: non-severe local irritation
Single dose, local tolerance Rabbit ear/ 7203-101/ GLP	NZW Rabbit/ 6/♂/group	Right ear: Vehicle[2] Left ear: Teduglutide 20 mg/ml. Gr.1: IV [c] Gr.2: PV [d] Gr.3: IA [c]	Single dose	**Histopathology** (day 4/day 15): All groups: No difference from vehicle control

a=dose volume 1 ml; b=dose volume 0.6 ml; c=dose volume 1.25 ml/kg; d=dose volume 0.1 ml
1=vehicle PBS+3% mannitol+ 50 mM L-histidine; 2=vehicle PBS+3% mannitol+ 20 mM L-histidine
IV= intravenous; PV= per-venous; IA= intraarterial

Daily s.c. injections of formulations containing ≥20 mg teduglutide for 14 days induced local irritation characterized as adverse in Goettingen minipigs. Three injections of ≤30 mg teduglutide applied every fourth day induced a local reaction comparable to that of the vehicle. The local tolerance of teduglutide following intravenous, perivenous or intraarterial administration in rabbits was similar to that of the vehicle. Reactions were mainly limited to haemorrhages and erythema which were reversible. Therefore, misadministration of the medicinal product is not suspected to cause irreversible lesions.

Other toxicity studies

Antigenicity/immunogenicity

Anti-Teduglutide antibodies were investigated in the repeated dose toxicity studies. Antibodies were detected by a validated ELISA method. The following table provides an overview on the results in the different species.

Summary of Antibody Findings from Repeat-Dose Studies

Species (study no.)	Doses (mg/kg/day)	Dosing Duration (weeks)	Antibody Findings at various dose levels (mg/kg/day)
Mouse (88730)	0.2, 0.6, 2	4	2: Antibodies in 5 out of 21 females (low titers) R: No antibodies
Mouse (0470MN12.001)	2, 10, 50	13	No antibodies
Mouse (7203-112)	2, 10, 50	26	No antibodies
Rat (800069)	10, 25, 50	13	No antibodies
Monkey (88729)	0.2, 0.6, 2	4	0.6: Antibodies in 1 out of 5 males and 1 out of 5 females 2: Antibodies in 2 out of 5 males and 1 out of 5 females R: Antibodies in 1 out of 2 males (3-fold reduction in titer)
Monkey (7203-100)	1, 5, 25	13	5: Antibodies in 1 out of 6 males; no antibodies in females 25: Antibodies in 5 out of 6 males and 5 out of 6 feamles R: Antibodies in 2 out of 2 males (lower titers); no antibodies in females
Monkey (1368-100)	1, 5, 25	52	25: Antibodies in 5 out of 6 males and 2 out of 6 females R: No antibodies

Mice and monkeys developed antibodies against teduglutide. In mice the antibody response was weak and not associated with a decrease of exposure or pharmacodynamic activity. In monkeys the occurrence of antibodies was much more pronounced. However, the pharmacodynamic activity was not affected.

2.3.5. Ecotoxicity/environmental risk assessment

According to the "Guideline on the environmental risk assessment of medicinal products for human use" (EMEA, 2006), peptides are exempted from the need to provide an environmental risk assessment, because they are unlikely to result in significant risk to the environment. Thus, an environmental risk assessment for teduglutide is not required.

2.3.6. Discussion on non-clinical aspects

From the results of non-clinical experiments, the primary effect of Teduglutide is represented by mucosal expansion of the small bowel due to the stimulation of cell proliferation in the crypt compartment and the inhibition of enterocyte apoptosis. Morphologically, teduglutide (and GLP-2) treatment caused an increase in villus height as well as crypt depth.

Summary of the non-clinical pharmacokinetics indicates that teduglutide was rapidly absorbed after subcutaneous administration. The systemic exposure increased mostly linear over the applied dose range with a bioavailability above 75 % in all species investigated. No gender or strain differences

were noted. The calculated apparent volume of distribution indicates that teduglutide was mainly distributed in the plasma compartment. Distribution results indicate that teduglutide did not readily penetrate the blood-brain barrier. The transfer of teduglutide across the rabbit placenta was minimal to nonexistent and the presence of teduglutide into rat milk is expected to be very low. Specific studies to investigate the metabolism of teduglutide are not presented, but it is expected that teduglutide will be cleaved into small peptides and subsequently amino acids. The excretion of teduglutide was not investigated in detail but publications show (Tavares et al, 2000; Marie et al, 2008), that the peptide and its break down products will likely be eliminated by the kidney. This is an expected result, since small peptides are hardly retained by the renal system.

Toxicity studies evidenced no effect on reproduction, pregnancy, lactation and off spring development. This was to be expected since the placental transfer of teduglutide in rabbits and milk excretion of teduglutide in rats is very limited. Still, as a precautionary measure and as reported in the SmPC, teduglutide use during pregnancy or during breast feeding is to be avoided.

Attention should be posed on immunogenicity even though phamacokinetics seemed not be affected by increase in anti-teduglutide antibody response reported in mice and monkey. To this end a further assessment of antibody and safety data are required to be collected in the on-going long term clinical study CL0600-021 and a separate presentation of respective case reports in a special section of the PSUR is considered.

Local injection site irritation after repeated s.c. administration has been evidenced in mini-pigs at doses higer that those meant to be used in clinical practice

In the repeat-dose toxicity studies, exaggerated pharmacological effects of teduglutide including biliary and pancreatic duct hyperplasia were observed in mice and monkeys at clinical relevant exposures. The applicant considered the exaggerated pharmacodynamic effects observed at high dose levels as non adverse as they were fully/partly reversible and there was no indication of tissue dysfunction.

Based on tumour initiation studies in mice, teduglutide may exert a tumour-promoting effect. Teduglutide does not have a direct growth promoting effect on isolated tumour cells thus it most likely acts indirectly via induction of release of growth mediators. Moreover, in the long term rat carcinogenicity study, jejunal neoplastic findings were made at plasma exposure levels ≥ 8-fold higher than is observed in patients administered the recommended daily dose. Therefore, considering that teduglutide and GLP-2 induce intestinotrophic effects, it is not unexpected that intestinal neoplasms may occur following life-long treatment of rats. Hence, it cannot be excluded that teduglutide may have a tumour-promoting effect in patients undergoing long-term treatment. As previously mentioned a series of precautions have been considered in order to address this issue.

To this end a recommendation has been adopted by the CHMP in which, for information purpose, the final study report for the 2 year mouse carcinogenicity study (NPS pharmaceuticals, study protocol P09 002) should be provided within the framework of the Risk Management Plan.

2.3.7. Conclusion on the non-clinical aspects

Overall, the primary pharmacodynamic studies provided adequate evidence that teduglutide may have a beneficial effect in the proposed patient population. Altogether, teduglutide displayed similar pharmacokinetic characteristics in the animals used for toxicity testing and in humans. Valuable pre-clinical information on fertility, pregnancy, lactation and off spring development have been reflected in the SmPC. Injection site irritation and immunogenicity evidenced in animals have then been assessed in humans. Carcinogenic risks as described above are reported in the SmPC (4.3 – 4.4 – 5.3) as

reflecting suggestions for patients exclusion, preventive monitoring of pre-existing neoplastic manifestation, for measures related to continuos monitoring and for possible withdrawn of the drug in case of malignancy diagnosis. Moreover, as post authorisation measure the CHMP requested a registry for a long term observational safety study.

Bibliography

Christensen M., Knop F.K., Vilsbøll T., Aaboe K., Holst J.J., Madsbad S., Krarup T., *Glucagon-like peptide-2, but not glucose-dependent insulinotropic polypeptide, stimulates glucagon release in patients with type 1 diabetes*. Regulatory Peptides (2010) 163, 96–101

de Heer J., Pedersen J., Ørskov C., Holst J. J.. *The alpha cell expresses glucagon-like peptide-2 receptors and glucagon-like peptide-2 stimulates glucagon secretion from the rat pancreas*. Diabetologia (2007) 50, 2135–2142

Estall J.L., Drucker D.J.. *Glucagone-Like Pepetide-2*. Annu. Rev. Nutr. (2006) 26, 391–411

Hartmann B., Johnsen A.H., Ørskov C., Adelhorst K., Thim L., Holst J.J.. *Structure, measurement, and secretion of human glucagon-like peptide-2*. Peptides (2000) 21, 73–80

Iakoubov R., Lauffer L.M., Trivedi S., Kim Y.I.J., and Brubaker P.L.. *Carcinogenic Effects of Exogenous and Endogenous Glucagon-Like Peptide-2 in Azoxymethane-Treated Mice.* Endocrinology (2009) 150(9), 4033–4043

Koehler J.A., Harper W., Barnard M., Yusta B., Drucker D.J.. *Glucagon-like Peptide-2 Does Not Modify the Growth or Survival of Murine or Human Intestinal Tumor Cells.* Cancer Res (2008) 68 (19), 7897-7904

Marier J.F., Beliveau M., Mouksassi M.S., Shaw P., Cyran J., Kesavan J., Wallens J., Zahir H., Wells D., Caminis J., *Pharmacokinetics, Safety, and Tolerability of Teduglutide, a Glucagon-Like Peptide-2 (GLP-2) Analog, Following Multiple Ascending Subcutaneous Administrations in Healthy Subjects*. J Clin Pharmacol November (2008) 48 (11), 1289-1299

Shirazi-Beechey S.P., Moran A.W., Batchelor D.J., Daly K., Al-Rammahi M.. *Glucose sensing and signalling; regulation of intestinal glucose transport.* Proc Nutr Soc. (2011) 70(2), 185-93.

Sørensen L.B., Flint A., Raben A., Hartmann B., Holst J.J., Astrup A.. *No effect of physiological concentrations of glucagonlike peptide-2 on appetite and energy intake in normal weight subjects*. International Journal of Obesity (2003) 27, 450–456.

Tang-Christensen M., Larsen P.J., Thulesen J., Romer J., Vrang N.. *The proglucagon-derived peptide, glucagon-like peptide-2, is a neurotransmitter involved in the regulation of food intake*. Nature Medicine (2000) 6(7), 802-807.

Tang-Christensen M., Vrang N., Larsen P.J.. *Glucagon-like peptide containing pathways in the regulation of feeding behaviour*. International Journal of Obesity (2001) 25, Suppl 5, S42–S47

Tavares W., Drucker D.J., Brubaker P.L.. *Enzymatic- and renal-dependent catabolism of the intestinotropic hormone glucagon-like peptide-2 in rats.* Am. J. Physiol. Endocrinol. Metab. (2000) 278, E134–E139.

Thulesen J., Knudsen L.B., Hartmann B., Hastrup S., Kissow H., Jeppesen P.B., Orskov C., Holst J.J., Poulsen S.S.. *The truncated metabolite GLP-2 (3-33) interacts with the GLP-2 receptor as partial agonist.* Regulatory pepetides (2002) 103, 9-15

Thulesen J., Hartmann B., Hare K.J., Kissow H., Ørskov C., Holst J.J., Poulsen S.S.. *Glucagon-like peptide 2 (GLP-2) accelerates the growth of colonic neoplasms in mice.* Gut (2004) 53, 1145–1150

Xiao Q., Boushey R.P., Drucker D.J., Brubaker P.L.. *Secretion of the Intestinotropic Hormone Glucagon-like Peptide 2 Is Differentially Regulated by Nutrients in Humans*. Gastroenterology (1999) 117, 99–105

2.4. Clinical aspects

2.4.1. Introduction

Revestive has been studied after s.c and i.v. injection in seven phase 1 study. S.c. administration has been used for the phase 2 and for two phase 3, double blind placebo controlled studies. Long term safety of Revestive has been further evaluated in two open label studies, extension of the two phase 3 studies. One already completed at the moment of the opinion and the other still on-going and which results submission are required as post authorisation measures. An overview of the clinical development program is given in the table below.

Revestive is indicated for the treatment of adult patients with Short Bowel Syndrome. Patients should be stable following a period of intestinal adaptation after surgery.

The recommended dose of Teduglutide is 0.05 mg/Kg body weight once daily. In 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%.

There are currently no scientific guidelines available for this indication. Protocol assistance has been received from the European Medicines Agency on clinical and paediatric development.

GCP

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

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

Tabular overview of clinical studies

Type of Study	Study Identifier	Primary location in module 5	Primary objective(s) of the Study	Study Design and Type of Control	Test Product(s); Control	Number of Subjects (enrolled)	Healthy Subjects or Diagnosis of Patients	Total duration of Treatment
BA (Bioavailability)	CL0600-006	5.3.1.1	To evaluate the bioavailability of an SC injection relative to a 1-hour IV infusion of 0.12 mg/kg ALX-0600 in fasted normal healthy male and female subjects	Phase 1, single centre, open-label, randomized, 2-way crossover (two treatment, two sequence) trial	Teduglutide (ALX-0600) (0.12 mg/kg IV or SC)	14	Healthy male and female subjects	Single 1-hour IV infusion or single SC injection

Type of Study	Study Identifier	Primary location in module 5	Primary objective(s) of the Study	Study Design and Type of Control	Test Product(s); Control	Number of Subjects (enrolled)	Healthy Subjects or Diagnosis of Patients	Total duration of Treatment
Comparative BA and BE (Bioequivalence)	CL0600-015	5.3.1.2	To determine the relative bioavailability of an SC injection of 10 mg Teduglutide in the thigh and arm, relative to the abdomen	Phase 1, randomized, open-label, 3-way crossover trial	Teduglutide (10 mg SC)	18	Healthy male and female subjects	Single dose on 3 separate occasions separated by 3 days
Healthy Subject PK and Initial Tolerability	1621/13	5.3.3.1	To determine the safety and tolerability of ascending single SC doses of Teduglutide (ALX-0600) in healthy male subjects	Phase 1, single-blind, placebo-controlled trial	Teduglutide (ALX-0600) (2.5, 5, 7 and 10 mg SC); placebo control	32	Healthy male subjects	Single administration
	CL0600-022	5.3.3.1	To investigate the safety and tolerability of Teduglutide, following once or possibly twice daily SC injection	Phase 1, double-blind, randomized, placebo-controlled, multi-dose trial	Teduglutide (20, 25, 10, 15, 30, 50, 80 mg); placebo control, SC injection in the abdomen	95	Healthy male and female subjects	8 days
Intrinsic Factor PK	CL0600-017	5.3.3.3	To evaluate the effect of moderate hepatic impairment on Teduglutide pharmacokinetics following SC administration of 20 mg Teduglutide	Phase 1, open-label, parallel-group, prospective, controlled trial	Teduglutide (single, fixed dose of 20 mg administered by SC injection in the abdomen)	24 subjects (12 hepatically impaired subjects; 12 healthy matched control subjects)	Hepatically impaired subjects and healthy matched control subjects	Single, fixed dose
	CL0600-018	5.3.3.3	To evaluate the effect of renal impairment on the PK of Teduglutide following SC administration of 10 mg Teduglutide	Phase 1, open-label, parallel group, prospective trial	Teduglutide (10 mg SC injection in the abdomen)	36	Patients with renal impairment (moderate or severe renal impairment, or end stage renal disease) or healthy subjects	Single dose
Healthy subjects PD and PK/PD	C09-001	5.3.4.1	To determine the effect of a single dose of Teduglutide on cardiac repolarisation (QT, QTc interval)	Phase 1, single centre, single dose, placebo and positive controlled, 4-period, change over design	Teduglutide (5 and 20 mg SC injection); moxifloxacin (400 mg PO; positive control); placebo to Teduglutide SC (negative control)	72	Healthy male or female subjects	A single dose will be administered on Day 1 of each of the 4 treatment periods
Patient PD and PK/PD	ALX-0600-92001	5.3.4.2	To determine the safety and tolerability of a 21-day, ascending, multidose, SC administration of Teduglutide (ALX-0600) in SBS patients	Phase 2, open-label, multicentre, dose-ranging, pilot study	Teduglutide (ALX-0600) (0.03, 0.1, 0.15 mg/kg/day) administered SC once (qd) or twice daily (bid) into the abdominal area	17	Male or female SBS patients without colon or with ≥50° of their colon continuity	Teduglutide (ALX-0600) administered daily (qd or bid) for 21 days

Type of Study	Study Identifier	Primary location in module 5	Primary objective(s) of the Study	Study Design and Type of Control	Test Product(s); Control	Number of Subjects (enrolled)	Healthy Subjects or Diagnosis of Patients	Total duration of Treatment
Efficacy and safety studies	CL0600-004	5.3.5.1	To evaluate the efficacy, safety, tolerability and pharmacokinetics of Teduglutide compared with placebo in patients with parenteral nutrition-dependent SBS.	Phase 3, placebo-controlled study	Teduglutide 0.05 mg/kg, 0.10 mg/kg or placebo, SC injection once daily	83	Male and female parenteral nutrition-dependent SBS patients	24 weeks
	CL0600-005	5.3.5.2	A Study of the Safety and Efficacy of Teduglutide in Subjects with Parenteral Nutrition-Dependent Short Bowel Syndrome Who Completed Protocol CL0600-004	Phase 3, extension study of CL0600-004	Teduglutide (0.05 or 0.10 mg/kg/day SC)	65	Patients with parenteral nutrition-dependent SBS who completed study CL0600-004	28 weeks
	CL0600-008	5.3.5.4	To assess the efficacy of different doses of Teduglutide in subjects with moderately active Crohn's disease (CD) as compared to placebo	Phase 2, randomized, double-blind, placebo-controlled study	Teduglutide (0.05, 0.10, or 0.20 mg/kg/day); one or two SC injections once daily Dose-matching placebo	100	Male and female subjects with moderately active Crohn's disease	8 weeks of self-administered dosing
	CL0600-009	5.3.5.4	An open label extension study of the safety & efficacy of Teduglutide (ALX-0600) in subjects with Crohn's Disease who completed the study protocol CL0600-008	Phase 2, open-label extension of the study CL0600-008	Teduglutide (0.10 mg/kg/ day SC)	67	Patients with Crohn's Disease who completed study CL0600-008	12 weeks
	CL0600-020	5.3.5.1	To evaluate the efficacy, safety, tolerability and pharmacokinetics of Teduglutide compared with placebo in patients with parenteral nutrition-dependent SBS.	Phase 3, placebo-controlled study	Teduglutide 0.05 mg/kg or placebo, SC injection once daily	86	Male and female parenteral nutrition-dependent SBS patients	24 weeks
	CL0600-021	5.3.5.2	A Study of the Safety and Efficacy of Teduglutide in Subjects with Parenteral Nutrition-Dependent Short Bowel Syndrome Who Completed Protocol CL0600-020	Phase 3, extension study of CL0600-020	Teduglutide 0.05 mg/kg/day SC	88	Patients with parenteral nutrition-dependent SBS who completed study CL0600 020	28 weeks (on-going study)

2.4.2. Pharmacokinetics

Analytical methods

Three different assays were used to determine the concentrations of teduglutide in the clinical pharmacology program: an enzyme-linked immunosorbent assay (ELISA) and two assays based on

liquid chromatography with tandem mass spectrometric detection (LC-MS/MS (Germany), LC-MS/MS (USA).

The ELISA assay's Lower Level of Quantification (LLOQ) (0.5 ng/ml) in plasma exceeded the usual systemic GLP-2 levels of 15-80 pmol/L (0.06-0.30 ng/ml) which corresponded to less than 60% of the LLOQ. The C_{max} values of teduglutide following therapeutical doses were always above 10 ng/ml. Therefore the expected levels of GLP-2 and its main metabolite did not significantly contribute to the measured teduglutide level.

Settings of the LC-MS/MS mass analyser allowed the selection of ions +/- 1 Dalton (Da). The peak of the teduglutide ion was 1.6 Da and the difference between teduglutide and GLP-2 was 3.5 Da. This difference assured a selective quantification of both molecules, as both signals did not overlap. The maximal theoretical influence of GLP-2 peak levels on the measured teduglutide concentration was less than 2% which was not relevant with regard to the accepted variability of the analytical method.

The differences in teduglutide concentrations obtained with the LC-MS/MS assay method compared with the ELISA method were not statistically significant for blood samples collected from 30 minutes through 10 hours post-dose. At lower teduglutide plasma concentrations (<20 ng/ml), greater differences between the methods were observed.

A non-compartmental analysis (NCA) has been performed using concentrations from ELISA and LC-MS/MS (study CL0600-015). The results from the comparison of PK parameters between ELISA (test) and LC-MS/MS (reference) showed that there was no statistically significant difference in C_{max}, T_{max}, and $T_{1/2}$ between the two assays used (p-values: 0.0559, 0.305, and 0.148, respectively). AUC_{last} and AUC_{∞} showed a statistically significant difference between the two assays (p-values: 0.0008 and 0.000002, respectively). However, the relative differences (geometric means of the ratios) are -7.86% for AUC_{last} and -11.08% for AUC_{∞}. These differences have been assumed not to be relevant as the variabilities (geometric CV%) are 24.8% and 27.6% (ELISA and LC-MS/MS) for AUC_{last} and 21.8% and 26.4% for AUC_{∞}.

Nonlinear mixed-effect population modelling approaches (PopPK) were used to characterize the typical PK profile of teduglutide and determine the mean and individual subject PK paramters. Various subject characteristics were tested as potential covariates affecting the PK parameters of teduglutide.

Absorption

Bioavailability

Teduglutide was absorbed with a peak concentration at 3-5 hours after subcutaneous administration, and rapidly eliminated with $t_{1/2}$ of approximately 2 hours that has been confirmed for the to-be-marketed concentration (10 mg/mL). Teduglutide, administered as a s.c. injection possessed an absolute bioavailability of 88%. No accumulation of Teduglutide was observed following repeated subcutaneous administration.

Bioequivalence

The applicant has provided data demonstrating a lower exposure after s.c. injection in the thigh and arm and also a low acceptance for the arm as injection site was seen. Considering the variability in plasma levels, the reduction of bioavailability as being proven for arm and thigh, compared to the abdomen might be of concern. According to the popPK sampling results according to injection site, a mixed application of the injections (into abdomen and thigh) has not been obviously associated with lower plasma levels. Therefore, although the thigh had a lower exposure than 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.

Drug products from 4 different manufactures were used. No bioequivalence study has been performed on the different drug preparations used in the different clinical trials but extensive in-vitro testing has demonstrated comparability between teduglutide drug products manufactured at different sites. The applicant presented a PopPK-analysis with all available PK parameters from all early and late clinical studies, comparing the impact of the different manufactures (Group 1-4). The applicant made a thorough analysis of AUC, considered in this case as the most important PK parameter showing that Group 1 and 2 AUC was comparable to Group 4 AUC, and since Group 4 is the to-be-marketed product, it was acknowledged that these groups were comparable. The same analysis revealed that relative bioavailability, the apparent volume of distribution and the exposure (AUC) were significantly different only in Group 3 (Can/BI; 54 mg/ml). a dose investigated in study CL0600-022 exploring tolerability. As a quite large CV% of AUC was seen overall (AUC_{∞} 21.8-26.4%), the app. 20% lower values of AUC seen was not suspected to influence the overall picture of exposure. Lagtime of absorption (ALAG) was different for all groups, but this was considered not relevant by the applicant due to the long term use of teduglutide. In conclusion, Group 1, 2 and 4 can be accepted as being equivalent concerning PK parameters.

Distribution

The volume of distribution has been determined for i.v. infusion, and for s.c. administration in different studies, and was given with markedly different values, ranging from 122 l to 28 l, depending on administration, type of study, and the concentration of the administered formulation. Further analyses showed that partly, the discrepant values are owed to different methods of administration of the study drug, and different method of determination of the value (steady state or single dose), and is obviously also dependant on the population studied.

Elimination

The mean clearance was approximately equivalent to the Glomerular Filtration Rate (GFR), which indicated that teduglutide was mainly cleared by the kidneys. Data from the PopPK analysis showed that Creatinine clearance (Cl_{cr}) depended on renal function. The renal clearance of teduglutide was confirmed by study CL0600-018 in renally impaired volunteers. Teduglutide was eliminated with a $t_{½}$ of 1.6 and 1.7 hours, respectively, in subjects with moderate and severe renal impairment, and 2.2 hours in subjects with end stage renal disease (ESRD) compared with 1.4 to 1.6 hours in healthy matched-control subjects.

Metabolism

The metabolism of Teduglutide in the body has not fully been investigated. Being a peptide, teduglutide is not likely to be metabolized by common drug metabolizing enzymes such as CYP, glutathione-S-transferase, uridine- diphosphate glucuronyltransferase. Instead it is likely to be metabolized by hydrolytic degradation like native GLP-2. It is assumed that the protein will be cleaved within the plasma to smaller proteins by unspecific proteinases, and by DDP-IV, which is responsible for the degradation of GLP-2. However, teduglutide has a markedly higher resistance to degradation from DDP-IV, resulting in longer half-life, as compared to its native counterpart. Therefore, considering the nature of the compound being a short-chain protein, almost similar to endogenous GLP-2, the expected consequence of teduglutide metabolism is degradation to small peptides and amino acids.

Dose proportionality and time dependencies

The exposure to teduglutide (C_{max} and AUC) increased in a dose-dependent manner thus possessing dose-proportional pharmacokinetics. In the tolerability study CL0600-022 the total exposure of teduglutide increased proportionally with increasing dose levels and peak plasma concentrations increased in a proportional manner over the dose range of 10 to 80 mg. The PK-parameters were very similar across dose ranges between 10 and 80 mg teduglutide administered daily on Day 1 compared to Day 8, suggesting minimal accumulation of the drug following repeated subcutaneous administrations.

Special populations

None of the covariates age, gender, race and dosing occasion had a significant effect on the PK parameters Cl/F, V/F, and Ka. This has been confirmed by an updated PopPK analysis. Similar PK results have been reported in healthy subjects, and patients with SBS or Crohn's disease. Moreover, moderate hepatic impairment (Child-Pugh classification, Grade B) has been demonstrated to slightly impact reducing the PK parameters of maximum and overall exposure of 10-15. On the other hand, subjects with renal impairment are expected to be exposed to higher teduglutide level due to reduction of elimination. Progressive renal impairment, including end stage renal disease, impacted on PK parameters of Teduglutide, with an increase up to a factor of 2.6 for AUCinf and 2.1 for Cmax when comparing patients to healthy subjects.

Weight of the subject/patient has been detected to be a significant factor for the PK of teduglutide during a first analysis. The addition of the prediction of the exposures according to body weight (based on the new Pop-PK model, which has – contrary to the original model – taken the higher clearance in SBS patients into account) has still a high variability, and an overall range from the lowest body weight of 40 kg to the highest of 120 kg of more than 100%. As this can overall obviously not be avoided – even with the fixed dosing – the final proposed dosing scheme has been considered acceptable, because this has been tested in the clinical studies.

Pharmacokinetic interaction studies

An *in vitro* pilot study has demonstrated that teduglutide did not inhibit the activity of any of the human cytochromes at concentrations 4- and 40-fold of the peak concentrations occurring in humans at a clinical dose of 0.05 mg/kg/day. In addition, teduglutide being administered subcutaneously determines that potential PK drug interactions associated with first pass metabolism or efflux mechanisms in the intestine or liver are of no consequence.

After in-vitro investigations of interaction with cytochrome metabolizing enzymes have shown that the potential drug drug interaction is low, the applicant, due also to the nature of the compound, did not investigate the potential for interactions any further. Moreover, the applicant has presented a PK evaluation for co-medication influence on teduglutide PK parameters, and was unable to find relevant changes

There appears to be a potential for DDIs following the PD activity of the compound, which might result in enhanced absorption of other compounds. The applicant analysis did not indicate that a relevant potential for drug-drug interactions with any of the identified concomitant medications used in the two clinical studies can be identified. Nonetheless a potential for increased absorption of concomitant medicinal products should be taken into consideration.

2.4.3. Pharmacodynamics (PD)

The clinical pharmacodynamics of the compound have been characterised in altogether 6 studies, of which 5 relate to the primary pharmacodynamics, and one relates to the secondary PD.

In three of the 5 studies dedicated to the primary PD, plasma citrulline was measured being regarded as a biomarker of enterocyte mass. These were the studies CL0600-015 in healthy volunteers (relative bioavailability of three different administration sites), study CL0600-008 (the study in CD patients), and in study CL0600-004 (the pivotal clinical study).

In general, plasma levels of citrulline increased after teduglutide treatment. However, the increase in citrulline was not associated with a decrease in PN volume. Hence, a key role of plasma citrulline in assessing the PD effect of teduglutide is not supported, and thus has not been further assessed.

In addition, PD effects were measured within study ALX-0600-92001 (the dose finding study) by measuring parameters of gastrointestinal absorption and structural changes, and in study CL0600-004, in which biopsy samples were taken from the small and large intestine.

The sixth study (C09-001) was a study to evaluate the effect of teduglutide on cardiac repolarisation (tQT study) and therefore relates to the secondary pharmacology.

Mechanism of action

The effects of native GLP-2 and teduglutide are mediated by the GLP-2R, which is a high-affinity, ligand-specific functional receptor coupled to a stimulatory G protein, which activates adenylate cyclase and thereby increases cyclic AMP concentration (Munroe et al., 1999).

Based on non-clinical data in animal models of SBS and normal animals (Drozdowski and Thomson, 2009, Estall and Drucker, 2006, Martin et al., 2004), teduglutide is expected to produce epithelial structural effects that would result in increases in absolute and relative absorption of fat, nitrogen, sodium, potassium, calories and gastrointestinal fluids and consequent decrease in faecal or stomal output of fat, nitrogen, sodium, potassium, calories and fluid.

Primary pharmacology

The 21 days dosing (Study ALX-0600-92001, for detailed description see 2.5.) with teduglutide resulted in increased jejunal villus height and crypt depth (as observed on biopsy samples) and enhanced gastrointestinal fluid absorption at doses of 0.10 and 0.15 mg/kg/day as well as improvement in the absorption of macronutrients and electrolytes, associated with decreased stomal or faecal volume and macronutrient content were observed. The absorption of all measured parameters returned to baseline level after stopping the treatment for 3 weeks.

The expansion of the absorptive epithelium by inducing significant changes in the villus height and crypt depth in the small and large intestine has been further confirmed after a 24-week treatment (study CL0600-004) with teduglutide at doses 0.05 mg/kg and 0.10 mg/kg daily. A dose response relationship could be seen regarding the expansion of the absorptive epithelium, but a dose response relationship was not seen in PN volume, probably due to the heterogeneity of the patients. The lowest dose of teduglutide, 0.05 mg/kg/day reduced the absolute amount of administered parenteral energy per week by 7916 KJ. The corresponding reduction for 0.10 mg/kg/day was 3278 KJ. The CHMP further acknowledges that this apparent lack of a dose-response relationship may be due to both doses eliciting close to the maximal effect of the drug.

Secondary pharmacology

Teduglutide appeared not to influence heart rate conduction velocity, as the results of the thorough QT study (Study C09-001) presented can exclude a relevant effect on QT. No validated cases of QTcF increase of >30 ms and no QTc values above 450 ms was seen.

Bibliography

Drozdowski L., Thomson A.B.R.. *Intestinal hormones and growth factors: Effects on the small intestine*. World J Gastroenterol (2009) 15(4), 385-406

Estall J.L., Drucker D.J.. *Glucagone-Like Pepetide-2*. Annu. Rev. Nutr. (2006) 26, 391–411

Martin G.R., Wallace L.E., Sigalet D.L.. *Glucagon-like peptide-2 induces intestinal adaptation in parenterally fed rats with short bowel syndrome*. Am J Physiol Gastrointest Liver Physiol (2004) 286, G964–G972.

Munroe D.G., Gupta A.K., Kooshesh F., Vyas T.B., Rizkalla G., Wang H., Demchyshyn L., Yang Z.J., Kamboj R.K., Chen H., McCallum K., Sumner-Smith M., Drucker D.J., Crivici A.. *Prototypic G protein-coupled receptor for the intestinotrophic factor glucagon-like peptide 2*. Proc. Natl. Acad. Sci. USA (1999) 96, 1569–1573.

2.4.4. Discussion on clinical pharmacology

Three different assays (one ELISA and two LC-MS/MS) were used in order to determine concentrations of teduglutide for characterising the pharmacokinetics of the drug. A non-compartmental analysis was performed showing no statistical significant difference in C_{max}, $T_{½}$ and T_{max} between the two assays. AUC_{last} and AUC_{∞} were different but not relevant due to large CV% for AUC. The assays have been demonstrated to be established and validated, demonstrating sufficient accuracy and precision. They have been, therefore, considered suitable for their intended use. Acceptable standard methodology has been applied for the evaluation of the PopPK

As a conclusion on bioequivalence of route of administration, the arm as injection site does not appear to be acceptable, and should be deleted from the dosing recommendations. The thigh, instead, is considered acceptable, however, only in case one of the four quadrants of the abdomen can no longer be used by the patient due to hardening, scarring, pain, etc..

In the comparison of the different drug preparation used during clinical trials the Applicant has finally provided documentation to support the claim for bioequivalence. PK parameters AUC, bioavailability and volume of distribution was comparable, except for the higher strength 54 mg/ml (can/BI), which was used in one tolerability study, and not in the dose finding study. Also for the different strengths comparable PK parameters were shown in the PopPK parameters.

The use of the Vd from the value obtained from the PopPK, as the actual Vd for Teduglutide, has been considered acceptable by CHMP, considering the fact that the distribution between volunteers and patients does not appear to be very discrepant, and the 90% CI of the value determined for patients does include the PopPK determined values for healthy volunteers (which was 31.73 l). The statement in the SPC specify that the Vd has been determined based on the data for patients.

Based on the Pharmacokinetic data on blood clearance of Teduglutide discussed by the applicant, and the questionable use of radiolabelled assay, as an appropriate method, to further investigate its metabolism and excretion, the above reported renal excretion is accepted. Furthermore, $T_{½}$ was

prolonged in patients with moderate to severe renal impairment and end stage renal disease, suggesting renal clearance of teduglutide. Creatinine clearance (CLcr) as a covariate in the PopPK analysis, predicted increasing AUC with decreasing CLcr. Therefore, it is likely that the main route of elimination is renal, and it has been acknowledged that a proper AME-study is not likely to lead to further interpretable results. Dose linearity and drug accumulation of teduglutide PK parameters are reassuring up to the dose of 20 mg either under single or repeated s.c. administration.

Special population studies indicate that particular attention should be posed on teduglutide treatment in renal impaired patients with a required dose reduction to 50% in patients with moderate and severe renal impairment. Mild and moderate hepatic impairment does not attract adjustment of the dose. Data on severly impaired hepatic patients are not available.

The conclusions stated by the applicant about drug drug interaction are endorsed: it is unlikely that clinically relevant drug-drug induction resulting from enzyme induction of CYP enzymes would occur at therapeutic doses. Nonetheless, based upon the pharmacodynamics effect of Teduglutide, there is a potential for increased absorption of concomitant medicinal products, therefore patients receiving oral medicinal products requiring titration or with a narrow therapeutic index should be monitored closely.

From the pharmacodynamic data presented, it can be deduced that teduglutide acts on the GLP-2 receptor, and exerts a roughly dose-related effect on the architecture of the epithelia of the large and small intestine with an obvious early “saturation” of the PD effects. Teduglutide increases the absorption of fluids and nutrients by increasing the expression of transporter proteins at the cellular level, and exerts a trophic effect by inducing an increase in gastrointestinal tissue mass, as proven by the increased villus height and crypt depth in the small and large intestine. Moreover, Teduglutide appears not to influence heart rate conduction velocity and, as the results of the thorough QT study presented, can exclude a relevant effect on QT.

2.4.5. Conclusions on clinical pharmacology

Further to the extensive discussion on the pharmacokinetic aspect of teduglutide, it is overall concluded that the pharmacokinetics of the compound have been studied in satisfactory manner.

The mechanism of action of teduglutide showed a dose response relationship regarding the expansion of the absorptive epithelium, even though this is not reflected in PN volume changings; the latter probably due to the heterogeneity of the patients. Teduglutide appears not to influence heart rate conduction velocity. Overall, the mechanism of action of teduglutide appears to be sufficiently clarified, and it is considered that no additional data/studies are necessary.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

Study ALX-0600-92001: The study “Open-label-multicenter, dose-ranging, pilot study to examine the safety, tolerability and effect of a 21 day, ascending, multidose subcutaneous treatment with ALX-0600 (Teduglutide) in patients with short bowel syndrome” was conducted between 2000 and 2001 in 5 trial centers in the US and Europe. The primary objective of the study was to determine the safety and tolerability of a 21-day s.c. dosing regimen of teduglutide in SBS patients. The secondary objective was to measure the PD effect on the capacity of the remaining bowel to absorb water and macronutrients after 21 days treatment. The patient population included consisted of males and

females over 18 years of age with a diagnosis of SBS due to vascular ischemic disease, malrotation, or volvulus, or with quiescent IBD. Patients should have undergone intestinal resection at least 12 months before entering the study and residual small intestine had to be less than 150 cm in length. Patients had also to present with normal body weight, normal albumin levels, and no use of glutamine supplementation for at least 4 weeks. Patients without colon were eligible and had to have at least 50% of their caloric intake by PN; patients with colon had to have at least 50% of their colon preserved with a fecal weight exceeding 1.0 kg/day (of a 72 hour stool collection period) and fecal energy loss of more than 2.0 MJ/day (or fecal fat loss of more than 50 g/day on their habitual diet). Patients with active IBD, history of pseudo obstruction, recent surgery, fistulae, and others had to be excluded.

Patients distribution to the different dose and treatment groups are summarized in the table.

Table: Dosing groups in Study 92001

Group Number	Group Description Abbreviation	Total Daily Dose of ALX-0600	Dose Frequency	No. of Treated Patients	Colon Status
1	0.03 qd	0.03 mg/kg/day	qd, 21 days	3	No colon in continuity
2	0.10 qd	0.10 mg/kg/day	qd, 21 days	5	No colon in continuity
3	0.15 qd	0.15 mg/kg/day	qd, 21 days	4	No colon in continuity
4	0.05 bid or 0.075 bid	0.10 or 0.15 mg/kg/day	bid, 21 days	5	No colon in continuity
5	0.10 colon	0.10 mg/kg/day	qd, 21 days	5	≥50% colon in continuity

The study consisted of four phases: screening phase (Days -14 to -1), a pre-dose phase (Days -3 to -1), 21-day dosing phase, and 21-day follow-up phase. The study was closed before all planned patients had been enrolled due to slow enrolment. Altoghether, 18 patients were enrolled. One study participant was discontinued before receiving study medication. A total of 17 patients therefore received study medication, of which 2 were discontinued prematurely. Of the 15 patients that completed the study, 3 patients from group 3 and 2 patients from group 3 re-enrolled into the study (Group 4).

The clinical evaluation part of the study was conducted on the PP population, which consisted of 16 patients (1 patient was excluded due to febrile episodes considered unrelated to study drug). The demographic characteristics of the study groups were approximately similar. Of the patients, 8 (47%) were male, 16 (94%) were Caucasian, and the mean age was 49 years, with a mean weight of 59 kg and mean height of 168 cm. 12 of the 17 patients had Crohn's Disease as underlying cause of SBS.

For the purpose of the PD/clinical parameters evaluation, three 72 hour nutrient absorption tests were used to measure the capacity of the intestine to absorb macronutrients. Urinanalysis test were used both for safety and for determining fluid excretion via the kidneys. D-Xylose tests with plasma and urine collections were also performed as a measure of malabsorption. The results from the 72-h nutrient absorption test were not consistent.

Table: Summary of absolute absorption by group

Nutrient	Period	0.03 qd (N=3)	0.03 qd (N=2)[1]	0.10 qd (N=5)	0.15 qd (N=3)	0.05/0.075 bid (N=5)	0.10 colon (N=5)	0.10 colon (N=4)[2]
Fat (g/day)	Baseline	14.4 ± 15.10	21.5	40.1 ± 24.96	99.9 ± 25.00	44.2 ± 26.37	30.5 ± 18.17	29.7 ± 20.86
	End of Treatment	43.7 ± 27.82	52.8	*64.4 ± 17.11	63.8 ± 12.73	*62.2 ± 13.43	39.6 ± 21.15	41.0 ± 24.17
	Follow Up		43.1	37.0 ± 28.15	65.4 ± 17.84	47.5 ± 35.30		39.9 ± 30.91
Nitrogen (g/day)	Baseline	5.6 ± 5.43	8.7	3.6 ± 6.82	9.0 ± 1.26	5.2 ± 2.12	5.5 ± 4.39	5.9 ± 4.95
	End of Treatment	6.6 ± 2.62	5.1	6.3 ± 5.81	6.5 ± 3.16	*8.1 ± 3.30	9.2 ± 6.40	8.6 ± 7.19
	Follow Up		7.1	3.7 ± 7.58	8.2 ± 2.05	6.4 ± 3.26		7.2 ± 5.43
Sodium (g/day)	Baseline	-0.7 ± 0.88	-0.6	-3.8 ± 3.88	-0.8 ± 2.01	-1.1 ± 1.73	2.2 ± 1.97	2.1 ± 2.26
	End of Treatment	-0.5 ± 2.41	-1.8	-1.7 ± 2.49	-0.3 ± 2.56	-0.8 ± 1.52	1.9 ± 0.82	1.6 ± 0.63
	Follow Up		0.1	-5.6 ± 7.14	-1.6 ± 2.64	-1.2 ± 1.44		0.6 ± 0.39
Potassium (g/day)	Baseline	0.2 ± 0.99	0.8	0.3 ± 1.36	2.6 ± 0.45	1.1 ± 0.36	0.7 ± 1.48	0.3 ± 1.33
	End of Treatment	1.3 ± 0.65	1.6	1.0 ± 1.19	2.2 ± 1.17	1.3 ± 0.53	1.1 ± 1.40	0.7 ± 1.30
	Follow Up		1.3	0.6 ± 1.45	1.8 ± 0.70	1.1 ± 0.39		0.3 ± 1.44
Calories (kcal/day)	Baseline	1119 ± 533.9	1375	943 ± 415.9	2259 ± 1093.2	1549 ± 237.8	1755 ± 593.2	1606 ± 566.2
	End of Treatment	1437 ± 206.5	1384	1346 ± 431.2	1871 ± 667.7	**1797 ± 234.6	*2000 ± 579.2	1866 ± 572.0
	Follow Up		1489	885 ± 658.8	1642 ± 106.2	1464 ± 544.3		1822 ± 412.8
Gastro-Intestinal Fluid (g/72h)	Baseline	1822 ± 852.2	1458	-2172 ± 5166.9	2827 ± 1677.0	1518 ± 2480.8	4838 ± 4510.1	3515 ± 3930.9
	End of Treatment	2208 ± 1693.0	1644	**702 ± 4723.4	5788 ± 453.0	**5021 ± 1682.9	**7090 ± 4279.1	*5942 ± 3954.1
	Follow Up		1294	-2348 ± 5419.3	1048 ± 3107.2	929 ± 3095.3		4570 ± 3104.4

Note: All data are mean ± SD.
[1]Patient 01-003 did not return for the Follow Up evaluation. Only subjects who completed all evaluations are represented in this column.
[2]Patient 06-019 did not return for the Follow Up evaluation. Only subjects who completed all evaluations are represented in this column.
0.03 qd = 0.03 mg/kg s.c. injection once daily, 0.10 qd = 0.10 mg/kg s.c. injection once daily, 0.15 qd = 0.15 mg/kg s.c. injection once daily, 0.05 bid = 0.05 mg/kg s.c. injection twice daily (rechallenge), 0.075 bid = 0.075 mg/kg s.c. injection twice daily (rechallenge), 0.10 colon = 0.10 mg/kg s.c. injection once daily in patients with >= 50% colon in continuity.
Absolute Absorption = Offered food - Declined food - Feces.
*Significant at 0.05. **Significant at 0.01. P-values are based on a two-tailed paired t-test testing change from baseline.
CROSS REFERENCES: Tables 14.2.2A to 14.2.6A, 14.2.2C to 14.2.6C, 14.2.7A REV, 14.2.7C REV. Page 1 of 1 - Program: adhoc.SAS

In this respect, it is important to take into account that this test was not fully controlled, i.e. though each patient in principle was offered identical food for three days to reflect his or her normal diet, it was not ensured that the intake was carefully monitored or identical for each patient in between study periods. This resulted in variations in the quantity and composition of ingested food between study periods.

In order to receive a more consistent picture of the activity of the compound, pooled groups were analysed and did, indeed, reveal more consistent results. For this purpose the 0.10 and 0.15 QD group (PG1), the 0.10, 0.15 QD plus colon 0.10 QD (PG2), the 0.10 QD plus 0.10 colon (PG 3), and all groups (PG4) were pooled.

2.5.2. Main studies

Study CL0600-004: 24-week double-blind, randomized, placebo-controlled, parallel group study comparing the efficacy, safety and tolerability of two doses of teduglutide (0.05 mg/kg/day and 0.10 mg/kg/day) and placebo in subjects with Parenteral Nutrition-Dependent Short Bowel Syndrome.

Methods

Study participants

A relevant adult study population with SBS due to the most common causes of SBS (surgical resections due to Crohn´s disease, cancer, vascular insufficiency and volvulus) was included in the study. SBS patients with possible fluctuating activity in the disease (due to radiation therapy, active crohn´s disease and celiac disease) were excluded. Patients had to be dependent on PN at least 3 times weekly for at least 12 months.; though the process of intestinal adaptation following major surgery (potentially influencing the effect of teduglutide) may expand beyond 12 months depending on the physiology of the remaining intestine, this is considered acceptable. Prior to randomisation to study treatment patients had to be stable in their disease for the past 4 weeks as measured by usage/volume of PN, urinary output, urine sodium, renal function, haematocrit, and motility altering medications.

Protocol criteria for inclusion included the following:

- SBS as a result of major intestinal resection, e.g. due to injury, volvulus, vascular disease, cancer (disease free for at least five years), Crohn's disease (if in clinical remission, as determined by clinical assessment)
- Body weight < 90 kg
- Major intestinal resection resulting in at least 12 months of PN dependency at least 3 times weekly to meet their caloric or electrolyte needs due to ongoing malabsorption
- Stable PN treatment for at least 4 weeks in:
    - Usage and volume of PN;
    - 48-hour urinary output (1.0 to 2.0 L/day);
    - Urine sodium (greater than 20 mmol/day);
    - Adequate renal function [serum creatinine and blood urea nitrogen (BUN) ≤ 1.5 x upper limit of normal (ULN)];
    - Hematocrit (Hct) indicating satisfactory hydration (≤ ULN);
    - Motility altering medications (as defined in Section 9.4.7)
- Body mass index (BMI) 18 to 27 kg/m2
- Adequate hepatic function: [Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) both less than 2.0 x ULN; total bilirubin less than 1.25 x ULN; and alkaline phosphatase less than 2.5 x ULN]

The main exclusion criteria were

- History of cancer or clinically significant lymphoproliferative disease with fewer than five years documented disease-free state (resected cutaneous basal or squamous cell carcinoma, or in situ cervical cancer excluded)
- History of alcohol or drug abuse (within previous year)
- Presence of any of the excluded disease states described in Table 9-1 by body system
- Failure to adhere to required washout periods for certain medications as indicated in Table 9-2.

Table 9-1 Excluded Diseases and Illnesses in Study CL0600-004

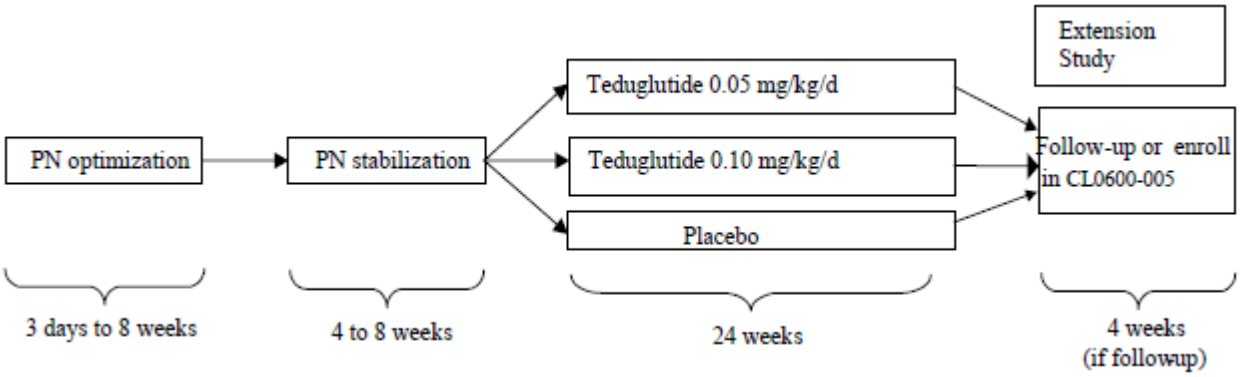
Body System	Conditions Excluded
Related to SBS	Radiation enteritis Scleroderma Celiac disease Refractory or tropical sprue Pseudo-obstruction
Gastrointestinal	Active inflammatory bowel disease Pre-malignant or malignant change in colonoscopy biopsy or polypectomy Surgery scheduled within the time frame of the study
Immune	Human immunodeficiency virus positive test Immunological disorders Possible allergies to teduglutide or its constituents
Cardiovascular, respiratory, renal, endocrine, hepatic, or central nervous system	Significant active, uncontrolled, untreated systemic diseases

Table 9-2 Prior Medications Subject to Washout in Study CL0600-004

Washout Time Required before Dosing Day 1	
12 weeks Washout Required:	**30 days Washout Required:**
Monoclonal antibody therapy: ○ eg, Infliximab (Remicade®) Growth hormone or growth factors	Systemic corticosteroids (short tapering courses possible: discuss with sponsor) other biologics methotrexate cyclosporin tacrolimus (FK506) sirolimus octreotide IV glutamine Any other investigational drugs

Treatments

The study CL0600-004 consisted of a screening-, PN optimisation- and a treatment period.



All subjects enrolled into the study were challenged prior to randomization during an optimisation period (3 days to 8 weeks) to attain their optimal (minimal) PN requirement. All subjects were subsequently to undergo a minimum 4-week stabilisation period on that volume of PN prior to randomization. The study visits for dosing of PN occurred at Weeks 4, 8, 12, 16 and 20, with the last scheduled visit at Week 24 of the dosing period. The extension study (CL0600-005) permitted all subjects on active treatment (if completing the 24 week treatment period) to continue on their assigned dose for a total of 12 months ("1-Year Active Group"), and allowed those subjects on placebo in study CL0600-004 to be prospectively randomized to either 0.05 or to 0.10 mg/kg/day teduglutide for 28 weeks in study CL0600-005 ("6-Month Active Group")

Teduglutide (0.05 or 0.10 mg/kg/day) or matching placebo was administered by the s.c. route once daily into one of the four quadrants of the abdomen or either thigh, for 24 weeks.

Relevant clinical criteria had been set up for optimisation and adjustment of the PN during the treatment period. The purpose of the optimisation period was to establish the minimal tolerated baseline level of PN that results in a urine output between 1.0 and 2.0 L/d.

Laboratory safety samples were evaluated at least once during the seven days following a PN reduction, accompanied by determination of 48-hour urine output. In addition, evidence of dehydration, such as body weight, clinical signs and symptoms, was assessed day 3 to 4 and day 6-7 following a reduction ().

The use of placebo treatment during the main study has been considered acceptable given that no other marketed comparator is available for this condition. Furthermore, the PN/i.v. fluid requirements were optimised (for up to 16 weeks) with the need for demonstration of stability in the PN/i.v. requirements for at least 4 weeks prior to double blind study treatment. In addition, the criteria for adjustments in PN were clear.

Objectives

The objectives of the study were to evaluate the efficacy, safety, tolerability and pharmacokinetics of teduglutide compared with placebo in subjects with parenteral nutrition(PN)-dependent Short Bowel Syndrome (SBS).

Outcomes/Endpoints

The initial planned primary endpoint was the dichotomous responder criterion ("Number and percentage of subjects who demonstrated a response (≥20% reduction from Baseline in weekly PN volume) at Week 20 maintained at Week 24"). In February 2007 (the last subject completed the study in July 2007) the initially planned primary endpoint was exchanged after an independent review of the protocol. The new primary endpoint was an ordered categorical (graded) criterion accounting for

duration (weeks 16 and 20 and weeks 20 and 24) as well as intensity of response (percentage reduction in PN volume; 20-100%) meaning that subjects with larger, earlier and/or more sustained response had higher "weight" in the outcome (score of 0-5, table 9.5 below).

Table 9-5 Criterion Values for Response in Study CL0600-004

	Weeks 20 to 24			
Weeks 16 to 20	< 20% Reduction	20%-39% Reduction	40%-99% Reduction	100% Reduction
< 20% Reduction	0	1	2	3
20%-39%Reduction	0	2	3	4
≧40% Reduction	0	3	4	5

The term "PN volume" was used to describe the efficacy of teduglutide regardless of the composition of PN (parenteral infusion of fluid, energy (nutrients) and/or electrolytes).

The secondary efficacy variables were the following:

- The number and percentage of subjects who demonstrated a response at week 20, and who maintained that response at week 24, which was defined as the achievement of at least a 20% reduction from baseline in the weekly PN volume.

- The number and percentage of subjects who achieved at least a 1-day reduction in weekly PN

- The absolute reduction from baseline in weekly PN kilojoules (transformed from Kcal).

- The absolute reduction of weekly volume of PN from baseline

- The change from baseline in plasma citrulline at dosing week 24

For a subset of selected study centers, an additional secondary variable was evaluated at weeks 8 and 24 with the testing of intestinal absorption of fluid, energy, nitrogen, fat, carbohydrate, sodium, potassium, magnesium and calcium

Exploratory efficacy variables were defined as:

- Time to 20% reduction in PN volume, time to discontinuation of PN, time to a 1-day reduction in weekly PN, number and percentage of subjects with reduced i.v. catheter access at week 24, change from baseline in bone markers BSAP and NTx, in lumbar spine ad hip BMD, and in PTH at week 24, change from baseline in QoL at weeks 4, 8, 12, 16, 20, and 24 (scores to be used were: SF-36, IBDQ, and abbreviated EuroQol)., the mucosal crypt-villus architecture and cellular composition within the small and large intestine.

Within the study, a 72-hour nutrient absorption study was to be conducted in selected centers, citrulline as marker of PD activity was evaluated, and, as mentioned above, endoscopic and histological evaluation of the small and large intestine was performed in subsets of patients. A PK substudy was also conducted.

Sample size

The sample size calculation was based on the initially planned primary endpoint providing 90% power to detect an anticipated minimum response (20% decrease in PN for Weeks 20 to 24) in 5% of the placebo treated- and 50% of the teduglutide patients. No formal justification for the anticipated response rates has been provided. The actual difference in responder rates between placebo vs. "total teduglutide" only amounted to 30% (please refer to the efficacy section). Thus, the power of the study

seems significantly reduced compared to the one forming the basis for the sample size calculation leading to a not negligible risk of type 2 error.

Randomisation

80 subjects were planned to be randomized in a 1:2:2 ratio to one of three treatment arms: placebo, 0.05 mg/kg/day teduglutide, or 0.10 mg/kg/day teduglutide (32 subjects in each of the teduglutide treatment groups and 16 subjects in the placebo group). The subjects have been randomized at the Baseline/Dosing Day 1 visit using an interactive response system called the Fisher Automated Clinical Trials Services (FACTS). The Randomization was balanced for treatment groups, participation in the 72-hour nutrient absorption test, and PN at three levels of consumption [PN consisting of IV fluid and electrolytes only (3-7 times weekly), PN 3-5 times weekly, and PN 6-7 times weekly]. Subjects were randomized across centers rather than within a center.

Blinding

Teduglutide and placebo vials and their content were identical in appearance. The study center personnel, the sponsor, and all personnel associated with monitoring or data management for the study were blinded to the treatment assignment. Persons responsible for assessment of PN requirements and adjusting doses of PN were to be different from the ones conducting physical examinations, and assessing safety. This was introduced in order to assure blinding due/despite to swelling of the stoma (as an effect of mucosal hyperplasia).

Statistical methods

The following populations were used for the statistical analyses:

The intention-to-treat (ITT) population: All randomised subjects who received at least one dose of study drug. The ITT population was used for analyses of efficacy (primary, secondary and exploratory efficacy outcomes).

The per-protocol (PP) population: All subjects in the ITT population who were compliant with study medication doses and had a week 20 visit and the additional post-Week 20 visit (i.e. approximately 24 weeks of dosing). The PP population was used for analyses providing additional support for the efficacy argument (primary and secondary efficacy outcomes).

The primary and several of the secondary efficacy outcomes were based on a weekly average of the daily diary PN volumes collected from the CRF raw datasets and then placed into the analysis datasets.

The “weekly” PN volume calculation for 14 days was [Sum (PN volume during the preceding 14 days)/(14 days)] x 7 days. Patients were classified as responders if they had ≥ 20% reduction in weekly PN volume from baseline to week 20 sustained through week 24 dichotomising the expanded variable´s responses into a yes/No variable.

For the primary variable, the response variable was to be summarized using descriptive statistics (mean, STD, median, min and max for continuous variables, no. and percent of subjects in specified categories and corresponding 95% CIs, etc). The pairwise comparisons were to be made using a rank analysis of covariance (an extension of the Wilcoxon rank sum test) with strata for baseline PN levels with the basleine weekly PN volume as a covariate. A step-down procedure will be used to adjust for multiple comparisons.

The secondary variable was to be summarized by the number and percentage of responders and the corresponding 95% CIs for each treatment group. Pairwise differences were to be presented, including

their 95% CIs. Pairwise comparisons between the groups were to be made using Fisher's Exact Test, also in a step-down procedure.

The additional secondary efficacy variables were to be summarized using descriptive statistics. For the change from baseline, pairwise differences between the treatment groups, the corresponding 95% CIS, and pairwise t-tests were to be made using estimates from a 2-way repeated measures ANCOVA with the model including effects for baseline PN consumption levels used for stratification (see above) and with the baseline weekly PN volume as a covariate. For rates, treatment group comparisons were to be made using a rank analysis of covariance with stratification for the baseline PN consumption level used for stratification with the baseline weekly N volume as a covariate.

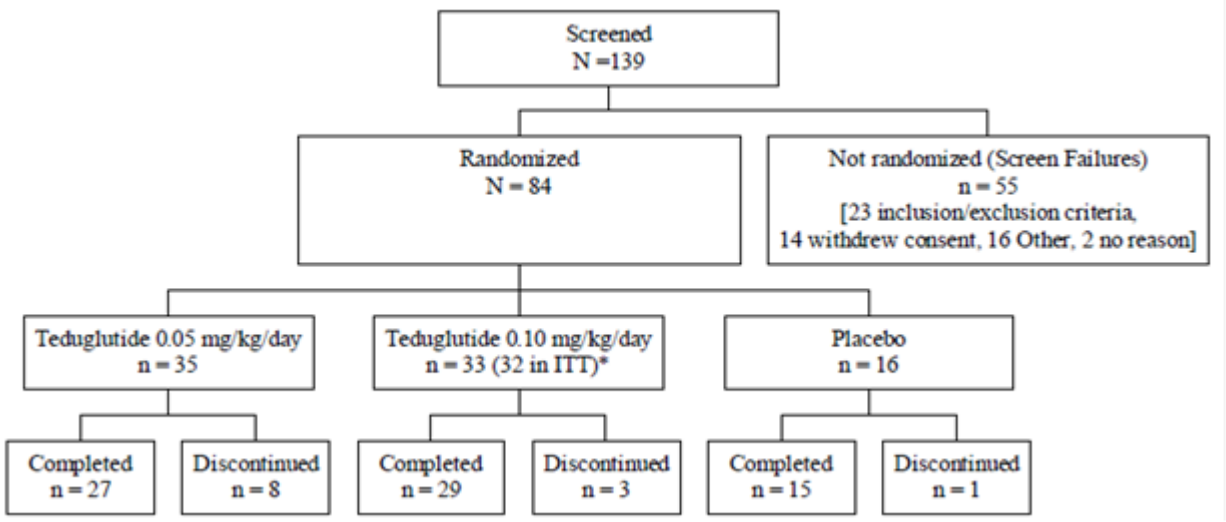
The statistical analysis plan further defined these analyses. It stated that the primary evaluation had to be based on the ITT population, with the PP population being secondary.

The SAP also defined more in detail the step-down procedure to be used for adjusting for multiple comparisons stating that if the 0.10 mg/kg/d teduglutide group is not statistically significantly different from the placebo group, no further comparison will be made. If it is, placebo will be compared to the lower dose group, and, as a final step, the two teduglutide groups will be compared.

There was a requirement to have at least 9 out of 14 daily PN volume data points for the weekly PN volume calculation. If less data were available for the specific period of time the patient was left out of the analysis for that specific time point. Thus, an imputation method for missing data for the weekly PN volume calculations was not implemented. The applicant subsequently provided evidence that the three study groups were well balanced as regards overall frequency of patients with missing values and frequency of patients with "many missing values" (i.e. more than ten). Thus differential "missingness" is unlike to have had any major effect on the results of this study. In study CL0600-020 (see below), sensitivity analyses utilising different ways of handling missing data, demonstrated that the results were not sensitive to this factor. Patients who discontinued the study prematurely was assigned the score "0" for the response variable (i.e. no response). This is considered the most conservative approach.

Results

Participant flow



93.8%, 77.1% and 90.6% in the placebo-, 0.05mg/kg/d- and 0.10 mg/kg/d groups completed study CL0600-004. As can be deducted from these data a considerable part of patients randomised to 0.05 mg/kg/d discontinued the study (8 patients, 22.9%). These discontinuations were due to AE (5 patients, 14.3%) and subject decision (3 patients, 8.6%).

Table Reasons for subjects' withdrawal:

Reason for Withdrawal	Treatment Group, n(%) of subjects			
	Placebo	Teduglutide		
		0.05 mg/kg/d	0.10 mg/kg/d	Total
Randomized and dosed (ITT population)	16 (100)	35 (100)	32 (100)	83 (100)
Completed study	15 (93.8)	27 (77.1)	29 (90.6)	71 (85.5)
Discontinued study early	1 (6.3)	8 (22.9)	3 (9.4)	12 (14.5)
Adverse event	1 (6.3)	5 (14.3)	2 (6.3)	8 (9.6)
Death	0	0	0	0
Lost to follow-up	0	0	0	0
Subject decision (withdrew consent)	0	3 (8.6)	1 (3.1)	4 (4.8)
Investigator's decision	0	0	0	0
Other	0	0	0	0

Recruitment

The first subject was screened on 25th May, 2004, and the last subjects evaluations were performed on 06th July, 2007. Considering the trial duration of half a year, the recruitment took approximately 2 ½ years to be completed. Considering the rareness of the disease, recruitment speed appears to be appropriate.

Conduct of the study

The study was conducted from May 2004 to July 2007 at 32 centers in the USA (15), Canada (4), and European countries (13 centers in the UK, France, Denmark, Poland, the Netherlands, Belgium, and Germany).

There were 39 (46.4%) subjects who were reported as having an Inclusion/Exclusion Criteria protocol violation during the course of the study. The most frequently reported Inclusion Criteria violation was Inclusion Criterion 8 (adequate hepatic function) with 16 subjects (41.0%) followed by Inclusion Criterion 6 (4- week stability before randomisation with respect to PN, urinary output, renal function, urinary sodium, Hct etc) with 13 subjects (33.3%)

During the course of the study, 4 protocol amendments were performed. The first one, introduced in December 2003, among minor amendments, introduced an additional 72-hour nutrient absorption test at week 8, removed the treatment satisfaction assessment, and added the citrulline assessment. Amendment 2, introduced in March 2004 included a multitude of changes, which were mostly minor (e.g. administrative information etc). Amendment 3 (and amendments 3a and 3b) were introduced in November 2004 (and July and October 2005). These amendments were also minor, the amendments 3a and 3b changed the site-specific requirements for the DXA scans.

The major protocol amendments took place with protocol amendment 4 (February 2007) which introduced the new primary efficacy endpoint (see above). Amendment 4b and and Amendment 4 (administrative) were again minor amendments introduced in June and September of the year 2007.

Baseline data

The mean age in the included study population was 48.8 years (median 52 years) and the percentage of female patients was 55.4%. The vast majority of included patients were Caucasian (92.8%) These parameters were balanced between the treatment groups. Also with respect to height, weight, BMI, smoking status, alcohol consumption and parenteral nutrition history the groups were balanced.

There was, however, a noticeable imbalance in the PN consumption level at study entry. Only 9.4% in the 0.10 mg/kg/d group were on i.v. fluids only as compared to 22.9% in the 0.05 mg /kg/d group and 25.0% in the placebo group. In contrast, 34.4% in the high dose group were patients with the highest PN requirements (6-7x weekly) compared to 25% in the placebo group and 22.9% in the 0.05 mg/kg/d group. Also in the *extension study* the percentage of patients receiving i.v. fluids only was approximately half of the percentage in the 0.10/0.10 compared to the 0.05/0.05 mg group.

Imbalance was also observed with respect to the cause of intestinal resection: Around 40% in the 0.10 mg/kg/day had a resection due to Crohn's disease and around 29% due to vascular disease whereas an inverse relationship was observed in the 0.05mg/kg/day group. More important than the aetiology of SBS in the prognosis of transition to enteral feeding are, however, the length of the remaining small intestine and the segment of the remnant intestine, if there is the colon and the ileocoecal valve is present.

More patients in the 0.10 mg/kg/day group had a stoma (mostly jejunostomy and ileostomy) compared to the 0.05 mg/kg/day group (43.8% vs. 28.6%). In addition, the high dose group had the lowest percentage of patients with colon in continuity (59.4% vs. 74.3% in the 0.05 mg/kg/day group and 68.8% in the placebo group). Furthermore, in the high dose group the percentage of patients with the shortest remaining colon (25-50% remaining colon) was highest (42.1%, compared to 26.9% in the 0.05mg/kg/day group and 36.4% in the placebo group). In contrast to the 0.05 mg/kg/day group where 80.3% of patients had an ileocecal valve, only 37.5% of patients in the 0.10 mg/kg/day group (and 33.3% in the placebo group) had an ileocecal valve.

Numbers analysed

The number of patients involved in the study and their subdivision based on treatment received is reported in the table.

	Treatment Group, n (%) of subjects			
		Teduglutide		
Population[a]	Placebo N = 16	0.05 mg/kg/d N = 35	0.10 mg/kg/d N = 33	All Subjects N = 84
Randomized population	16 (100)	35 (100)	33 (100)	84 (100)
Intent-to-treat population (ITT)	16 (100)	35 (100)	32 (97.0)	83 (98.8)
Per-protocol population (PP)	15 (93.8)	26 (74.3)	29 (87.9)	70 (83.3)
Continued to Extension Study – (0600-005)	13 (81.3)	25 (71.4)	27 (81.8)	65 (77.4)

The percentage of patients continuing to the extension study 0600-005 was lowest in the 0.05 mg/kg/day group (71.4% compared to 81.3% and 81.8% in the placebo and 0.10 mg/kg/d groups, respectively). The applicant subsequently clarified that among patients who had completed the study, the fraction of patients continuing into the open label extension study was similar in both dosing

groups. The difference in overall fraction of randomised patients who continued into the open label study was due to differences in discontinuation rates during the placebo controlled study.

Outcomes and estimations

There was no statistical significant difference between teduglutide 0.10 mg/kg/day vs. placebo in the graded response score (p=0.161) used as primary endpoint. According to the statistical analysis plan (SAP) no further statistical testing was then planned. Still, a decision to proceed to analysis of the low dose was taken based on clinical evidence of efficacy. A low p-value was generated for teduglutide 0.05 mg/kg/day vs. placebo (p=0.007). There were 1 (6.3%), 16 (45.7%) and 8 (25%) responders in the placebo-, 0.05 mg/kg/day- and 0.1mg/kg/day group, respectively. The total effect of teduglutide (pooled response: 35.7% were responders) was much lower than expected in the power calculation, thus forming the basis for a type 2 error. Most responders had a score of 1 and 2 (of note one placebo subject – the only responder- had a score of 2). Still, 19 patients (54%) and 24 patients (75%) in the low- and high dose groups were non-responders with a score of 0 (<20% reduction in weekly PN volume).

Overall, these results obtained in the low dose group are promising but can only be considered for hypothesis generation.

Secondary efficacy results

Whereas no statistically significant difference was observed on the binary efficacy endpoint (+/- 20% reduction in weekly actual PN infusion volume from baseline to Week 20 and maintained at Week 24), for 0.1 mg/Kg/day teduglutide vs. placebo (25.0% vs. 6.3%. p=0.172), a low p-value was also observed for this endpoint for 0.05 mg/kg/day teduglutide vs. placebo (45.7% vs. 6.3%, p=0.005). The responder rates were higher at the end of the extension study CL0600-005 (after 52 weeks treatment) being 68% for 0.05mg/kg/day and 51.9% for 0.1mg/kg/day. There was no evidence of loss of efficacy of teduglutide after 52 weeks treatment. The responder rates for patients initially treated with placebo switching to teduglutide in the extension study were 83.3% and 42.9% for 0.05 mg/kg/day and 0.10 mg/kg/day, respectively. The results from the extension phase seem promising, but careful interpretation is deemed, due to the low number of study subjects and lack of control group.

The ultimate goal of treatment in SBS is weaning-off PN. It is indeed noteworthy that 4 subjects (3 in the 0.05mg/kg/day and 1 in the 0.1mg/kg/day) were weaned off after teduglutide treatment (3 in study CL0600-004 and 1 in study CL0600-005).

Although 4 patients were in fact able to be weaned off PN in the study CL0600-004, the efficacy as such did unfortunately not translate into other positive efficacy parameters such as reduced days on PN, reduced weekly PN volume, improved quality of life or reduced frequency of complications.

Achievement of at least one day reduction in weekly PN: 4 (25%), 11 (31.4%) and 3 (9.4%) subjects in the placebo, low- and high dose treatment groups, respectively achieved at least one-day reduction in weekly PN. The difference vs. placebo was not statistically significant for any of the teduglutide groups. In fact, the high dose group did worse than placebo.

The algorithm for decreasing PN support did not specify that accumulated effects of teduglutide should be converted into decreased number of days on PN. Furthermore, it was possible to rearrange the weekly PN support without decreasing the weekly volume infused. These conditions could potentially explain the poor response for the high dose and the seemingly large placebo response (25% achieved

at least one day reduction in weekly PN). However, the data provided do not allow conclusions in this regard.

After 52 weeks of treatment the percentage of subjects achieving at least 1-day reduction in PN-use was also higher in the 0.05 mg/kg/day group (68%) vs. the 0.10 mg/kg/day group (37%). The rate in the initial placebo group switched to 0.05mg/kg/day seemed similar after 28 weeks (66.7%) as for subjects treated with 0.05 mg/kg/day for 52 weeks. In view of the high placebo response in study CL0600-004, the low numbers in each treatment group, the large number of centers included in the study each with a potential differentiated approach to PN adjustments and finally that no placebo group was included in the extension study CL0600-005, the results should be interpreted cautiously.

Absolute Change from Baseline in Weekly PN Kilojoules: The reductions in weekly PN kilojoules were numerically higher for teduglutide 0.05 mg/kg/day (-6994KJ). The weekly reductions for placebo (-3545KJ) were higher than for teduglutide 0.10 mg/kg/day (-1587KJ). The difference 0.05 mg/kg/d vs. placebo was not statistically significant (P=0.136). Data from study CL0600-005 seem to indicate a similar response in placebo treated subjects switched to 0.05 mg/kg/day and 0.10 mg/kg/day, respectively. A post-hoc analysis was performed excluding those patients requiring i.v.-fluid PN only. Based on this analysis teduglutide 0.05 mg/kg/day (mean (SD) change from baseline -7916 (9329) KJ) was proven superior to placebo ((mean (SD) change from baseline -1958 (3527) KJ) (P=0.0375).

Change from baseline in Weekly PN volume: The low- and high dose of teduglutide induced mean (SD) reductions in weekly PN volumes from baseline to week 24 of – 2.48L (2.34) and -2.47L (3.33), respectively. The corresponding reduction for placebo was -0.90L (1.41). The difference for active treatment vs. placebo was not statistically significant. The Applicant argues that these similar reductions in weekly PN volumes between the two teduglutide arms indicate similar effect of the two dosages. While the data may indicate that the maximal effect of teduglutide may have been reached upon administration of 0.05mg/kg/day and that no additional effect will be obtained by increasing the dose to 0.1mg/kg/day no firm conclusions can be drawn. The two teduglutide treatment groups had several imbalances in baseline data but the applicant subsequently provided evidence that these imbalances were not likely to explain the difference in efficacy.

48-Hour Oral Fluid Intake and Urinary Output: 48 hr urine collections were to be completed 2 days ahead of a visit. Patients were told to try to keep the timing, quantity and quality of beverages as constant as possible during the 48 hours collection period. The quantity of urine collected may however have been influenced by +/- PN infusion during the collection period. From baseline to week 24 both active treatment arms had reductions in 48-hr oral fluid intake (0.05 mg/kg/day -95.0mL (range:-3340 to 5990); 0.10 mg/kg/day -410.0mL (range: -4570 to 950); median values) and increases in 48-hr urine output (0.05mg/kg/day 420.0mL (range:-500 to 3740); 0.10 mg/kg/day 132.5mL (range: -3900, 1450); median values). This was in contrast to subjects in the placebo arm, who had both increased 48-hr fluid intake and – urine output (390.0mL (range: -4261 to 2400) and 200.0 (range -975 to 1895), respectively; median values).

Change from baseline in plasma citrulline at week 24: Plasma citrulline levels are believed to be a predictive marker of absorptive enterocyte mass and intestinal failure (< 20µmol/L) in patients with SBS (Crenn P et al, gastroenterology 2000, 119: 1496 and Santarpia L et al, Ann Nutr Metab 2008; 53: 137). However, no correlation between the increased plasma citrulline levels and PN volume reduction was established for teduglutide treated subjects.

Changes from Baseline in Crypt-Villus Architecture and Cellular Composition within the Small and Large Intestine at Week 24, and Intestinal Absorption of Fluids, Energy, and Nutrients Over 72-hour Period: Both teduglutide doses increased villus height in the small intestine. Only the high dose caused a significant change vs. placebo on large intestine crypt depth and small intestine villus height and

surface area. The structural composition of the small and large intestinal mucosa expressed as mucosal DNA concentration did not change from baseline in any of the treatment groups. Despite attempts to conduct 72-hr nutrient absorption tests in 6 selected sites at baseline, dosing week 8 and at the end-of-study, reliable data supporting a beneficial effect of teduglutide on nutrient absorption is not available from this phase 3 study.

Exploratory outcomes:

No statistically significant differences were noted for i.v. catheter access associated with infusion of PN among treatment groups at Baseline, Dosing Week 24 and Last Dose Visit.

There were no statistically significant changes in bone mineral density (BMD) of spine and whole body. For the whole body bone mineral content (BMC), a statistically significant increase was observed for the mean difference between placebo and 0.10 mg/kg/day teduglutide treatment groups (p= 0.046)

No statistically significant changes in mean change from baseline (SD) in serum PTH (pg/ml) was observed for teduglutide 0.05 mg/kg/day and 0.10 mg/kg/day vs. placebo.

No effect on quality of life was detected by use of the SF-36 health survey, EuroQoL EQ-5D and the Inflammatory Bowel Disease Questionnaire (IBDQ) after 24 weeks treatment with teduglutide. It is acknowledged that these questionnaires have not been developed for assessment of QoL in patients with SBS, and that disease specific questionnaires were not available, when the study was conducted. Considering the low numbers of patients included in each treatment group in addition to the heterogeneity in symptoms in between SBS patients, it is conceded that these tools may not have been appropriately sensitive to catch any potential difference.

As study CL0600-004 was not a fully satisfying study, unable to provide confirmatory evidence of efficacy, the applicant subsequently performed a new confirmatory study, CL0600-020, testing the dose of teduglutide which in the exploratory analysis of study CL0600-004 was found to be effective.

Study CL0600-020: A 24-Week Study of the Efficacy and Safety of Teduglutide in Subjects with Parenteral Nutrition-Dependent Short Bowel Syndrome. A randomized, double-blind, placebo-controlled, parallel-group study.

Methods

Study Participants

A relevant adult study population with SBS due to the most common causes of SBS (surgical resections due to Crohn´s disease, cancer, vascular insufficiency and volvulus) was included in the study. SBS patients with possible fluctuating activity in the disease (due to radiation therapy, active crohn´s disease etc.) were excluded. Patients had to be dependent on PN at least 3 times weekly for at least 12 months. Prior to randomisation to study treatment, patients had to be stable in their disease for the past 4 weeks.

The inclusion criteria are largely comparable to those of study -004 with the following exceptions:

1. Stability of PN defined as:
    - Actual PN/IV usage should match prescribed PN/IV

- Baseline (V2) 48-hour oral fluid intake and urine output (I/O) volumes should fall within ±25% of the respective 48-hour I/O volumes at the time subject is optimized and enters stabilization. (See Section 3 for detailed explanation.)
- Urine output volume should NOT fall below 2 L and not exceed 4 L per 48 hours when the subject completes the optimization and stabilization periods

2. Body mass index (BMI) ≥15 kg/m2
3. Adequate hepatic and renal function:
    - Total bilirubin < 2xULN
    - Aspartate aminotransferase (AST) < 5xULN
    - Serum creatinine < 2xULN

The main exclusion criteria include the following:

- History of cancer or clinically significant lymphoproliferative disease with fewer than 5 years documented disease-free state. (resected cutaneous basal or squamous cell carcinoma, or in situ non-aggressive and surgically resected cancer excluded)
- More than 4 SBS-related or PN-related hospital admissions (eg., catheter sepsis, bowel obstruction, severe water-electrolytes disturbances) within 12 months prior to screening visit
- Hospital admission, other than scheduled, within 1 month prior to screening
- Body weight > 88 kg
- Body mass index (BMI) <15 kg/m2
- Presence of any of the excluded disease states described in Table 9-1.

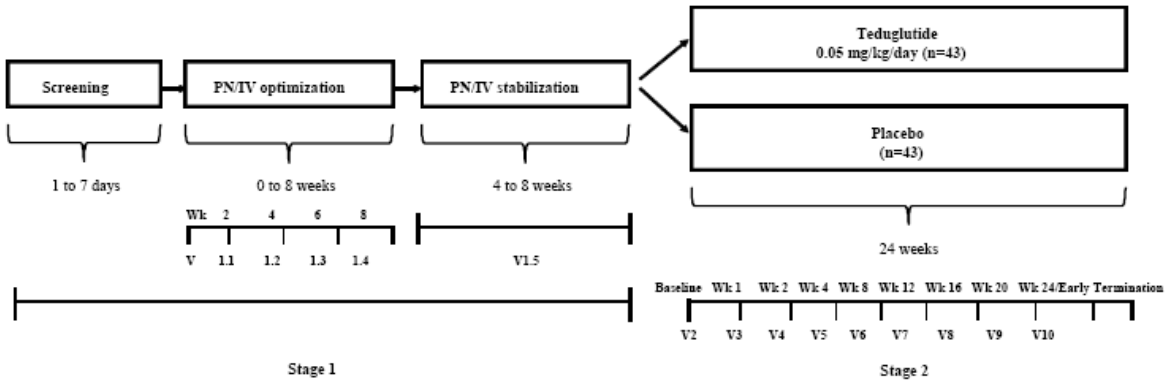
Table 9-1 Excluded Diseases and Illnesses

Body system	Conditions excluded
Related to SBS	Ongoing radiation enteritis or the presence of damaged enteral tissue due to radiation enteritis
	Celiac disease
	Refractory or tropical sprue
	Pseudo-obstruction
Gastrointestinal (GI)	Active inflammatory bowel disease (IBD) which required chronic systemic immunosuppressant therapy that had been introduced or changed during the last 3 months
	IBD that required chronic systemic immunosuppressant therapy for symptom control
	Untreated pre-malignant or malignant change in colonoscopy biopsy or polypectomy
	Intestinal or other major surgery scheduled within the time frame of the study
	Chronic pancreatitis or cholecystitis
Immune	Compromised immune system (e.g., acquired immune deficiency syndrome, severe combined immunodeficiency), hypersensitivity or allergies to teduglutide or its constituents or GLP-2
Psychiatric	Alcohol or drug addiction within the previous year
	Major uncontrolled psychiatric illness
General	Significant active, uncontrolled, untreated systemic diseases (e.g., cardiovascular, respiratory, renal, infectious, endocrine, hepatic, or central nervous system)

Treatments

The study design is presented in Figure 9-1.

Figure 9-1 Study Design



PN/I.V.= Parenteral nutrition/intravenous fluids; V=Visit; Wk=Week.

Stage 1 included screening, optimization, and stabilization periods. At screening, if the subject did not have a stable PN/i.v. volume as indicated by a targeted urine output of 1.0-2.0 L/day, the subject was to enter an optimization period (8 weeks maximum) to find the subject's minimally tolerated stable volume of PN/i.v. Prior to randomization, all subjects were to undergo a stabilization period on that volume of PN/i.v. that was to last 4 weeks minimum and 8 weeks maximum. The 48-hour oral fluid intake and urinary output (I/O) volumes measured before the visit when the subject was deemed

stable would contribute to the determination of stability. Once the subjects had demonstrated PN/i.v. volume stability for 4 to 8 weeks, Stage 2 of the study began with baseline assessments of hydration and nutritional status. Eighty-six subjects were randomized in a 1:1 ratio to 1 of 2 treatment groups: 0.05 mg/kg/day teduglutide or placebo.

All subjects who completed the study had the option to continue taking teduglutide 0.05 mg/kg/day for up to 2 years in a long-term safety study (CL0600-021). The clinical duration of the study was 26 months.

Teduglutide 0.05 mg/kg/day or placebo was administered by the s.c. route once daily into one of the four quadrants of the abdomen or either thigh, for 24 weeks. Matching placebo, for s.c. injection, was provided as a lyophilized powder containing L-histidine, mannitol, monobasic and dibasic sodium phosphate (as for teduglutide) that was to be reconstituted using 0.5 mL sterile water for injection, and administered immediately. As no generally accepted or licensed medical treatment exist for SBS, the use of placebo is considered acceptable.

The dose of teduglutide selected for this study was based on the efficacy and safety results of the prior clinical Study CL0600-004. Teduglutide 0.05 mg/kg or placebo was administered once daily by SC injection into 1 of the 4 quadrants of the abdomen or into either thigh or arm, for the 24 weeks of Stage 2. The dose was administered at approximately the same time each day. If a subject forgot to administer drug, that daily dose was to be administered as soon as possible, even if this was later in the day or evening. However, consecutive doses were to be separated by at least 12 hours. The investigator was responsible for contacting the sponsor or designee prior to interrupting the subject's daily study drug dosing regimen. A single discontinuation period of study drug was not to exceed 10 consecutive days. Dosage interruptions of study drug for a maximum of 21 days total during the entire 24 weeks were permitted.

Objectives

The objectives of this clinical study were to evaluate the efficacy, safety, and tolerability of teduglutide compared with placebo in SBS subjects dependent on parenteral support (PN and/or i.v. fluids). Subject's qualify of life (QoL) was evaluated by using a newly developed subject-reported outcome SBS-specific QoL questionnaire.

Outcomes/endpoints

Efficacy

The primary efficacy variable was the percentage of subjects who demonstrated a response at Week 20 and who maintained that response through Week 24. A response was defined as the achievement of at least a 20% reduction from Baseline (Visit 2) in weekly PN volume.

The secondary efficacy variables were based on reductions in PN/i.v. volume or the direct effects of improved intestinal absorption of fluid. The variables include among others: duration of response (ie., total number of weeks at ≥ 20% reduction from Baseline); the proportion of subjects with a ≥ 20% reduction or a ≥ 2 liter (L) reduction from Baseline in weekly PN at Week 20 and maintained through Week 24; the number of subjects who stopped PN and time of discontinuation; and absolute change and percent change in PN between Baseline and last dosing visit.

An additional secondary efficacy variable was an ordered categorical (or graded) response that accounts for both intensity and duration of the response at the end of the 24-week treatment period. The intensity of the response relied on a reduction from Baseline in weekly PN volume at a minimum of

20% and a maximum of 100%. Duration of the response incorporated responses at Weeks 16 through 20 and at Weeks 20 through 24.

Quality of Life

Subjects' quality of life (QoL) have been evaluated by using a subject-reported outcome SBS specific QoL scale. It is agreed that QoL is an important secondary endpoint. Previously, generally accepted and validated QoL instruments specifically for this condition has not been available. Consequently, the sponsor has developed an instrument (SBS-QoL™) specifically designed to measure QoL in short bowel syndrome. The development appears to adhere to generally accepted criteria in this field and the instrument has been validated. The use of SBS-QoL™ is considered acceptable.

Safety

Adverse events, 12-lead ECG, vital signs, laboratory safety data, antibodies to teduglutide and/or E. coli protein (ECP), and changes in urine output and body weight were evaluated.

Sample size

Samples size calculations were based on the primary efficacy endpoint. Eighty-six subjects were randomized at a 1:1 ratio to detect a difference in responder rates between teduglutide and placebo groups of 35% and 6%, respectively, α alpha=0.05, 2-sided test and power=90%. Grounded on these assumptions, nQuery Advisor (v. 6.0) based on a Fisher's Exact Test was used to calculate the power. The sample size calculations are considered acceptable.

Randomisation

Acceptable methods for randomisation were applied. 86 patients were randomized in a 1:1 ratio via the interactive voice response system (IVRS) or interactive web response system (IWRS). The randomization was stratified at 2 levels of baseline PN/i.v. volume ($\leq$6 L/week or >6 L/week). Subjects were randomized across centers rather than within centers.

Blinding (masking)

Study drug was administered in a double-blind fashion during the 24 weeks that constituted the dosing period in Stage 2. Every effort was made to maintain the blinding of this clinical study. Teduglutide and placebo were identical in appearance. The study center personnel, the sponsor, and all personnel associated with the monitoring or data management for the clinical study were blinded to the treatment assignment. However since the test drug may induce visible changes in the appearance of the intestinal mucosa, patients with jejunostomy/ileostomy may be aware of what kind of the treatment they receive. While the effect on objective endpoints may be minimal, an effect on subjective endpoints cannot be ruled out.

Statistical methods

The analysis populations used in this study were the intent-to-treat (ITT) population, the Safety population, and the per protocol (PP) population. The ITT population included all subjects who were randomized into the study. This was the primary study population from which efficacy claims were made. All efficacy analyses were conducted on this study population. Subjects were included in the treatment group to which they were randomized, regardless of the actual drug they received.

The Safety population included all subjects in the ITT population who received at least one dose of double-blind study drug. For reporting purposes, these subjects were included in the treatment group reflective of the treatment they actually received. All safety analyses were conducted on this population, unless otherwise specified. The PP population included all subjects in the ITT population who completed this study without any major protocol violations.

The number and percentage of responders (20 to100% reduction in PN/i.v. volume) were presented by treatment group. The analysis compared the event rates for the two treatment groups using the Cochran-Mantel-Haenszel (CMH) test statistics adjusted for the randomization stratification variable (≤6 or >6 L/week of PN at baseline). The percent and absolute change in PN/i.v. volume from baseline to the last dosing visit, as well as all scheduled visits starting at Week 4, are presented by treatment group using descriptive statistics. Treatment group differences were compared using an analysis of covariance (ANCOVA) model with effects for treatment and baseline PN volume, with the potential for the interaction of the two variables also included as an effect. The least squares means and standard error, along with 95% CIs, are presented for each treatment.

Duration of response

The duration of response based on the number of consecutive visits (categorized as 0, 1, 2, and ≥3) for which the subject had a 20 to 100% reduction in weekly PN/i.v. volume from baseline at Week 24 plus previous scheduled visits with a 20 to 100% reduction from baseline were presented based upon the number and percentage of subjects for each category. The two treatment groups were compared using extended CMH test statistics (with standardized mid-ranks) adjusted for the randomization stratification variable.

Graded response: The number and percentage of subjects' individual graded response categories were presented by treatment group. No statistical testing was performed for these individual items. The number and percentage of subjects with each level of the graded (or ordered categorical) response were presented by treatment group. The analysis compared the graded response categories for the two treatment groups using extended CMH test statistics (with standardized mid-ranks) adjusted for the randomization stratification variable.

Missing data

All subjects in the analysis population were included in the associated analyses, except where specified in select sensitivity analyses. Comprehensive and acceptable rules for handling missing data were defined and a number of pre-specified sensitivity analyses were performed using different ways of handling missing data.

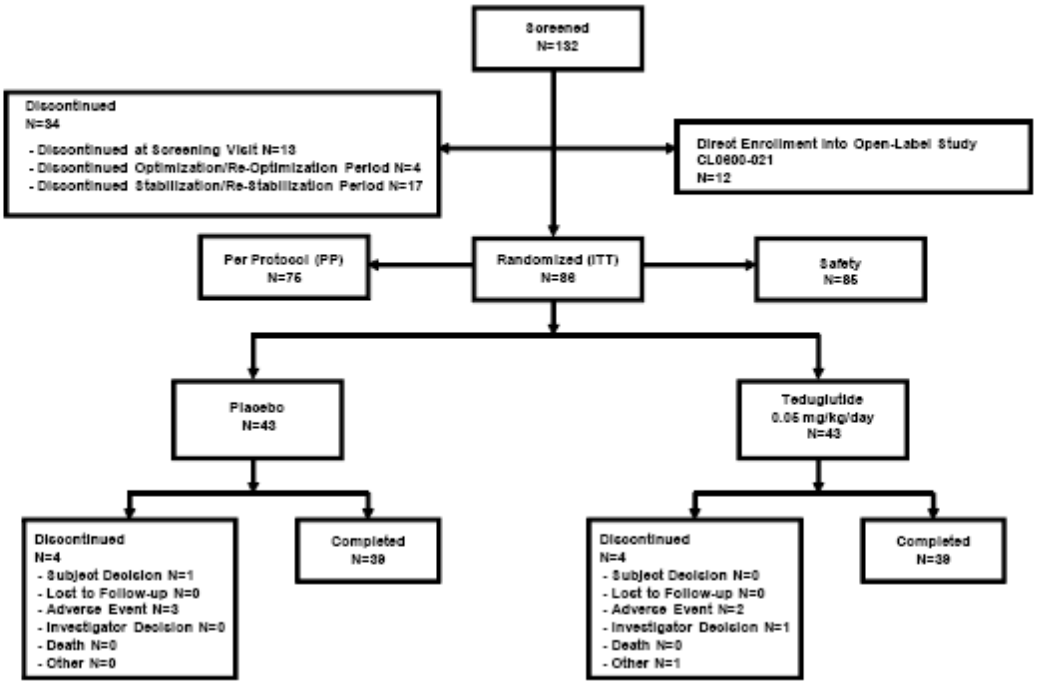
In general, the statistical methods are considered acceptable.

Results

Participant flow

Figure 10-1 Disposition of Subjects in Study CL0600-020

Figure 10-1 Flow Diagram



Recruitment

The study has been conducted from November 2008 to January 2011 at 27 sites in 10 countries (USA 6, Canada 4, Poland 4, Germany 2, Italy 3, France 2, Spain 2, United Kingdom 2, Denmark 1, Netherlands 1). The first subject was enrolled on 25 November 2008, and the last subject, last visit was on 04 January 2011.

Conduct of the study

The vast majority of protocol violations are deemed to be of minor significance and not to have had any significant impact on the results of the study. In total 11 patients deviated so much from the protocol that they were excluded from the PP analysis. Relative to the total number patients randomised, this is considered acceptable.

Baseline data

The groups were well balanced in terms of demographics. The majority of subjects enrolled in this study were Caucasian (83/86 subjects, 96.5%), between 45 and 65 years of age (mean age 50.3 years), and 13/86 (15.1%) of subjects were ≥65 years of age. Subjects ranged in age from 18 to 82 years. The distribution of participating males and females was 40/86 (46.5%) male and 46/86 (53.5%) female. There were no statistically significant differences between treatment groups in any of the demographic and baseline characteristics at baseline.

The SBS history for the Safety population is summarized in Table 11-2.

Table 11-2 Demographic and Baseline Characteristics: Short Bowel Syndrome History – Safety Population

Parameter	Statistic	Placebo (N=43)	Teduglutide 0.05 mg/kg/day (N=42)	All Subjects (N=85)
Reason for Major Intestinal Resection	**n**	**43**	**42**	**85**
Crohn's Disease	n (%)	8 (18.6)	10 (23.8)	18 (21.2)
Vascular Disease	n (%)	16 (37.2)	13 (31.0)	29 (34.1)
Injury	n (%)	4 (9.3)	4 (9.5)	8 (9.4)
Volvulus	n (%)	6 (14.0)	3 (7.1)	9 (10.6)
Cancer	n (%)	2 (4.7)	1 (2.4)	3 (3.5)
Other	n (%)	7 (16.3)	11 (26.2)	18 (21.2)
Stoma	**n**	**43**	**42**	**85**
Yes	n (%)	17 (39.5)	21 (50.0)	38 (44.7)
No	n (%)	26 (60.5)	21 (50.0)	47 (55.3)
Type of Stoma	**n**	**17**	**21**	**38**
Jejunostomy	n (%)	5 (29.4)	11 (52.4)	16 (42.1)
Ileostomy	n (%)	9 (52.9)	6 (28.6)	15 (39.5)
Colostomy	n (%)	1 (5.9)	4 (19.0)	5 (13.2)
Other	n (%)	2 (11.8)	0	2 (5.3)
Colon-in-continuity	**n**	**43**	**42**	**85**
Yes	n (%)	23 (53.5)	25 (59.5)	48 (56.5)
No (includes no colon)	n (%)	20 (46.5)	17 (40.5)	37 (43.5)
Percent of Colon Remaining	**n**	**25**	**24**	**49**
	Mean (SD)	70.3 (27.1)	55.6 (20.8)	63.1 (25.1)
	Median	70.0	50.0	60.0
	Min, Max	10, 100	20, 100	10, 100
Estimated Remaining Small Intestine Length (cm)	**n**	**40**	**39**	**79**
	Mean (SD)	68.7 (63.9)	86.2 (64.5)	77.3 (64.4)
	Median	48.0	70.0	60.0
	Min, Max	5, 343	20, 250	5, 343
<60 cm	n (%)	24 (55.8)	15 (35.7)	39 (45.9)
≥60 cm	n (%)	16 (37.2)	24 (57.1)	40 (47.1)
Presence of Distal/Terminal Ileum	**n**	**43**	**42**	**85**
Yes	n (%)	14 (32.6)	10 (23.8)	24 (28.2)
No	n (%)	29 (67.4)	32 (76.2)	61 (71.8)
Presence of Ileocecal Valve	**n**	**14**	**10**	**24**
Yes	n (%)	10 (71.4)	3 (30.0)	13 (54.2)
No	n (%)	4 (28.6)	7 (70.0)	11 (45.8)

The most prevalent causes for major intestinal resection were vascular disease (29/85 subjects, 34.1%), Crohn's (18/85 subjects, 21.2%) or "other" reason (18/85 subjects, 21.2%). Stoma was present in 38/85 subjects (44.7%), with the most common types being jejunostomy/ileostomy (31/38 subjects, 81.6%). The mean length ±SD of the remaining small intestine was 77.3±64.4 cm (range: 5 to 343 cm). Subjects in the teduglutide group had a numerically greater length of small intestine (86.2 cm) than the placebo group (68.7 cm).There appeared to be at least a numerical difference between groups as regards fraction of patients with ileostomy and jejunostomy. Thus the placebo group had a higher frequency of ileostomy/lower frequency of jejunostomy compared to the teduglutide group. However as groups were well balanced in terms of baseline PN/i.v. requirements and length of remaining small intestine, this imbalance is not considered to have had any significant effect on results.

Numbers analysed

A total of 136 subject numbers were assigned in this study. However, 4 subjects were screened twice, i.e., under two separate subject numbers, thus only 132 unique subjects were screened for participation in this study. 86 suitable subjects have been identified after screening and no subject was randomized more than once. Of the remaining 46 subjects, 34 subjects were considered screen failures. The 12 additional subjects were eligible for randomization. However, because randomization had been completed they were allowed to directly enter the long-term safety study (CL0600-021). Of the 86 subjects randomized, 78 completed the study and 8 discontinued from the study during the dosing period, including 1 subject who was randomized but not dosed.

Outcomes and estimation

Primary efficacy results

The primary efficacy variable was the responder rate as previously defined. The number and percentage of responders in the ITT population is presented by treatment group in Table 11-6. Results were similar in the PP population ($p<0.001$).

Table 11-6 Responder Rate – ITT Population

Response Status	Statistic	Placebo (N=43)	Teduglutide 0.05 mg/kg/day (N=43)
Non-responder	n (%)	30 (69.8)	16 (37.2)
Responder	n (%)	13 (30.2)	27 (62.8)
	p-value		0.002

Note: Percentages were based on the number of subjects in the ITT population.
Note: Responder was defined as a 20 to 100% reduction from baseline in weekly PN/I.V. volume at both Weeks 20 and 24.
Note: The treatment comparison is based on a CMH test adjusted for the randomization stratification variable.
Source: Table 14.2.1.1

Efficacy was maintained across a number of different sub groups (male/female, different age groups). For subjects both without colon-in-continuity and in those with colon-in-continuity, the responder rate was higher in the teduglutide group, 13/17 subjects (76.5%) and 14/26 subjects (53.8%), respectively, compared with 4/20 subjects (20.0%) and 9/23 subjects (39.1%), respectively, in the placebo group. The teduglutide responder rate was higher for subjects without colon-in-continuity (13/17 subjects, 76.5%) than for subjects with colon-in-continuity (14/26 subjects, 53.8%).

For subjects both with stoma as well as in those without stoma, the responder rate was higher in the teduglutide group (15/21 subjects, 71.4% and 12/22 subjects, 54.5%, respectively) than in the placebo group (3/17 subjects, 17.6% and 10/26 subjects, 38.5%, respectively). The teduglutide responder rate was higher for subjects with stoma (15/21 subjects, 71.4%) than without stoma (12/22 subjects, 54.5%). For subjects without an ileocecal valve, the results were similar to the overall population, with the higher response rate seen in the teduglutide group (27/40 subjects, 67.5%), compared with the placebo group (8/33 subjects, 24.2%). However, the low number of subjects with an ileocecal valve makes interpretation of these results uncertain.

Additional analyses to support the primary analysis

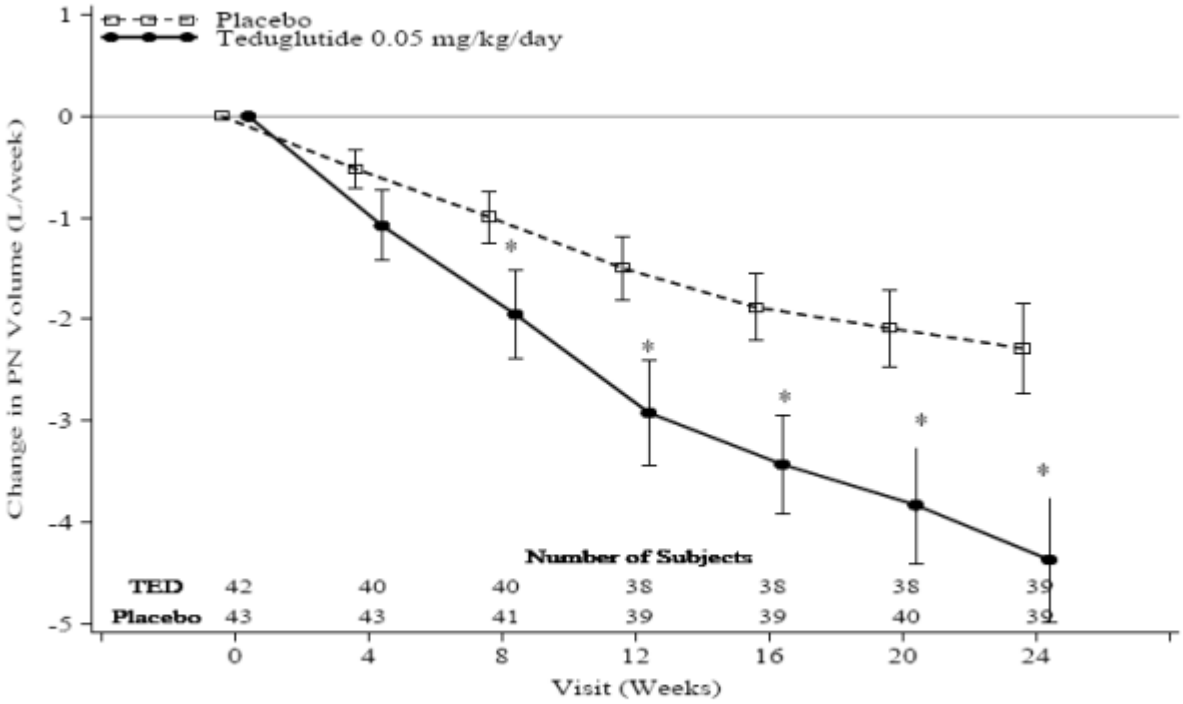
A number of sensitivity analyses were performed and these demonstrated that the results were not influenced by different rules for exclusion of patients depending on the completeness of data. Even in the “worst case scenario” where all patients with any missing data where regarded as “non-responders”, teduglutide was superior to placebo.

Secondary efficacy results

Percent and absolute change in PN/i.v. volume from baseline to last dosing visit

At all visits, change from baseline in actual PN/i.v. volume was greater in the teduglutide group than in the placebo group.

Figure 11-2 Absolute Change in PN Volume (L/week ± SE) – ITT Population



L=liter; SE=standard error, TED=teduglutide
* $p < 0.05$
Source: Table 14.2.2.1

The absolute change from baseline in teduglutide was about twice that of placebo at all visits. At Week 24, the mean reduction in the teduglutide group was 4.4 L/week from a baseline of 12.9 L/week and in the placebo group was 2.3 L/week from a baseline of 13.2 L/week. The percentage change in actual PN/i.v. reduction volume at Week 24 was 32% compared with 21%.

The difference in absolute change between the treatment groups was statistically significant at Week 8 ($p=0.011$) and remained significant through Week 24 ($p<0.001$). The difference in percent change between the treatment groups was significant at Week 12 ($p=0.028$) and remained significant through Week 24 ($p=0.030$). The PP population analyses were consistent with the ITT population analyses. Analyses across subgroups yielded results similar to those obtained for the primary endpoint.

Duration of response (number of consecutive visits)

The time to achieve and maintain responder status was significantly shorter in the teduglutide group than in the placebo group. The percentage of subjects with a duration of response for ≥3 consecutive visits was higher in the teduglutide group (24/43 subjects, 55.8%) than in the placebo group (12/43 subjects, 27.9%).

Response based on a 20 to 100% or 2 liter reduction in PN/i.v. volume from baseline

The proportion of subjects with a 20 to 100% reduction or a 2 L reduction in PN/i.v. volume at Weeks 20 and 24 was higher in the teduglutide group (30/43 subjects, 69.8%) than in the placebo group (16/43 subjects, 37.2%,). This was statistically significant (p=0.002) between the treatment groups. Similar results were seen for the PP population (p<0.001).

While oral intake in subjects on teduglutide was generally unchanged during the trial, subjects on placebo increased oral intake by approximately 1.5 L/week.

Subjects who stopped PN/i.v. and the time of stopping

No subjects had been weaned off PN/i.v. as of Week 20. There was only one subject (0209-1002) in the placebo group who had stopped PN/i.v. during the 14 days prior to Week 24 according to the e-diary. This subject was not considered successful in weaning off PN/i.v. infusion since PN/i.v. was only temporarily interrupted due to hospitalization and catheter replacement.

Graded response

The graded response score was higher in the teduglutide group than in the placebo group (p=0.004). Similar differences between treatment groups were present in the PP population. The so-called graded response is an attempt to combine duration of response and magnitude of response.

The results of the secondary efficacy analyses generally support the primary efficacy analysis. Complete avoidance of PN/I.V. fluid would indeed constitute a clinically relevant effect. None of the subjects in the present study could be weaned off PN/I.V. fluid.

Exploratory Variables

Logistic regression of the primary efficacy parameter

Logistic regression analysis was performed on the binary primary efficacy parameter utilizing the baseline PN/i.v. volume as a covariate. The results were consistent with the primary analysis (p=0.002).

Reduction in days of PN/i.v. volume per week

The percentage of subjects with at least a 1-day reduction in weekly actual PN/i.v. use at Week 24 was statistically significantly higher in the teduglutide group (21/39 subjects, 53.8%) than in the placebo group (9/39 subjects, 23.1%). As one or more days without having to be chained to an i.v. line constitutes a real benefit for the patient, this difference support the clinical relevance of the observed effect.

Reduction from baseline of 20 to 100% in prescribed weekly PN/I.V.

The proportion of responders in the teduglutide group (27/43 subjects, 62.8%) was higher than in the placebo group (16/43 subjects, 37.2%). These results support the responder conclusions based on the actual PN/i.v. data.

Absolute and percent change in prescribed PN/i.v. volume

At all visits, change from baseline (both absolute and percentage [%]) in prescribed PN/i.v. volume was greater in the teduglutide group than in the placebo group. The absolute change from baseline in the teduglutide group was about twice of that in the placebo group at all visits.

Fluid composite effect

At all visits, greater reduction in fluid composite effect was seen in the teduglutide group than in the placebo group. At Week 24, the mean reduction in the teduglutide group was 5.4 L/week, as compared with 1.1 L/week in the placebo group. The fluid composite effect (defined as PN/i.v. volume + volume of oral intake minus urine volume) is an indirect measure of the loss of fluid trough the intestine (assuming that other sources of fluid production/fluid loss, such as perspiration and water generated through metabolism remains constant) and as such a valuable parameter to judge the pharmacodynamic effect of teduglutide. As presented above the average weekly fluid composite effect was reduced. This supports the results of the primary efficacy analysis in terms of efficacy

Change from baseline in plasma citrulline

In the teduglutide group, the mean change in plasma citrulline from baseline (18.4 µmol/L ± 9.5) was 20.6 µmol/L (±17.5) at Week 24. The corresponding Week 24 change from baseline (17.5 µmol/L ± 9.0) for subjects on placebo was 0.7 µmol/L (±6.3).

Quality of Life Assessment

Health-related QoL was assessed in study CL0600-020 using a subject-reported SBS-specific QoL scale (SBS-QoL™) which was particularly designed and developed to measure treatment induced QoL changes over time. The study did not show statistically significant QoL differences between the teduglutide and the placebo group after 24 weeks treatment in this heterogeneous population. Thus, there is no evidence that teduglutide, compared to placebo, has any significantly positive effect on overall QoL and consequently this parameter cannot support clinical relevance of the primary endpoint either. However, it should be noted that the change in single SBS-QoL items from baseline to evaluation at Week 24 was numerically larger and in many instances statistically significant in patients treated with teduglutide (9/17 items) as compared to placebo patients (1/17 items).

Summary of main studies

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

Table: Summary of Efficacy for study CL0600-004

Title: A study of the efficacy and safety of teduglutide in subjects with parenteral nutrition-dependent Short Bowel Syndrome.		
Study identifier	CL0600-004	
Design	Randomized, double-blind, placebo-controlled, parallel-group multicentre study that aimed at evaluating the efficacy, safety, tolerability and pharmacokinetics of teduglutide in patients with PN-dependent SBS.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	6 months 4 weeks 6 months
Hypothesis	Superiority of teduglutide over placebo (hierarchical testing, starting with high dose)	
Treatments groups	Placebo	6 months, n=16
	Teduglutide 0.05 mg/kg b.w.	6 months, n=35
	Teduglutide 0.10 mg/kg b.w.	6 months, n=33

Endpoints and definitions	Primary endpoint	Graded response	Patients were graded according to the levels of reduction of PN (no, <20%, 20-40%, more than 40%, with scores attributed also according to timing of response (week 16-20 and 20-24; scores were 0-5.
	Secondary	- 20% reduction in PN need - Absolute reduction in PN need	- Dichotomous endpoint which evaluated durability of the response from week 20 to 24 - Continuous endpoint based on baseline comparison difference to week 24
	Secondary	Time to 20% reduction in weekly PN vol.	Time to graded response and to 20% response
	Secondary	Quality of Life	SF-36, IBDQ and EQ-5D
Database lock	Last subject completed 06. July 2007; database lock not reported		

Results and Analysis

Analysis description	Primary Analysis			
Analysis population and time point description	All following results are based on the ITT population. PP evaluations – if performed – were in accordance with these results. Due to the number of comparisons a step-down procedure was chosen to account for multiple comparisons. The high-dose group was to be compared to placebo first, followed by the comparison of the low-dose group, if the first comparison was statistically significant.			
Descriptive statistics and estimate variability	Treatment group	Placebo	Teduglutide 0.05 mg/kg	Teduglutide 0.10 mg/kg
	Number of subject	16	35	32
	Graded response No response: Level 1 Level 2 Level 3 Level 4 Level 5	 93.8% 0 6.3% 0 0 0	 54.3% 17.1% 17.1% 0 5.7% 5.7%	 75.0% 6.4% 12.5% 0 6.3% 0
	20% reduction (week 20 to 24)	6.3%	45.7%	25.0%
	PN volume reduction (l/week) SD	-0.90 1.41	- 2.48 2.34	-2.47 3.33

Effect estimate per comparison	Primary endpoint	High-dose vs. placebo	Low-dose vs. placebo
		Pairwise ANCOVA with adjustment for baseline PN consumption level and baseline PN volume as covariates	
		0.161	0.007 (“exploratory” only due to step-down procedure)
	Secondary endpoint 20% reduction of PN	High-dose vs. placebo	Low-dose vs. placebo
		Pairwise ANCOVA with adjustment for baseline PN consumption level and baseline PN volume as covariates	

		0.172	0.005
	Secondary endpoint PN volume reduction	High-dose vs. placebo	Low-dose vs. placebo
		Repeated measures model (Proc Mixed) with effects for treatment, visit, and treatment by visit interaction, and baseline PN and baseline PN consumption level as covariates	
		0.0755	0.0768
Exploratory endpoints:	Time to 20% reduction in weekly PN vol.	0.2031	0.1167
	Quality of Life	No relevant changes	

Table: Summary of Efficacy for study CL0600-020

Title: A 24-Week Study of the Efficacy and Safety of Teduglutide in Subjects with Parenteral Nutrition-Dependent Short Bowel Syndrome. A randomized, double-blind, placebo-controlled, parallel-group study.			
Study identifier	CL0600-020		
Design	Randomized, double-blind, 2-arm, placebo-controlled, parallel-group, multinational, multicenter, 2-stage study. Subjects were randomized to either teduglutide or placebo (1:1). Stage 1 included a screening visit; an optimization period, if needed, of a maximum of 8 weeks, and a stabilization period that demonstrated stable administration of parenteral nutrition/intravenous (PN/I.V.) volume for a minimum of 4 weeks up to a maximum of 8 weeks.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24 weeks Optimization + Stabilization period: up to 16 weeks not applicable (treatment continued for 2 years in the scope of trial CL0600-021)
Hypothesis	The primary efficacy variable was the percentage of subjects who demonstrate a response at Week 20 and who maintain that response through Week 24. A response was defined as the achievement of at least a 20% reduction from baseline in weekly PN volume. The study was designed to detect a higher responder rate among subjects randomized to teduglutide.		
Treatments groups	Teduglutide		teduglutide 0.05 mg/kg/day; duration of treatment: 24 weeks, 43 patients randomized
	Placebo		placebo; duration of treatment: 24 weeks, 43 patients randomized
Endpoints and definitions	Primary endpoint	Responder rate	Number and percentage of subjects who demonstrate at least a 20% reduction in PN volume at Week 20 and maintain at least a 20% reduction in weekly PN volume at Week 24
	Secondary endpoint	Percent change from Baseline in PN volume	Percent change in PN volume between baseline and last dosing visit, where the last dosing visit is the last scheduled visit (including early termination visits) for which there was at least 14 days since the previously scheduled study visit.

	Secondary endpoint	Absolute change from Baseline in PN volume	Absolute change in PN volume between baseline and last dosing visit
	Secondary endpoint	Duration of response	Duration of response (number of consecutive visits with at least 20% reduction)
	Secondary endpoint	Subjects with at least 20% reduction or at least a 2 liter (L) reduction	Proportion of subjects with at least 20% reduction or at least a 2 liter (L) reduction from baseline in weekly PN at Week 20 and maintained through Week 24
	Secondary endpoint	Subjects who stop PN	Number of subjects who stop PN and the time of stopping PN
	Secondary endpoint	Graded response	Graded (or ordered categorical) response that accounted for both intensity and duration of the response at the end of the 24-week treatment period.
	Other endpoint	Response by visit	Response (at least 20% reduction from baseline in weekly PN) by visit
	Other endpoint	Reduction in days on PN	Reduction in days on PN per week
	Other endpoint	Reduction in prescribed weekly PN	Reduction from baseline of at least 20% in prescribed weekly PN at Week 20 and maintained through Week 24
	Other endpoint	Absolute and percent change in prescribed PN volume	Absolute and percent change in prescribed PN volume (not based on patient diaries, but prescription of physician)
	Other endpoint	Composite fluid balance	An analysis of the fluid composite effect (PN/I.V. volume + Oral Fluid Intake volume – Urine Output volume) was performed. This evaluation takes into account the day-to-day variations of fluid inputs into the body (PN volume, oral fluid intake) and the urine output.

	Other endpoint	Change from baseline in plasma citrulline	According to literature, plasma citrulline levels are correlated to small bowel length and to net digestive absorption of fat in untreated SBS patients. Therefore, plasma citrulline was evaluated as a potential pharmacodynamic marker to assess absorptive enterocyte mass.
	Other endpoint	Quality of life	The effect of the SBS-QoL™ Baseline value, treatment and PN volume reduction on the change of subjects' QoL from Baseline to Week 24 was investigated within an ANCOVA model, and the change in QoL was considered as dependent variable.
Database lock	25 January 2011		

Results and Analysis

Analysis description	Primary Analysis		
Analysis population and time point description	Intent-to-treat (with per protocol analysis as supportive), based on data from scheduled visits at Weeks 20 and 24		
Descriptive statistics and estimate variability	Treatment group	Teduglutide	Placebo
	Number of subjects	43	43
	Non-responder n (%) Responder n (%)	16 (37.2) 27 (62.8)	30 (69.8) 13 (30.2)

Effect estimate per comparison	Primary Endpoint: Responder rate	Comparison groups	Teduglutide vs. Placebo
		P-value	0.002
	Exploratory Endpoint: Response rate	Comparison groups	Teduglutide vs. Placebo
		Contrast Estimate Teduglutide versus Placebo	2.041
		95% confidence interval	1.296, 3.215
		P-value	0.002
Notes	Primary endpoint responder rates were evaluated using CMH test statistics adjusted for the randomization stratification variable (<=6 or >6 L/week of PN at baseline). Exploratory endpoint responder rates were evaluated using logistic regression with effects for treatment group and Baseline PN volume.		
Analysis description	Secondary Analysis: Percent change from baseline in PN volume		
Analysis population and time point description	Intent-to-treat (with per protocol analysis as supportive), based on subject data at last dosing visit		
Descriptive statistics and estimate variability	Treatment group	Teduglutide	Placebo
	Number of subjects	40	43
	Mean	-32.13	-21.01
	SD	18.71	24.35

Effect estimate per comparison	Percent Change from Baseline in PN Volume	Comparison groups	Teduglutide vs. Placebo
		Difference Teduglutide minus Placebo	-10.99
		95% confidence interval	-20.44, -1.54

		P-value	0.023
Notes	Treatment comparison was based on ANCOVA model with treatment and interaction of treatment by baseline PN volume as effects and baseline PN volume as a covariate. Number of subjects represents the number of intent-to-treat subjects with a nonmissing value at the last dosing visit. This parameter is the first of the six secondary parameters which were scheduled to be evaluated as part of a step-down testing procedure.		
Analysis description	Secondary Analysis: Absolute change from baseline in PN volume		
Analysis population and time point description	Intent-to-treat (with per protocol analysis as supportive), based on subject data at last dosing visit		
Descriptive statistics and estimate variability	Treatment group	Teduglutide	Placebo
	Number of subjects	40	43
	Mean	-4.28	-2.38
	SD	3.81	2.79
Effect estimate per comparison	Absolute Change from Baseline in PN Volume	Comparison groups	Teduglutide vs. Placebo
		Difference Teduglutide minus Placebo	-2.07
		95% confidence interval	-3.19, -0.94
		P-value	<0.001
Notes	Treatment comparison was based on ANCOVA model with treatment and interaction of treatment by baseline PN volume as effects and baseline PN volume as a covariate. Number of subjects represents the number of intent-to-treat subjects with a nonmissing value at the last dosing visit. This parameter is the second of the six secondary parameters which were scheduled to be evaluated as part of a step-down testing procedure.		
Analysis description	Secondary Analysis: Duration of response		
Analysis population and time point description	Intent-to-treat (with per protocol analysis as supportive), based on subject data at Week 24		
Descriptive statistics and estimate variability	Treatment group	Teduglutide	Placebo
	Number of subjects	43	43
	0 visits n (%) 1 visit n (%) 2 visits n (%) >=3 visits n (%)	13 (30.2) 3 (7.0) 3 (7.0) 24 (55.8)	25 (58.1) 5 (11.6) 1 (2.3) 12 (27.9)
Effect estimate per comparison	Response rate	Comparison groups	Teduglutide vs. Placebo
		P-value	0.005
Notes	Response rates were evaluated using CMH test statistics adjusted for the randomization stratification variable (<=6 or >6 L/week of PN at baseline). The number of visits is based on consecutive visits at Week 24 and scheduled previous visits, where a value of 0 visits represents no response at Week 24 or no visit conducted at Week 24. This parameter is the third of the six secondary parameters which were scheduled to be evaluated as part of a step-down testing procedure.		

Analysis description	Secondary Analysis: Subjects with at least 20% reduction or at least a 2 liter (L) reduction		
Analysis population and time point description	Intent-to-treat (with per protocol analysis as supportive), based on data from scheduled visits at Weeks 20 and 24		
Descriptive statistics and estimate variability	Treatment group	Teduglutide	Placebo
	Number of subjects	43	43
	Non-response n (%) Response n (%)	13 (30.2) 30 (69.8)	27 (62.8) 16 (37.2)
Effect estimate per comparison	Response rate	Comparison groups	Teduglutide vs. Placebo
		P-value	0.002
Notes	Response rates were evaluated using CMH test statistics adjusted for the randomization stratification variable (<=6 or >6 L/week of PN at baseline). This parameter is the fourth of the six secondary parameters which were scheduled to be evaluated as part of a step-down testing procedure.		
Analysis description	Secondary Analysis: Subjects who stop PN		
Analysis population and time point description	Intent-to-treat (with per protocol analysis as supportive), based on data from scheduled visits		
Descriptive statistics and estimate variability	Treatment group	Teduglutide	Placebo
	Number of subjects	43	43
	Non-response n (%) Response n (%)	43 (100.0) 0	42 (97.7) 1 (2.3)
Effect estimate per comparison	Response rate	Comparison groups	Teduglutide vs. Placebo
		P-value	>0.999
Notes	Response rates were evaluated using CMH test statistics adjusted for the randomization stratification variable (<=6 or >6 L/week of PN at baseline). This parameter is the fifth of the six secondary parameters which were scheduled to be evaluated as part of a step-down testing procedure and the first of those six not to be significant at alpha of 0.05.		
Analysis description	Secondary Analysis: Graded response		
Analysis population and time point description	Intent-to-treat (with per protocol analysis as supportive), based on data from scheduled visits at Weeks 16, 20, and 24		
Descriptive statistics and estimate variability	Treatment group	Teduglutide	Placebo
	Number of subjects	43	43
	Graded response total 0 n (%) 1 n (%) 2 n (%) 3 n (%) 4 n (%) 5 n (%)	 16 (37.2) 3 (7.0) 13 (30.2) 4 (9.3) 7 (16.3) 0	 30 (69.8) 1 (2.3) 6 (14.0) 2 (4.7) 4 (9.3) 0
Effect estimate per comparison	Graded response total	Comparison groups	Teduglutide vs. Placebo
		P-value	0.004
Notes	Response rates were evaluated using CMH test statistics adjusted for the randomization stratification variable (<=6 or >6 L/week of PN at baseline). The graded response total is the total number of five criteria met by a subject based on percent reduction of PN at Weeks 16, 20, and 24. This parameter is the sixth of the six secondary parameters which were scheduled to be evaluated as part of a step-down testing procedure and falls after a parameter which was not significant at alpha of 0.05.		

Analysis description	Exploratory Analysis: Response by visit		
Analysis population and time point description	Intent-to-treat, based on data from scheduled visits at four week intervals and the last dosing visit		
Descriptive statistics and estimate variability	Treatment group	Teduglutide	Placebo
	Number of subjects	43	43
	Week 4 Non-response n (%) Response n (%)	 34 (85.0) 6 (15.0)	 38 (88.4) 5 (11.6)
	Week 8 Non-response n (%) Response n (%)	 27 (67.5) 13 (32.5)	 35 (85.4) 6 (14.6)
	Week 12 Non-response n (%) Response n (%)	 19 (50.0) 19 (50.0)	 29 (74.4) 10 (25.6)
	Week 16 Non-response n (%) Response n (%)	 14 (35.9) 25 (64.1)	 26 (65.0) 14 (35.0)
	Week 20 Non-response n (%) Response n (%)	 11 (28.9) 27 (71.1)	 26 (65.0) 14 (35.0)
	Week 24 Non-response n (%) Response n (%)	 9 (23.1) 30 (76.9)	 21 (53.8) 18 (46.2)
	Last Dosing Visit Non-response n (%) Response n (%)	 9 (22.5) 31 (77.5)	 23 (53.5) 20 (46.5)
Notes	Percentages are based on the number of subjects attending the visit.		
Analysis description	Exploratory Analysis: Reduction in days on PN per week		
Analysis population and time point description	Intent-to-treat, for subjects who completed the study only, based on data from Week 24		
Descriptive statistics and estimate variability	Treatment group	Teduglutide	Placebo
	Number of subjects	39	39
	<1 day reduction n (%) >= 1 day reduction n (%)	18 (46.2) 21 (53.8)	30 (76.9) 9 (23.1)
Effect estimate per comparison	Reduction in day on PN per week	Comparison groups	Teduglutide vs. Placebo
		P-value	0.005
Notes	Response rates were evaluated using CMH test statistics adjusted for the randomization stratification variable (<=6 or >6 L/week of PN at baseline).		
Analysis description	Exploratory Analysis: Reduction from baseline of at least 20% in prescribed PN at Week 20 and maintained through Week 24		
Analysis population and time point description	Intent-to-treat, based on data from scheduled visits at Weeks 20 and 24		
Descriptive statistics and estimate variability	Treatment group	Teduglutide	Placebo
	Number of subjects	43	43
	Non-response n (%) Response n (%)	16 (37.2) 27 (62.8)	27 (62.8) 16 (37.2)
Notes	Prescribed PN volume is based on the volume prescribed at the start of the visit, rather than the prescribed volume at the completion of the visit.		
Analysis description	Exploratory Analysis: Absolute change from baseline in prescribed PN volume		
Analysis population and time point description	Intent-to-treat, based on subject data at last dosing visit		

Descriptive statistics and estimate variability	Treatment group	Teduglutide	Placebo
	Number of subjects	42	43
	Mean	-3.95	-2.12
	SD	3.44	2.80
Notes	Prescribed PN volume is based on the volume prescribed at the start of the visit, rather than the prescribed volume at the completion of the visit. Number of subjects represents the number of intent-to-treat subjects with a last dosing visit for this parameter.		
Analysis description	Exploratory Analysis: Percent change from baseline in prescribed PN volume		
Analysis population and time point description	Intent-to-treat, based on subject data at last dosing visit		
Descriptive statistics and estimate variability	Treatment group	Teduglutide	Placebo
	Number of subjects	42	43
	Mean	-31.42	-18.22
	SD	21.58	23.40
Notes	Prescribed PN volume is based on the volume prescribed at the start of the visit, rather than the prescribed volume at the completion of the visit. Number of subjects represents the number of intent-to-treat subjects with a last dosing visit for this parameter.		
Analysis description	Exploratory Analysis: Composite Fluid Balance		
Analysis population and time point description	Intent-to-treat, based on data from scheduled visits at four week intervals and the last dosing visit		
Descriptive statistics and estimate variability	Treatment group	Teduglutide	Placebo
	Number of subjects	40	42
	Week 4 Mean	13.69	14.85
	SD	9.74	9.00
	Week 8 Mean	13.14	14.32
	SD	9.95	10.66
	Week 12 Mean	11.17	14.45
	SD	8.85	10.30
	Week 16 Mean	12.57	14.50
	SD	9.66	8.89
	Week 20 Mean	11.57	14.38
	SD	7.67	10.51
	Week 24 Mean	10.43	13.52
	SD	7.24	9.98
	Last Dosing Visit Mean	11.21	14.08
	SD	8.43	10.02
Notes	Composite fluid balance is not calculated whenever one of the three components has a missing value. Number of subjects represents the number of intent-to-treat subjects with a last dosing visit value for this parameter.		
Analysis description	Exploratory Analysis: Change from baseline in plasma citrulline		
Analysis population and time point description	Intent-to-treat, based on data from scheduled visits Weeks 4, 8, 16, 24, and the last dosing visit		
Descriptive statistics and estimate	Treatment group	Teduglutide	Placebo
	Number of subjects	42	43

variability	Week 4 Mean	9.5	-0.1
	SD	9.1	3.4
	Week 8 Mean	12.7	-0.5
	SD	14.0	5.3
	Week 16 Mean	17.0	0.2
	SD	15.1	4.1
	Week 24 Mean	20.6	0.7
	SD	17.5	6.3
	Last Dosing Visit Mean	19.0	0.4
	SD	17.8	6.2
Notes	Number of subjects represents the number of intent-to-treat subjects with a last dosing visit value for this parameter.		
Analysis description	Exploratory Analysis: Quality of life		
Analysis population and time point description	Intent-to-treat, based on subject data at last dosing visit		
Descriptive statistics and estimate variability	Treatment group	Teduglutide	Placebo
	Number of subjects	43	43
Effect estimate per comparison	Quality of life total score	Comparison groups	Teduglutide vs. Placebo
		Treatment Comparison p-value	0.8112
		Baseline covariate p-value	<0.0001
		PN volume reduction (yes/no) covariate p-value	0.0051
		Treatment-by-PN reduction interaction p-value	0.0117
Notes	In case QoL data were not available at Week 24, the last observation carried forward (LOCF) approach was applied.		

Analysis performed across trials (pooled analyses and meta-analysis)

A recommendation to evaluate the treatment effect after 6 months and stop the treatment if no effect is seen has been considered, along with proper justification including proposals for measurements to be implemented to assess whether a patient should be allowed to continue or stop the treatment. To this end, combined analysis of study CL0600-020 and its prolongation study, CL0600-021, show that in the time period up to 6 months after initiating treatment there is a gradual increase in the number of patients achieving the primary endpoint. After that time point only few additional patients achieve the primary endpoint. Thus the proposal to evaluate efficacy after 6 months is supported. It is agreed that defining a general realistic goal for treatment applicable to all patients is neither realistic nor desirable. Thus a more general approach has been considered and reported in the SmPC in section 4.2

Clinical studies in special populations

Clinical studies in special population have not been conducted

Supportive study(ies)

Study CL0600-005 was a double-blind 28-week extension study to the study CL0600-004, and was designed as a randomized, parallel-group, multinational, multicenter study. This supportive study had the objective to evaluate the long-term safety and efficacy of teduglutide.

Only patients who completed study CL0600-004 were eligible for the study CL0600-005. In total, 65 of the 71 patients who had completed the study CL0600-004 were enrolled. Only 6 patients (2 from each arm in study CL0600-004) decided not to continue into study CL0600-005. The patients from the active treatment arms maintained their treatment regimen. The previous placebo patients were randomized to receive 0.05 or 0.10 mg/kg/day of teduglutide. The patients who completed the 28-week dosing period of the study CL0600-005 entered a 4-week non-dosing follow-up period.

5/25 (20%) patients in the 0.05/0.05 group and 4/27 (14.8%) of the 0.10/0.10 group discontinued. There were 0/6 and 1/7 discontinuations in the placebo/0.05 and the placebo/0.10group, respectively.

54 of the 71 patients completed study CL0600-005.

In the extension study the imbalance due to the cause of intestinal resection is preserved. There were 28% of patients with stoma in the 0.05/0.05 group (hereof 57.1% with jejunostomy) and 37% of patients with stoma in the 0.10/0.10 group (hereof 60% with ileostomy). Four patients in the 0.05/0.05 group (16%) had a terminal ileum (all with ileocecal valve) and 6 patients in the 0.10/0.10 group (22.2%) (thereof 3 with ileocecal valve). The difference between groups of patients with colon in continuity was less compared to study 0600-004 (76% in the 0.05/0.05 group and 66.7% in the 0.10/0.10 group)

The main efficacy results according to the binary endpoint are shown in the following table:

Table: Number and percentage of patients achieving at least a 20% reduction in weekly PN volume at week 28 of study CLO600-005

	Teduglutide Treatment Group (mg/kg/day) N (%) of Subjects				
	6-Month Active Group		1-Year Active Group		
Variable	Placebo/0.05[a] N=6	Placebo/0.10[a] N=7	0.05/0.05 N=25	0.10/0.10 N=27	Total[b] N=65
> 20% Reduction	5 (83.3)	3 (42.9)	17 (68.0)	14 (51.9)	39 (60.0)

The following table shows these results stratified by study 004 treatment group (for the 1-year active group only):

Table: Proportion of responder at week 28 of study 005 stratified by study 004

	Study 004	Study 005 n (%) of Subjects	
Teduglutide Treatment Group	Response Outcome	Responder	Non-Responder
0.05 mg/kg/day	Responder	12 (75.0)	4 (25.0)
	Non-responder	5 (55.6)	4 (44.4)
0.10 mg/kg/day	Responder	6 (75.0)	2 (25.0)
No	n-responder	8 (42.1)	11 (57.9)
Total R	esponder	18 (75.0)	6 (25.0)
	Non-responder	13 (46.4)	15 (53.6)

As can be seen, 25% of the responders during study 004 became non-responders at the end of study 005. However, the applicant claims that these were not efficacy related non-response, but other reasons which are given in the study report as lost diary, moved to a different country, AE (one hyperplastic colon polyp and one due to abdominal pain and vomiting), and temporary PN increase due to infection.

One subject on the 0.05/0.05 group additionally was completely weaned off PN.

The number and percentage of subjects with an at least one day reduction from baseline weekly PN use is given in the following table:

Table: Number and percentage of subjects who achieved at least a one day reduction in PN use

	Teduglutide Treatment Group (mg/kg/day) n (%) of Subjects				
	6-Month Active Group		1-Year Active Group		
Response status	Placebo/0.05[a] N=6	Placebo/0.10[a] N=7	0.05/0.05 N=25	0.10/0.10 N=27	Total N=65
Yes	4 (66.7)	2 (28.6)	17 (68.0)	10 (37.0)	33 (50.8)
No	2 (33.3)	5 (71.4)	8 (32.0)	17 (63.0)	32 (49.2)
95% CI of % responders[b]	(22.3, 95.7)	(3.7, 71.0)	(46.5, 85.1)	(19.4, 57.6)	-

The changes seen in the summary of the PN energy needs and the reductions in PN volume were substantial in the different groups.

The study report further states a 60% and 42% reduction in the i.v. catheter access at week 28 in the 0.05/0.05 and 0.10/0.10 groups, and a 50% and 17% reduction in the placebo/0.05 and placebo/0.10 groups.

Quality of Life data indicated no systematic improvement in QoL scores.

Study CL0600-021 was designed as a long-term, open-label study. The study is still ongoing. An interim analysis of the results is presented here. The interim analysis was not planned per the currently approved protocol version. This interim analysis was prepared to evaluate the long-term safety data to support a marketing application review. The data presented represent information collected at completed visits from 21 September 2009 (first subject enrolled) through data cut-off on 30 June 2011.

There were 2 subject populations in this study: 1) subjects already exposed to active treatment with teduglutide for 24 weeks in Study CL0600-020 (called TED/TED group, N=37); 2) subjects not treated or treated with placebo (called NT, PBO/TED group, N=51) in Study CL0600-020.

As this is an ongoing trial, efficacy data in this report represent information collected at completed visits in the first 6 months (through Visit 6 of this extension study), which the majority of subjects have completed.

In the TED/TED Group, the response to teduglutide observed during 24 weeks of treatment in Study CL0600-020 was maintained in the TED/TED group during continued, long-term treatment in this interim reporting period of the extension study. After an additional 6 months of treatment with teduglutide, the mean reduction was 5.16 L/week from a baseline level of 12.76 L/week, with a mean reduction of 34.18%. In the NT, PBO/TED Group Teduglutide 0.05 mg/kg/day also showed signs of efficacy in subjects who had not received previous treatment with teduglutide in Study CL0600-020, with reductions from baseline in mean absolute PN/i.v. volume observed at every visit. After 6 months

of treatment, the mean reduction in absolute PN/i.v. volume in the NT, PBO/TED group was 2.19 L/week from a baseline level of 11.97 L/week, with a mean reduction of 17.60% (Table 11-6).

Table 11-6 Absolute and Percent Change in PN/I.V. Volume by Visit and at the Last Dosing Visit – ITT Population

Visit	Statistic	NT, PBO/TED (N=51)		TED/TED (N=37)	
		Absolute Change (L/week)	Percent Change	Absolute Change (L/week)	Percent Change
Month 1	**n**	**48**	**48**	**37**	**37**
	Baseline Mean	11.70		12.85	
	Mean (SD)	-0.97 (1.802)	-6.19 (11.139)	-5.28 (3.819)	-40.65 (21.546)
	Median	-0.09	-0.83	-3.89	-41.61
	Min, Max	-7.0, 2.5	-37.4, 20.0	-14.0, 0.0	-100, 0.0
Month 2	**n**	**46**	**46**	**37**	**37**
	Baseline Mean	11.96		12.85	
	Mean (SD)	-1.48 (2.180)	-10.84 (16.065)	-5.62 (3.873)	-44.24 (21.823)
	Median	-0.77	-8.85	-4.23	-42.86
	Min, Max	-7.5, 2.1	-66.7, 20.0	-13.8, 0.0	-100, 0.0
Month 3	**n**	**45**	**45**	**36**	**36**
	Baseline Mean	11.59		13.06	
	Mean (SD)	-1.85 (2.607)	-13.43 (25.890)	-5.72 (3.771)	-45.80 (22.681)
	Median	-1.20	-12.57	-4.65	-43.15
	Min, Max	-11.0, 2.8	-75.0, 110.0	-13.0, 3.0	-100, 35.7
Month 6	**n**	**41**	**41**	**34**	**34**
	Baseline Mean	11.97		12.76	
	Mean (SD)	-2.19 (3.047)	-17.60 (20.490)	-5.16 (4.787)	-34.18 (56.653)
	Median	-1.54	-15.60	-4.38	-42.23
	Min, Max	-13.8, 3.5	-66.3, 12.8	-13.6, 9.0	-100, 221.0
Month 9	**n**	**26**	**26**	**21**	**21**
	Baseline Mean	11.15		11.72	
	Mean (SD)	-2.62 (3.570)	-20.85 (26.662)	-5.37 (3.402)	-48.84 (25.240)
	Median	-1.54	-14.62	-4.26	-42.10
	Min, Max	-14.6, 1.0	-94.6, 9.4	-13.0, 0.0	-100, 0.0
Month 12	**n**	**15**	**15**	**16**	**16**
	Baseline Mean	8.42		12.82	
	Mean (SD)	-2.25 (4.155)	-23.61 (34.606)	-6.29 (4.644)	-49.64 (26.637)
	Median	0.00	0.00	-4.77	-41.85
	Min, Max	-14.6, 1.0	-100, 9.4	-18.9, 0.0	-100, 0.0

Continued on next page

Table 11-6 Absolute and Percent Change in PN/I.V. Volume by Visit and at the Last Dosing Visit – ITT Population (continued)

		NT, PBO/TED (N=51)		TED/TED (N=37)	
Visit	**Statistic**	**Absolute Change**	**Percent Change**	**Absolute Change**	**Percent Change**
Month 15	**n**	**6**	**6**	**5**	**5**
	Baseline Mean	10.15		15.79	
	Mean (SD)	-3.04 (5.099)	-20.75 (31.146)	-6.68 (5.248)	-40.92 (7.846)
	Median	-0.87	-13.00	-3.63	-41.61
	Min, Max	-12.0, 0.9	-57.9, 9.1	-15.4, -3.1	-49.0, -29.1
Month 18	**n**	**1**	**1**	**1**	**1**
	Baseline Mean	10.50		32.85	
	Mean (SD)	-6.90 (NA)	-65.71 (NA)	-15.35 (NA)	-46.73 (NA)
	Median	-6.90	-65.71	-15.35	-46.73
	Min, Max	-6.9, -6.9	-65.7, -65.7	-15.4, -15.4	-46.7, -46.7
Month 21	**n**	**0**	**0**	**1**	**1**
	Baseline Mean	NA	NA	32.85	
	Mean (SD)	NA	NA	-15.35 (NA)	-46.73 (NA)
	Median	NA	NA	-15.35	-46.73
	Min, Max	NA	NA	-15.4, -15.4	-46.7, -46.7
Last Dosing Visit		**45[a]**	**45[a]**	**37**	**37**
	Baseline Mean	12.16		12.85	
	Mean (SD)	-2.30 (3.242)	-15.95 (30.121)	-5.53 (4.968)	-36.93 (55.244)
	Median	-1.24	-12.57	-4.79	-46.23
	Min, Max	-12.0, 3.5	-100, 110.0	-15.4, 9.0	-100, 221.0

SD=standard deviation; NA=not applicable

[a] Six of the 51 subjects in the NT, PBO/TED group did not have a visit that met the definition for the last dosing visit, which is defined as the last visit, either a scheduled dosing visit or the early termination visit, for which there are at least 9 days since the previously scheduled study visit.

Note: Individual adjustments in PN/I.V. volume and PN/I.V. days per week are provided for all subjects screened in Appendix 16.2 (Listing 16.2.6.1).

Source: Table 14.2.1.1

Although observations in the subgroup analyses were limited due to the nature of the interim reporting in an ongoing trial, the observations in the subgroups examined supported the findings regarding reductions in weekly PN/i.v. volume in the overall population.

After 6 months of treatment, 31 of 34 subjects (91.2%) in the TED/TED group had a 20 to 100% decrease from baseline in weekly PN/i.v. volume and 17 of 43 subjects (39.5%) in the NT, PBO/TED group had a 20 to 100% decrease from baseline in weekly PN/i.v.

Table 11-7 Binary Response Status of 20 to 100% – ITT Population

Response Status	Statistic	NT, PBO/TED (N=51)	TED/TED (N=37)
Response Level 20%			
Month 1	**n**	**49**	**37**
Non-response	n (%)	43 (87.8)	5 (13.5)
Response	n (%)	6 (12.2)	32 (86.5)
Month 2	**n**	**48**	**37**
Non-response	n (%)	31 (64.6)	5 (13.5)
Response	n (%)	17 (35.4)	32 (86.5)
Month 3	**n**	**45**	**36**
Non-response	n (%)	27 (60.0)	1 (2.8)
Response	n (%)	18 (40.0)	35 (97.2)
Month 6	**n**	**43**	**34**
Non-response	n (%)	26 (60.5)	3 (8.8)
Response	n (%)	17 (39.5)	31 (91.2)
Month 9	**n**	**26**	**21**
Non-response	n (%)	14 (53.8)	1 (4.8)
Response	n (%)	12 (46.2)	20 (95.2)
Month 12	**n**	**16**	**16**
Non-response	n (%)	9 (56.3)	1 (6.3)
Response	n (%)	7 (43.8)	15 (93.8)
Month 15	**n**	**6**	**5**
Non-response	n (%)	3 (50.0)	0
Response	n (%)	3 (50.0)	5 (100.0)
Month 18	**n**	**1**	**1**
Non-response	n (%)	0	0
Response	n (%)	1 (100.0)	1 (100.0)
Month 21	**n**	**0**	**1**
Non-response	n (%)	0	0
Response	n (%)	0	1 (100.0)
Last Dosing Visit	**n**	**51**	**37**
Non-response	n (%)	31 (60.8)	4 (10.8)
Response	n (%)	20 (39.2)	33 (89.2)

Note: Percentages were based on the number of subjects who attended the applicable analysis visit.
Note: Response is defined as at least the identified response level reduction from baseline in weekly PN/I.V. volume.
Note: Individual adjustments in PN/I.V. volume and PN/I.V. days per week are provided for all subjects screened in Appendix 16.2 (Listing 16.2.6.1).
Source: Table 14.2.1.9

Three subjects were weaned from PN/i.v. and at month 6 visit 18 of 34 (52.9%) subjects in the TED/TED group achieved at least a 1 day reduction in the number of days on PN/i.v. The corresponding numbers were 10 of 43 (23.3%) subjects in the NT, PBO/TED group.

Table 11-8 Summary of the Reduction in Days of PN/I.V. per Week – ITT Population

Parameter	Statistic	NT, PBO/TED (N=51)	TED/TED (N=37)
At Least a 1-day Reduction/Week	**n**	**43**	**34**
Month 6			
Non-response	n (%)	33 (76.7)	16 (47.1)
Response	n (%)	10 (23.3)	18 (52.9)
Month 12	**n**	**16**	**16**
Non-response	n (%)	10 (62.5)	5 (31.3)
Response	n (%)	6 (37.5)	11 (68.8)
Last Dosing Visit	**n**	**51**	**37**
Non-response	n (%)	39 (76.5)	15 (40.5)
Response	n (%)	12 (23.5)	22 (59.5)
At Least a 2-day Reduction/Week	**n**	**43**	**34**
Month 6			
Non-response	n (%)	40 (93.0)	21 (61.8)
Response	n (%)	3 (7.0)	13 (38.2)
Month 12	**n**	**16**	**16**
Non-response	n (%)	13 (81.3)	8 (50.0)
Response	n (%)	3 (18.8)	8 (50.0)
Last Dosing Visit	**n**	**51**	**37**
Non-response	n (%)	46 (90.2)	23 (62.2)
Response	n (%)	5 (9.8)	14 (37.8)
At Least a 3-day Reduction/Week	**n**	**43**	**34**
Month 6			
Non-response	n (%)	41 (95.3)	26 (76.5)
Response	n (%)	2 (4.7)	8 (23.5)
Month 12	**n**	**16**	**16**
Non-response	n (%)	13 (81.3)	11 (68.8)
Response	n (%)	3 (18.8)	5 (31.3)
Last Dosing Visit	**n**	**51**	**37**
Non-response	n (%)	47 (92.2)	29 (78.4)
Response	n (%)	4 (7.8)	8 (21.6)

Note: Response is defined as at least the identified response level reduction from baseline in days of PN/I.V. per week. A non-response includes no reduction or an increase in the number of days of PN/I.V. per week.
Note: Individual adjustments in PN/I.V. volume and PN/I.V. days per week are provided for all subjects screened in Appendix 16.2 (Listing 16.2.6.1).
Source: Table 14.2.1.13

Due to the nature of the study (open label extension study in patients who completed the placebo-controlled part), selection of patients based on previous response both in terms of efficacy and safety has occurred. The TED/TED group has an overrepresentation of subjects who tolerate teduglutide and has experienced a positive effect of the drug. The NT, PBO/TED group has not experienced this selection during the previous placebo controlled trial and the subjects in this group are more likely to report safety problems and lack of effect. Thus the two groups are not comparable in terms of safety and efficacy. While the present study can provide knowledge about the persistence of effect and the safety after extended duration of exposure, results must be interpreted with great caution, especially as concerns the magnitude of the effect observed and the clinical relevance of the observed effect.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The applicant originally submitted one pivotal study in this proposed orphan indication. A dose-finding study was conducted before this pivotal study, supporting only a vague dose-response relationship, based on selected pharmacodynamic effects. Based on this information, two final doses were chosen to be investigated in phase III.

The initial pivotal efficacy study (study CL0600-004) was conducted in USA, Canada and Europe, as a multicenter double-blind study. The overall design of the study can be considered to be appropriate, with a careful selection of patients, including an optimisation and a run-in period, in order to exclude ongoing adaptation to the short-bowel state.

The difficulties related to blinding of treatment due to the stomal swelling induced by teduglutide treatment have been acknowledged. The use of third party blinded to the treatment assignment, for collection and assessment of study results has been appreciated. However full blinding of the study appears to be questionable, at least in patients with a stoma where the pharmacodynamic effect (mucosal hyperplasia seen as swelling) could easily be detected. The applicant subsequently provided evidence to support that accidental unblinding, albeit not completely ruled out, is not likely to have had any major effect of the assessment of efficacy and safety. However, unblinding could of course have an influence on the assessment of some of the secondary endpoints, namely the Quality of Life (QoL) parameters.

The study was conducted within a reasonable time-frame considering the rareness of the disease, and has obviously been conducted in experienced centres, both in Europe and North America. No GCP violations have become obvious.

The initially planned primary endpoint - a dichotomous responder criterion ("number and percentage of subjects who demonstrated a response ≥20% reduction from baseline in weekly PN volume at Week 20 maintained at Week 24") was exchanged with an ordered categorical (graded) criterion accounting for both duration (weeks 16 and 20 and weeks 20 and 24) and intensity of response (>20% to 100% reduction in weekly PN volume). This amendment was implemented late during the conduct of the study (February 2007; the last patient completed the study in July 2007) after an independent review of the protocol. The CHMP noted that the graded response used for scoring of patients is not validated and of unclear clinical relevance. Regarding endpoints, however, the studies still included a chance to appropriately assess a benefit for the patients with the 1-day reduction of PN need endpoint, as well as with the Quality of Life, and the healthcare utilisation data/measurements.

The overall design of the phase 3 study CL0600-020 is acceptable. The use of an optimisation and stabilisation period is considered acceptable and necessary in order to minimise variability in this inherently variable condition. As there are no licensed treatment options available for this condition, the choice of placebo as comparator is also supported. Duration of study (6 months) is considered the minimally acceptable and data supporting long term (beyond 6 months) safety is needed. In that respect, the extension study CL0600-021 could be sufficient. The inclusion and exclusion criteria are extensive but acceptable.

There are no generally accepted efficacy parameters in the field of SBS. In the present study primary and secondary endpoints are largely based on changes in the volume of fluid administered parentally ("PN/IV volume"). Overall this is acceptable, however in order to make the results reliable, stringent, objective algorithms (and adherence to these) for investigator decision on when and how to

reduce/increase PN/i.v. volume is critical. Based on the protocol such algorithms were in place and are considered acceptable. The secondary efficacy endpoints are generally acceptable.

It is agreed that QoL is an important secondary endpoint. Previously, generally accepted and validate QoL instruments specifically for this condition has not been available. Consequently, the applicant has developed an instrument (SBS-QoL™) specifically designed to measure QoL in short bowel syndrome. The development appears to adhere to generally accepted criteria in this field and the instrument has been validated. The use of SBS-QoL™ is considered acceptable.

In general, sample size calculations, randomisation procedures and statistical methods are considered acceptable

Efficacy data and additional analyses

In study CL0600-004 results demonstrated that there was no statistical significant difference between teduglutide 0.1mg/kg/d vs. placebo in the graded response score (p=0.161), but a further analysis of the 0.05 mg/Kg/day dose evidenced promising results, which could have only been considered for hypothesis generation and for dose finding. Indeed, the results of the exploratory analyses of study CL0600-004 indicated that 0.05 mg/kg/day of teduglutide significantly reduced volume of PN/i.v. in SBS. Consequently the applicant performed a new phase 3 study (CL0600-020) intended to provide confirmatory evidence of the safety and efficacy of teduglutide administered at the dose of 0.05 mg/kg/day.

Study CL0600-020 demonstrated that compared to placebo, teduglutide had statistically significant effect on the primary efficacy parameter, 20% or greater reduction in volume of PN/i.v. at weeks 20 and 24. The results were robust and confirmed in a number of sensitivity analyses. Considering the strict inclusion/exclusion criteria and the inherent diversity of the target population, the relative large number of screened patients compared to the relative small number of patients randomised is understandable and acceptable. A large fraction of patients randomised did ultimately complete the study and the study groups were well balanced in terms of discontinuations. Indeed, the effect was observed across a number of subgroups such as male/females, age groups, stoma/no stoma and colon-in-continuity/colon-not-in-continuity. The secondary endpoints generally supported the primary endpoint. Compared to placebo, teduglutide had superior effect after 8 to 12 weeks. Duration of effect was also superior in teduglutide treated patients compared to placebo treated patients. Thus, the present study has demonstrated that teduglutide does reduce the need for PN/i.v. in SBS.

Complete avoidance of PN/I.V. fluid would constitute a clinically relevant effect. However, none of the subjects in the CL0600-020 study could be weaned off PN/i.v. fluid. In the present setting complete weaning off does not seem realistic. In a less severe population, complete weaning off PN/i.v. could be feasible, but this would on the other hand raise the question of the appropriateness of treating such less severe patients. In the present setting with patients with a very short segment of remaining intestine and a substantial requirement for PN/i.v. other clinically relevant endpoints, short of complete weaning off PN/I.V. have been defined by the applicant. The primary efficacy endpoint (percentage of patients who achieve a 20% or greater reduction in weekly PN/IV volume at week 20 and 24) proposed by the applicant was considered clinically relevant by a group of experts in the field. Moreover, the clinical relevance of the observed effect was also backed by the positive effect on the exploratory endpoint “reduction in number of days with PN/i.v.”. One or more days without having to be chained to an i.v. line constitutes a real benefit for the patient. Another way of supporting the clinical relevance of the observed effect is to demonstrate that patient satisfaction/QoL is improved. In the present study with the instrument applied (SBS-QoL™) it was not possible to demonstrate any significant difference in QoL between placebo and teduglutide treated patients. The lack of effect on this secondary endpoint

was considered to be related to the heterogeneity of the study population as well as the lack of sensitivity of the QoL instrument used. Thus the lack of effect on this endpoint was not considered to undermine the clinical relevance of the observed effect on reduction in PN/i.v. volume.

Study CL0600-021, a Long-term, Open-label Study with Teduglutide for Subjects with Parenteral Nutrition Dependent Short Bowel Syndrome, has been designed to further analyse efficacy of Teduglutide treatment and the safety during long term use of the drug. It is acknowledged that this study indicates that efficacy of teduglutide is maintained beyond 6 months and for at least 12 months. Moreover, the interim report from study CL0600-021 indicates a high frequency of subjects being able to reduce number of days on PN/i.v. by at least 1 day (a clinically relevant benefit for the patient) and even a few patients being able to discontinue PN/I.V. altogether (the ultimate goal of treatment). This seemingly provides evidence of the clinical relevance of the observed effect.

Study CL0600-021 is an on-going study at the time of the opinion, designed to monitor the safety, tolerability and further prove efficacy (reduction in PN/i.v. volume) for PN/i.v. dependent SBS subjects taking Teduglutide. So far only an interim report of the study could be submitted and the study will be finalised about December 2012. Final results of the study are required as post authorisation commitment in order to further assess both efficacy and safety of the treatment which could affect the benefit/risk balance for the substance.

Moreover, following a request from the CHMP, the applicant submitted extrapolation of data on long term non responders from the on-going long term study CL0600-021, indicating the ground for discontinuation of the Teduglutide treatment if no effects are visible after a defined period of time from the beginning of the treatment. Indeed, the number of patients showing a PN volume response (defined as at least 20% reduction in PN volume from baseline) is continuously increasing over time, reaching more then 70% of patients after 6 months in trial CL0600-020. Thereafter, only a small increase is seen in the open extension trial CL0600-021. It seems therefore appropriate to evaluate the treatment effect after 6 months, because only very few patients with potential PN volume response might stop treatment inappropriately after this point in time. On the other hand, due to the unknown long-term risks associated with teduglutide treatment, a life-long treatment without clear signs of efficacy is not justified. Thus the proposal to evaluate efficacy after 6 months of treatment (as reflected in the SmPC) is supported. It is agreed that defining a general realistic goal for treatment applicable to all patients is neither realistic nor desirable. Thus it is agreed that a more general assessment by the physician should consider individual treatment objective and patient preferences. Treatment should be stopped if no overall improvement of the patient condition is achieved (as reflected in the SmPC).

Additional expert consultation

During the procedure at the CHMP's request an ad-hoc expert group meeting was organized to provide their view on specific issues related to efficacy identified during the assessment. The responses to the questions asked to the experts by the CHMP are reproduced below.

Clinical relevance of the results of the clinical trials.

The experts acknowledged that in study CL0600-020 a significant number of patients had at least 1 day reduction in PN volume per week at week 24. In the combined database of the phase III trials 11 patients could be weaned off, mostly after 24 weeks of teduglutide treatment (8/11).

The primary study endpoint of 20% reduction in PN/IV fluid was considered by the experts an adequate endpoint for the study; the results in study CL0600-020 were deemed clinically meaningful.

The experts emphasised that the group of SBS patients is heterogeneous (different baseline requirements ranging from 3.6 to 34 l/week, different length of remaining bowel, remaining Colon or not etc.). In the experts' opinion the expected benefit, based on the available data, would be for patients having low volume requirements to be potentially weaned off, and for patients having high volume requirements to have the weekly PN/IV fluid intake reduced.

Overall, all clinicians as well as the experts including the patient representative were in agreement that the shown results are clinically relevant.

The high unmet medical need, the rareness of the disease and the fact that 7 patients were weaned off PN/I.V. infusions, but no statistically significant difference between teduglutide and placebo as regards fraction of patients being able to reduce PN/I.V. infusions by one day for the primary efficacy population (ITT), the observed effect on volume of PN/I.V fluid did not have a positive effect on quality of life

In an update to previously presented results, data presented by the applicant during the meeting showed that a significant number of patients had at least one day reduction in PN volume per week at week 24 in Study CL0600-020.

The experts noted that patients rarely withdrew due to side effects and that the negative overall outcome on QoL might be triggered due to the side effect abdominal pain as a result from reducing diarrhea and increased bloating. From a patient's perspective being weaned off for one day needs to be weighted against the side effects such as GI pain as well as the need for daily injections.

The experts stressed the methodological challenges in demonstrating QoL in this patient population. In this context the expert group acknowledged that due to the heterogeneity of the SBS patients and the rarity of the disease it seems not feasible to power a study adequately to get an overall significant outcome on the 17 item instrument used in the study. At the same time, the experts were in agreement that the instrument used by the applicant was the best possible choice given the current scientific knowledge in this disease, and that there is currently no better instrument available.

Therefore, the experts considered that the positive trend seen in the sub-items needs to be considered for the overall evaluation.

Is it possible to identify a subgroup of patients who will benefit from therapy with teduglutide: a. patients who may be weaned off PN/I.V.fluid, b. patients needing a high volume (> 6 liter per week) of PN/I.V.fluid in whom a 20% reduction in volume would be considered a clinical benefit.Considering the rarity and heterogeneity of the disease it was not considered useful to define subgroups of patients. The experts advised that patients with higher volume requirements can possibly benefit from a significant reduction of PN/I.V. fluid and patients with lower requirements might have the chance to be weaned off completely.

Is it possible to identify a subgroup of patients who may benefit from treatment beyond 24 weeks since some of the few patients who were weaned off PN/IV fluid only achieved that clinical status in the extension part of the controlled study. In that context is it possible to set up rules for stopping teduglutide in patients without a clear reduction in volume.The expert group noted that there is a high number of late responders to teduglutide after 24 weeks of treatment. Taking this late response into consideration as well as safety profile, the experts

recommended to evaluate the treatment effect after 6 to 9 months and stop the treatment if no effect is seen.

The experts stressed that treatment with teduglutide should not be initiated before the patient is stabilized after the surgery leading to the condition i.e. after the adaptation period.

2.5.4. Conclusions on the clinical efficacy

The results of the provided trial CL0060-004 can only be regarded as hypothesis generating. On the other hand, study CL0600-020 clearly demonstrated that, compared to placebo, teduglutide 0.05 mg/kg/day caused a statistically significant effect. There was a statistically significantly higher fraction of teduglutide patients that achieved a 20 % (or greater) reduction in the PN/i.v. volume (primary efficacy endpoint) than in the placebo group. The results are robust and the clinical relevance of the primary efficacy endpoint is acknowledged; this clinical relevance was also confirmed by an ad-hoc expert group. The results of the secondary/exploratory efficacy parameters are considered to overall support the clinical relevance of the observed reduction in PN/i.v. volume, even if no statistically significant difference between teduglutide and placebo in terms of quality of life or, complete weaning off PN/i.v. was observed.

The CHMP considers the following measures necessary to address issues related to efficacy:

- Study CL0600-021: A Long-term, Open-label Study with Teduglutide for Subjects with Parenteral Nutrition Dependent Short Bowel Syndrome. The applicant should submit the final study report of a Long-term, Open-label Study with Teduglutide for Subjects with Parenteral Nutrition Dependent Short Bowel Syndrome. Due date: Q4 2013

2.6. Clinical safety

The primary safety analysis is based on the pooled safety evaluation for all placebo controlled SBS studies (CL0600-004 and CL0600-020). It is considered that the specific safety profile of teduglutide is best described by the analysis of the placebo controlled SBS studies (CL0600-020 and CL0600-004).

In addition, safety data from phase 2/3 studies in SBS patients has been provided.

Patient exposure

A total of 59 patients were exposed to placebo during the placebo controlled SBS studies with an overall placebo exposure of 26.2 person years. A total of 109 patients were exposed to teduglutide during the placebo controlled SBS studies; 77 patients to 0.05 mg/kg/day and 32 patients to 0.10 mg/kg/day, with an overall exposure to teduglutide of 46.5 person years.

The mean and median exposure time of placebo treated patients (mean (±SD): 23.07 ± 4.46 weeks; median: 24 weeks) was similar to that of teduglutide treated patients (mean (±SD): 22.2 ± 6.62 weeks; median: 24.14 weeks).

Generally, there were no differences in demographic characteristics between placebo and teduglutide dose groups. However, the distribution of the type of stoma was slightly different between the placebo and teduglutide groups. More placebo treated patients than teduglutide treated patients had an ileostomy (placebo: 10 patients [45.5%]; teduglutide 15 patients [33.3%]), and more teduglutide patients than placebo patients had a colostomy (placebo: 1 patient [4.5%]; teduglutide 9 patients

[20.0%]). However, these numerical differences are unlikely to cause imbalances that are relevant for safety assessment.

With regard to the additional Phase 2/3 studies in SBS patients, these were studies ALX0600-92001, CL0600-004, CL0600-005, CL0600-020 and CL0600-021. A total of 190 SBS patients were exposed to teduglutide during the Phase 2/3 SBS studies; 134 patients to 0.05 mg/kg/day and 49 patients to 0.10 mg/kg/day, with an overall exposure to teduglutide of 143.13 person years. Overall, 92 (48.4%) SBS patients were exposed to active treatment for ≥ 48 weeks during the Phase 2/3 SBS studies. The mean duration of exposure of all SBS patients exposed to teduglutide was 39.17 weeks.

Adverse events

Pooled safety evaluation for all placebo controlled SBS studies

An overall summary of treatment-emergent adverse events (TEAEs) in the placebo controlled SBS studies (CL0600-004 and CL0600-020) is presented in Table Q76 a

Table Q76 a Overall Summary of Treatment Emergent Adverse Events, placebo controlled SBS studies

Parameter	Statistic	Placebo (N=59)	Teduglutide (mg/kg/day)		
			0.05 (N=77)	0.10 (N=32)	All (N=109)
Any TEAE					
No	n (%) E	10 (16.9%) 0	9 (11.7%) 0	1 (3.1%) 0	10 (9.2%) 0
Yes	n (%) E	49 (83.1%) 372	68 (88.3%) 530	31 (96.9%) 248	99 (90.8%) 778
TEAE Severity					
Mild	n (%) E	45 (76.3%) 184	58 (75.3%) 286	26 (81.3%) 155	84 (77.1%) 441
Moderate	n (%) E	34 (57.6%) 145	50 (64.9%) 182	24 (75.0%) 86	74 (67.9%) 268
Severe	n (%) E	16 (27.1%) 43	25 (32.5%) 62	6 (18.8%) 7	31 (28.4%) 69
TEAE Maximum Severity (Per Patient)					
Mild	n (%)	13 (22.0%)	15 (19.5%)	7 (21.9%)	22 (20.2%)
Moderate	n (%)	20 (33.9%)	28 (36.4%)	18 (56.3%)	46 (42.2%)
Severe	n (%)	16 (27.1%)	25 (32.5%)	6 (18.8%)	31 (28.4%)
TEAE Relationship					
Not Related	n (%) E	47 (79.7%) 310	62 (80.5%) 392	31 (96.9%) 184	93 (85.3%) 576
Related	n (%) E	21 (35.6%) 62	38 (49.4%) 138	19 (59.4%) 64	57 (52.3%) 202
Any TESAE	n (%) E	17 (28.8%) 34	28 (36.4%) 64	11 (34.4%) 16	39 (35.8%) 80
TESAE Severity					
Mild	n (%) E	5 (8.5%) 6	6 (7.8%) 8	7 (21.9%) 9	13 (11.9%) 17
Moderate	n (%) E	7 (11.9%) 9	16 (20.8%) 25	2 (6.3%) 3	18 (16.5%) 28
Severe	n (%) E	8 (13.6%) 19	12 (15.6%) 31	4 (12.5%) 4	16 (14.7%) 35
TESAE relationship					
Not Related	n (%) E	17 (28.8%) 34	23 (29.9%) 52	9 (28.1%) 14	32 (29.4%) 66
Related	n (%) E	0	8 (10.4%) 12	2 (6.3%) 2	10 (9.2%) 14

Parameter	Statistic	Placebo (N=59)	Teduglutide (mg/kg/day)		
			0.05 (N=77)	0.10 (N=32)	All (N=109)
TEAEs Leading to Premature Discontinuation	n (%) E	4 (6.8%) 5	8 (10.4%) 14	2 (6.3%) 3	10 (9.2%) 17
TEAE death	n (%) E	0	0	0	0

source: FU-ISS NPS table 9.1.2

For the pooled safety data of the placebo controlled SBS trials no exposure adjustment was deemed necessary, because the mean and median duration of exposure of the teduglutide (mean (±SD): 22.2 ± 6.62 weeks; median: 24.14 weeks) and the placebo treated patients (mean (±SD): 23.07 ± 4.46 weeks; median: 24 weeks) was very similar.

There were 6 System Organ Classes (SOCs) where the rate of TEAEs was at least 5% or greater in the teduglutide group compared with the placebo group. The SOCs include:

- Gastrointestinal Disorders (66/109 subjects [60.6%] in the teduglutide group vs. 26/59 subjects [44.1%] in the placebo group).
- General Disorders and Administration Site Conditions (49/109 subjects [45.0%] in the teduglutide group vs. 20/59 subjects [33.9%] in the placebo group).
- Infections And Infestations (63/109 subjects [57.8%] in the teduglutide group vs. 31/59 subjects [52.5%] in the placebo group).
- Injury, Poisoning And Procedural Complications (32/109 subjects [29.4%] in the teduglutide group vs.13/59 subjects [22.0%] in the placebo group).
- Nervous System Disorders (26/109 subjects [23.9%] in the teduglutide group vs. 9/59 subjects [15.3%] in the placebo group).
- Psychiatric Disorders (10/109 subjects [9.2%] in the teduglutide group vs. 1/59 subjects [1.7%] in the placebo group).

TEAEs that occurred in at least 5% or more patients of the teduglutide group are presented in Table Q76 b. Preferred Terms, which were reported clearly more frequently (more than 5% rate difference) in the teduglutide than in the placebo groups included Abdominal Pain, Nausea, Abdominal Distension, Gastrointestinal Stoma Complication, Headache, Vomiting, Nasopharingitis, Injection Site Haematoma, Influenza, and Injection Site Erythema.

Table Q76 b Treatment Emergent Adverse Events by Preferred Term in more than 5% of patients, placebo controlled SBS studies

Preferred Term	Statistic	Placebo (N=59)	Teduglutide (mg/kg/day)		
			0.05 (N=77)	0.10 (N=32)	All (N=109)
Abdominal Pain	n (%)	12 (20.3%) 16	20 (26.0%) 26	11 (34.4%) 12	31 (28.4%) 38
Nausea	n (%)	12 (20.3%) 16	18 (23.4%) 27	10 (31.3%) 13	28 (25.7%) 40
Abdominal Distension	n (%)	1 (1.7%) 2	15 (19.5%) 21	3 (9.4%) 4	18 (16.5%) 25
Gastrointestinal Stoma Complication	n (%)	3 (5.1%) 3	13 (16.9%) 14	4 (12.5%) 5	17 (15.6%) 19
Headache	n (%)	8 (13.6%) 12	10 (13.0%) 31	7 (21.9%) 13	17 (15.6%) 44
Vomiting	n (%)	6 (10.2%) 12	9 (11.7%) 14	6 (18.8%) 8	15 (13.8%) 22

Preferred Term	Statistic	Placebo (N=59)	Teduglutide (mg/kg/day)		
			0.05 (N=77)	0.10 (N=32)	All (N=109)
Nasopharyngitis	n (%)	2 (3.4%) 3	9 (11.7%) 12	5 (15.6%) 7	14 (12.8%) 19
Urinary Tract Infection	n (%)	7 (11.9%) 8	10 (13.0%) 14	4 (12.5%) 5	14 (12.8%) 19
Injection Site Haematoma	n (%)	3 (5.1%) 4	4 (5.2%) 4	8 (25.0%) 9	12 (11.0%) 13
Fatigue	n (%)	5 (8.5%) 5	5 (6.5%) 6	5 (15.6%) 7	10 (9.2%) 13
Pyrexia	n (%)	5 (8.5%) 6	7 (9.1%) 8	3 (9.4%) 3	10 (9.2%) 11
Catheter Sepsis	n (%)	2 (3.4%) 3	5 (6.5%) 11	4 (12.5%) 5	9 (8.3%) 16
Flatulence	n (%)	4 (6.8%) 4	7 (9.1%) 14	2 (6.3%) 2	9 (8.3%) 16
Oedema Peripheral	n (%)	2 (3.4%) 3	8 (10.4%) 9	1 (3.1%) 1	9 (8.3%) 10
Decreased Appetite	n (%)	2 (3.4%) 2	5 (6.5%) 6	3 (9.4%) 3	8 (7.3%) 9
Influenza	n (%)	1 (1.7%) 1	4 (5.2%) 4	4 (12.5%) 4	8 (7.3%) 8
Injection Site Erythema	n (%)	0	3 (3.9%) 3	5 (15.6%) 5	8 (7.3%) 8
Arthralgia	n (%)	3 (5.1%) 4	4 (5.2%) 7	3 (9.4%) 3	7 (6.4%) 10
Diarrhoea	n (%)	6 (10.2%) 9	4 (5.2%) 5	3 (9.4%) 3	7 (6.4%) 8
Abdominal Pain Upper	n (%)	1 (1.7%) 1	4 (5.2%) 5	2 (6.3%) 4	6 (5.5%) 9
Catheter Related Infection	n (%)	1 (1.7%) 1	6 (7.8%) 7	0	6 (5.5%) 7

source: FU-ISS NPS table 9.6.2

Additional data from phase 2/3 studies in SBS patients

180/190 [94.7%] of the patients treated with teduglutide reported 1897 TEAEs. There were slightly less patients who reported TEAEs in the 0.05 mg/kg/day teduglutide group [93.3%] than in the 0.10 mg/kg/day teduglutide group [98.0%]. This small difference probably cannot be interpreted as dose dependence. The majority of TEAEs was mild or moderate in severity in both treatment groups.

Treatment emergent serious adverse events (TESAEs) were reported by 95/190 (50.0%) patients treated with teduglutide, reporting a total of 223 TESAEs. No dose dependence of TESAEs could be seen between the two teduglutide doses. TESAEs were similar in severity between the different teduglutide dose groups.

There is a tendency of ADRs to increase in a dose-dependent manner, with 74 [55.2%] patients reporting 180 ADRs in the 0.05 mg/kg/day teduglutide group and 30 [61.2%] patients reporting 109 ADRs in the 0.10 mg/kg/day teduglutide dose group. However, this tendency was less prominent in the Phase 2/3 SBS study pool than in the placebo controlled SBS study pool. Serious ADRs were observed in 18 [9.5%] teduglutide treated patients reporting 25 events.

Overall, 28 (14.7%) teduglutide treated patients were reported with a TEAE which led to premature discontinuation from the studies. The discontinuation rates in the 0.05 mg/kg/day teduglutide group and in the 0.10 mg/kg/day teduglutide dose group were identical at 15.7%.

There were 8 SOCs where the incidence of TEAEs was at least 5% or greater in the teduglutide group compared with the placebo group. The SOCs include:

- Endocrine Disorders (teduglutide 0.035 events/year; placebo: 0 events/year)
- Hepatobiliary Disorders (teduglutide 0.140 events/year; placebo: 0.076 events/year).
- Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps) (teduglutide 0.056 events/year; placebo: 0 events/year).
- Nervous System Disorders (teduglutide 0.992 events/year; placebo: 0.916 events/year).

- Psychiatric Disorders (teduglutide 0.210 events/year; placebo: 0.115 events/year).
- Renal And Urinary Disorders (teduglutide 0.321 events/year; placebo: 0.191 events/year).
- Skin And Subcutaneous Tissue Disorders (teduglutide 0.314 events/year; placebo: 0.267 events/year).
- Vascular Disorders (teduglutide 0.314 events/year; placebo: 0.229 events/year).

For the interpretation of the exposure adjusted data, it is an important observation that the SOC Gastrointestinal Disorders does not occur at a higher incidence under teduglutide treatment than under placebo treatment. Also General Disorders And Administration Site Conditions and Infections And Infestations did not show a higher incidence, as in the analysis of the placebo controlled SBS studies. This may be explained by the fact that adverse events in general are often reported at higher frequencies shortly after the start of a study. This transient occurrence of TEAEs can for example be clearly observed in the case of Gastrointestinal Disorders in teduglutide treated patients. Thus, with increasing exposure times, incidences of adverse events tend to equilibrate and it may become increasingly difficult to detect safety signals. On the other side, medical conditions which may prevent patients from participating in a study may incidentally occur under longer term treatment as adverse events (e.g. the SOC Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)). Under these circumstances, a medical condition which occurs incidentally may be noted as an increased incidence of adverse events.

The comparison of the exposure adjusted summary of adverse events in teduglutide treated patients of the five phase 2/3 SBS studies with the placebo treated patients from the two placebo controlled SBS studies basically confirmed what had been found in the review of the placebo controlled SBS studies only.

Serious adverse event/deaths/other significant events

Deaths

No deaths occurred during the placebo controlled SBS studies (CL0600-004 and CL0600-020). One patient died during the screening period of study CL0600-004, prior to randomization of the patient into the study. In the opinion of the Investigator, the patient's death was due to a massive upper gastrointestinal haemorrhage. In the safety follow up study CL0600-021 which is currently ongoing two patients died due to cancer (for causality assessment see relevant chapter "Neoplasia" and "Discussion on clinical Safety" below):

Patient […] with lung cancer had a relevant history of smoking (about 30 cigarettes per day for about 30 years) and was treated with teduglutide only for relatively short time (85 days).

Patient […], a 48-year-old man with a history of Hodgkin's disease (diagnosed in 1988 and treated with chemotherapy and radiotherapy), cecal necrosis caused by radiation, and primary liver disease, was diagnosed with a metastatic adenocarcinoma 11 months after the start of treatment (treatment start date 29 July 2010; onset date of TESAE 19 June 2011). The subject entered the study directly (ie, was not treated in Study CL0600-020). Six months prior to starting teduglutide therapy, the subject had computed tomography (CT) of the abdomen, which showed liver enlargement, without focal lesions. The primary tumor was considered to be probably in the GI tract, but its precise location was unknown. A biopsy performed on 21 June 2011 revealed metastatic adenocarcinoma. The subject died on 29 June 2011, 10 days after the reported onset of this TESAE. An autopsy performed on 01 July 2011 was inconclusive as to the primary site of the cancer, and the primary cause of death was

generalized malignancy of intestinal cancer. The event was considered by the investigator to be severe and related to treatment. The study drug was discontinued.

Other Serious Adverse Events

Pooled safety evaluation for all placebo controlled SBS studies

There were 2 SOCs where the rate of TESAEs was at least 5% or greater in the teduglutide group compared with the placebo group. The SOCs include:

Gastrointestinal Disorders (7/109 subjects [6.4%] in the teduglutide group vs. no subject [0%] in the placebo group).

Infections And Infestations (25/109 subjects [22.9%] in the teduglutide group vs. 10/59 subjects [16.9%] in the placebo group).

Most frequently reported TESAEs on a Preferred Term level were Small Intestinal Obstruction, Pyrexia, Cholecystitis Acute, Catheter Sepsis, Catheter Related Infection, Urinary Tract Infection, Central Line Infection, Bacteraemia, Device Dislocation, Device Breakage, and Device Malfunction.

Additional data from phase 2/3 studies in SBS patients

There were four SOCs where the rate of TESAEs was at least or larger than 5%. The SOCs include:

- Gastrointestinal Disorders (16/190 subjects [8.4%] reporting 23 TESAEs; incidence: 0.161 events per year).
- General Disorders And Administration Site Conditions (12/190 subjects [6.3%] reporting 14 TESAEs; incidence: 0.098 events per year).
- Infections And Infestations (55/190 subjects [28.9%] reporting 102 TESAEs; incidence: 0.713 events per year).
- Injury, Poisoning And Procedural Complications (14/190 subjects [7.4%] reporting 17 TESAEs; incidence: 0.119 events per year).

Neoplasia

The applicant has presented a display of the evaluation of the cases of benign intestinal neoplasias in the study programme.

It could be shown that for four cases no histological diagnosis was available, two cases in the teduglutide group in study CL0600-020/021 have been identified for which histological diagnosis is available. Both have been identified as tubular or tubulo-villous adenoma with low grade dysplasia. An imminent danger of malignancy was therefore obviously not present.

One additional patient in study CL0600-020 has been identified with colonic benign neoplasia that was treated with placebo. This enables to present a comparison of the placebo-controlled data, showing that a relevant difference in the occurrence rate of colonic polyps does obviously not exist.

Whereas it has therefore to be acknowledged that the data available do by no means indicate an increased risk for colonic neoplasia development – it also has to be stated that the theoretical risk of the induction and/or promotion of neoplasias could by no means be excluded.

The development and/or promotion of neoplasias would according to theoretical considerations not become obvious during a short course of treatment, such as 6 months as during the placebo-controlled part of the studies. However, SBS patients would potentially need treatment for long periods, if not life-long, which could of course put them under increased risk of the development/accelerated growth of neoplasia (including malignant transformation) compared to an untreated population (disregarding the increased risk that might or might not be present due to underlying disease).

It is noted that in addition to the two cancer cases, which occurred after submission of the MAA in study CL0600-021 (patients […] and […]), a third patient ([…]) of the currently ongoing study CL0600-021 reported "Carcinoma planoephiteliale of the right lung". The investigator considered the event planoepithelial carcinoma of the right lung not related to the study drug. It is noted by the CHMP that this patient took teduglutide for more than a year and had not smoked for 25 years (and before that only 2.5 package years of smoking). Therefore a causal relationship cannot completely be ruled out.

As mentioned above there was 1 death due to a metastatic adenocarcinoma ([…]) during this study that was considered to be an unanticipated problem. NPS instructed all participating investigators to submit the case to their respective IRBs. An Expert Panel met on 08 July 2011 to discuss the case and the following was decided:

- based on the available data, there was no need to stop the trial;
- the subjects in the study with a prior history of cancer should remain in the study as they were not at increased risk;
- the DSMB used in the CL0600-020 trial will reconvene to monitor the safety of the trial and to review the CL0600-021 protocol to possibly enhance the safety monitoring in this study.

However, the report of a fatal malignancy (adenocarcinoma derived from the gastrointestinal tract, primary tumour unknown) which apparently was a "de novo" case while the patient was treated with teduglutide gives reason to some concern. Teduglutide promotes hyperplasia of intestinal mucosa and this effect could at least in theory promote growth of gastrointestinal epithelium derived tumours.

The applicant has provided data that suggest that the overall incidence of cancer is not increased in teduglutide treated patients compared to what has been observed in comparable population with short bowel syndrome. While reassuring, the data presented does not remove completely the concern about the tumor promoting effect of teduglutide. The number of patients as well as the duration of exposure is too limited to allow firm conclusions. Appropriate warnings are included in the SmPC regarding the potential risk of intestinal neoplasia furthermore Post-marketing surveillance will focus in particular on this issue (see below Discussion on Safety).

Other Significant Adverse Events

Overall, 10 (9.2%) teduglutide treated patients were reported with a TEAE leading to premature discontinuation from the placebo controlled SBS studies (placebo: 4 [6.8%] patients). Eight (10.4%) patients in the 0.05 mg/kg/day teduglutide dose group and 2 (6.3%) patients in the 0.10 mg/kg/day teduglutide dose group discontinued due to a TEAE. Gastrointestinal Disorders led most frequently to early discontinuations (placebo: 3 patients [5.1%]; teduglutide 7 patients [6.4%]). No SOC could be identified leading to remarkably more discontinuations under teduglutide than under placebo treatment. The only TEAEs leading to premature discontinuation which were reported by more than one patient in any of the treatment groups during the placebo controlled SBS studies were "Abdominal Distension" (two teduglutide patients (1.8%)) and "Constipation" (two teduglutide patients (1.8%)) in

the SOC Gastrointestinal Disorders. No case of “abdominal distension” or “constipation” leading to discontinuation was reported in the placebo group.

Laboratory findings

Clinical Chemistry

Examining liver function tests of Alkaline Phosphatase, ALT, AST, Total Bilirubin, and GGT revealed a decrease in all liver biochemical markers of disease and injury at Week 24 in teduglutide treated subjects versus placebo treated subjects.

Albumin as a surrogate marker of overall nutrition was reported to be lower in placebo treated subjects (-1.7 g/L) vs. those subjects treated with teduglutide (-1.1g/L).

Another analyte of interest measured was C-reactive protein (CRP). Modest increase of CRP of approximately 25 mg/l have been observed within the first seven days of Revestive treatment, which decreased continuously under on-going daily injections. After 24 weeks of Revestive treatment, patients showed small overall increase in CRP of approximately 1,5 mg/l on average. The clinical significance of CRP increase is unclear as its values have been found to fluctuate throughout the trials and considering the different baseline characteristics of the study population, this magnitude of change from baseline may not be clinically significant. Due to this uncertainty, monitoring of CRP has been added to the international Short Bowel Syndrome Registry.

Shifts from baseline in Placebo Controlled SBS Studies

Shifts from low/normal to high are seen in Liver biochemical markers of AST and ALT in both teduglutide and placebo treated subjects: AST; 9.6% and 8.7% in the teduglutide treated subjects versus placebo treated subjects respectively, ALT; 7.9% and 8.7% in the teduglutide treated subjects versus placebo treated subjects respectively. Other common chemistries related to hepatobiliary enzymes reveal that shifts from normal/high to low total bilirubin levels are seen in teduglutide treated subjects versus placebo treated subjects (10.9% vs. 4.0 %; respectively). In regards to GGT, shifts from normal/low to high were seen in the teduglutide treated subjects versus placebo treated subjects (13.6% vs. 3.6%; respectively).

The most common shifts for all subjects treated with teduglutide in these studies from low/normal to high were changes in CRP (17.9%).

For the remainder of the analytes, the percentages of teduglutide and placebo-treated subjects with shifts from low/normal to high or high/normal to low were similar or greater in placebo-treated subjects.

Post-baseline markedly abnormal clinical chemistry

The most common post-baseline markedly abnormal analyte among subjects treated with teduglutide was CRP (24%) vs. placebo treated subjects (8.6%). In regards to liver biochemical markers of Alkaline Phosphatase > 2X NL, ALT > 3X NL, AST > 3X NL, Total Bilirubin > 2X NL, and Albumin similar rates were observed for teduglutide treated subjects versus placebo treated subjects.

Safety in special populations

Subgroup analyses for gender, age, race and stoma yes/no on exposure, demography, and adverse events have been presented. Overall it appears that there are no relevant differences for the investigated subgroups compared to the overall population.

Immunological events

Teduglutide is a peptide, produced by biotechnology, which may induce an antibody response towards teduglutide or towards endogenous GLP-2.

Assays for measuring antibodies to teduglutide, neutralizing antibodies to teduglutide and anti-ECP antibodies have been developed and validated. These assays were mainly applied in the two pivotal studies CL060-020 and CL060-021 but also on available samples from previous studies. In the pivotal studies, development of antibodies to teduglutide increased as exposure increase with roughly one fourth of patients having antibodies to teduglutide after 1 year of treatment. However, none of the antibodies were neutralising and no effect on safety and efficacy of teduglutide could be demonstrated. Generally antibodies to teduglutide cross-reacted with native GLP-2, which due to the high degree of homology between teduglutide and GLP-2 is to be expected. Anti ECP antibodies developed in more than 1 out 3 patients but no effect on safety could be demonstrated.

The data collected so far does not indicate that immunogenicity poses a significant risk to the safety and efficacy of the drug. However, as only relative short term studies are available, immunogenicity and potential impact on safety and efficacy should remain under observation. The RMP targets this issue and a further assessment of antibody and safety data are required to be collected in the on-going long term clinical study CL0600-021 and a separate presentation of respective case reports in a special section of the PSUR is considered.

Safety related to drug-drug interactions and other interactions

Considering that teduglutide is a peptide that is believed to undergo hydrolytic degradation rather than being metabolised by drug metabolising enzymes no information safety-related drug-drug-interactions are expected. No clinical drug-drug interaction studies have been performed. An in-vitro study indicates that Teduglutide does not inhibit cytochrome P450 drug metabolising enzymes. However, based upon the pharmacodynamics effect of teduglutide, there is a potential for increased absorption of concomitant medicinal products. Therefore patients receiving oral concomitant medicinal products requiring titration or with a narrow therapeutic index should be monitored closely due to potential increased absorption.

Discontinuation due to adverse events

An inverse dose relationship was suggested for teduglutide with respect to discontinuations due to AEs. From the pooled analyses of phase 2 and 3 studies, discontinuations due to AEs were highest in the 0.05 mg/kg/d group. Overall, 10 (9.2%) teduglutide treated patients were reported with a TEAE leading to premature discontinuation from the placebo controlled SBS studies (placebo: 4 [6.8%] patients). Eight (10.4%) patients in the 0.05 mg/kg/day teduglutide dose group and 2 (6.3%) patients in the 0.10 mg/kg/day teduglutide dose group discontinued due to a TEAE. Gastrointestinal Disorders led most frequently to early discontinuations (placebo: 3 patients [5.1%]; teduglutide 7 patients [6.4%]). No SOC could be identified leading to remarkably more discontinuations under teduglutide than under placebo treatment. The only TEAEs leading to premature discontinuation which were reported by more than one patient in any of the treatment groups during the placebo controlled SBS studies were “Abdominal Distension” (two teduglutide patients (1.8%)) and “Constipation” (two teduglutide patients (1.8%)) in the SOC Gastrointestinal Disorders. No case of “abdominal distension” or “constipation” leading to discontinuation was reported in the placebo group.

Post marketing experience

Since the product is not yet licensed, no post-marketing experience is available.

2.6.1. Discussion on clinical safety

In order to describe the safety of teduglutide, the applicant has provided a pooled analysis of safety data from the placebo controlled studies (CL0600-004 and CL0600-020) as well as an analysis of all safety data from phase 2/3 studies in SBS.

The size of the pooled analysis of safety data from placebo controlled studies with teduglutide is considered acceptable for this orphan indication; further safety data will be generated through a dedicated registry (International Short Bowel Syndrome Registry prospective described in the RMP), which was requested by the CHMP. In addition, in the pooled analysis of placebo controlled studies there were no imbalances (in terms of demographics and disease characteristics) between groups that are likely to have had any significant effect on the safety results. Furthermore, duration of exposure was very similar in placebo and teduglutide treated patients. Thus, the present pooled analysis provides a reasonably unbiased evaluation of the safety of teduglutide compared to placebo.

The overall number of TEAE and TESAE was only slightly higher in the teduglutide treated patients compared to the placebo treated patients. Severity was also comparable in the two groups. However, serious adverse drug reactions (TESAEs considered possibly related to treatment) occurred more often in the teduglutide group than in the placebo group. The same was the case for TEAEs leading to discontinuation.

There were 6 SOCs where the rate of TEAEs was at least 5% or greater in the teduglutide group compared with the placebo group:

1. Gastrointestinal Disorders (primarily abdominal pain/distension, nausea/vomiting but difference regarding number of patients reporting intestinal obstruction). Although a large fraction was mild to moderate in severity, GI adverse events were the main AE leading to premature discontinuation. From the presented data, it is obvious that gastrointestinal obstruction occurs more frequently in teduglutide treated patients than in placebo treated patients. The mechanism behind these events appears reasonably well explained on the basis of the pharmacological effects of the drug and the predisposition of the treated patients. It is considered a real, but manageable risk. Adequate warnings have been included in the SmPC. In addition monitoring of intestinal obstruction has been included in the International Short Bowel Syndrome Registry (described in the RMP).

2. General Disorders and Administration Site Conditions (primarily injection site reactions). As regards injection site reactions, detailed review of this problem did not indicate that injection site reactions were more common for teduglutide (in the proposed dose, 0.05 mg/kg/day) than for placebo. Thus injection site reactions do not constitute a major problem for teduglutide in the proposed dose (this risk is addressed in the RMP and in the section 4.8 of SmPC).

3. Infections and Infestations. Of particular interest has been the apparent difference between placebo and teduglutide in terms of catheter sepsis. However, number of cases is small and somewhat divergent classification has been used. When grouping all AEs indicative of catheter related infection there was no apparent difference between placebo and teduglutide in the proposed dose. Catheter sepsis remains a serious complication in the patient population but there is no indication that teduglutide increases this risk (as described in the RMP).

4. Injury, Poisoning And Procedural Complications. It is noted that gastrointestinal stoma complications were more frequent in the teduglutide group compared to placebo. The mechanism behind these events appears reasonably well explained on the basis of the pharmacological effects of the drug and the predisposition of the treated patients. It is considered a real, but manageable risk. Adequate warnings have been included in the SmPC.

5. Psychiatric Disorders. 'sleep disorders' and 'anxiety' was clearly more common among teduglutide treated patients than among placebo treated patients. These adverse events have been included in the SmPC. Anxiety has been also addressed in the RMP.

There were 3 reports of cancer during teduglutide treatment (including open label treatment). Two of these subsequently died of their cancers. While it is agreed that one of the fatal cases (non-small lung cell cancer in a heavy smoker having received teduglutide for only 85 days) most certainly is not related to teduglutide treatment, the causality assessment is more uncertain for the two other cases. One (fatal) case was adenocarcinoma of unknown primary origin (but most likely GI tract) with metastasis to the liver in a patients receiving teduglutide for almost a year. The other was a (non-fatal) case of planocellular carcinoma of the lung in a patient taking teduglutide for more than a year who had not smoked for 25 years (and before that only 2.5 package years of smoking). In the two latter cases a causal relationship cannot be ruled out. Even though the number of events is small and it is not possible to determine if this rate of events during teduglutide is higher than what can be expected in a similar population, these reports give cause for concern. From the theoretical point of view, due to its character of being a growth factor inducer and inducing epithelial hyperplasia, there is some concern of induction and/or promotion of benign and/or malignant tumours. In addition to the above, the concerns are corroborated by the data derived in animals, where benign biliary tumours have been induced by high doses. The applicant has evaluated the occurrence of tumours and its precursors during the clinical studies and has found some colonic adenomatous changes, one being dysplastic in nature. Although from a theoretical point of view, the induction of colonic neoplasia appears to be more remote than in the small intestine, it is on the other hand known that small intestine neoplasia is in general a much rarer event compared to colonic neoplasia. Therefore, with the current data available, neither of these concerns (and in addition also biliary neoplasia) can be completely ruled out. Adequate warnings and recommendations regarding screening for intestinal neoplasia have been included in the SmPC. Furthermore, the applicant will design and implement a registry of teduglutide treated patients specifically aiming at monitoring the risk of neoplasia (as described in Annex II).

The combined analyses of data from the placebo controlled SBS studies CL0600-004 and CL0600-020 showed a small overall increase in average CRP during teduglutide treatment (1.43 mg/L above baseline at end of study) compared placebo treatment. In addition, the fraction of patients exhibiting a shift from low/normal to high CRP was higher in the teduglutide treated patients and the fraction of patients exhibiting a markedly abnormal post-baseline CRP was higher in the teduglutide group than in the placebo group. Increased CRP values are a known predictor for an increased cardiovascular risk. However, there is no robust data showing a causal link between the increase of CRP and the occurrence of cardiovascular disease. In addition, in the SBS population an increased rate of cardiovascular AEs has not been observed in clinical trials with teduglutide. This observed modest increase in CRP is addressed in the RMP Section as the important potential risk "Increased C reactive protein" and in the SmPC.

On an individual level, the proposals put forward as risk minimisation measures are considered acceptable. At a population level, the proposed registry study (as described in Annex II) is considered relevant for monitoring of CRP/cardiovascular events.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Additional expert consultations

The CHMP had asked an Ad-Hoc Expert Group to provide their view on specific issues related to safety identified during the assessment.

The known adverse effects (pancreatic and biliary tract disease, bowel obstruction) and uncertainty about any potential tumour promoting effect (as evidenced by the reports of a number of malignant and benign neoplasias) as well as uncertainty about the consequences of the observed effect on average CRP (potential negative effect on cardiovascular risk).

The clinicians considered the adverse effects of teduglutide manageable. It was not considered useful to add a special monitoring procedure for patients taking this treatment except the standard monitoring as recommended by relevant guidelines for the underlying disease, the standard screening for SBS and patients being under parenteral nutrition as additional monitoring would create a new burden to the patient without generating additional information. With regards to the potential tumor promoting effect and the effect on average CRP/potential CV risk the experts acknowledged the uncertainty with regards to the additional effect of the compound but noted that growth might have been accelerated by teduglutide but an effect on initiating tumors was not shown by the data. Therefore the experts supported to generate the relevant long term data within the registry proposed by the applicant and agreed by the CHMP.

2.6.2. Conclusions on the clinical safety

Based on the available data it is concluded that teduglutide has an acceptable safety profile for treatment duration of up to 1 year. The CHMP noted that, effects obviously directly related to the pharmacodynamic action of the compound may lead to a relatively high burden of treatment withdrawals, and serious, and sometimes severe adverse events. Considering the serious and disabling nature of condition with a considerable impact on QoL and only limited symptomatic treatment options, this AE-profile is considered acceptable.

The events affecting tolerability are mostly related to the gastrointestinal tract, ranging from abdominal pain and constipation, to bowel obstruction, stoma complications, and ileus and to biliary problems including cholecystitis. While these events are important, the risk is well known and considered manageable (as described in the RMP).

Hepatobiliary and pancreatic events were only reported in teduglutide patients. In this respect, it is a concern that a considerable part of the reports were serious. That these events most probably represent the PD-action of teduglutide is further supported by the non-clinical studies which revealed hyperplastic and/or hypertrophic effects of teduglutide on intrahepatic and extrahepatic bile ducts, the gallbladder and pancreatic ducts. These risks are addressed in the RMP and the SmPC. In addition, the non-interventional study (NIS, described in Annex II) will provide further safety data on these events.

The observed modest increase in CRP is addressed in the RMP and in the SmPC. The proposed registry study (as described in Annex II) is considered relevant for monitoring of CRP/cardiovascular events.

Regarding the potential of neoplasia induction, the applicant will design and implement a registry of teduglutide treated patients specifically aiming at monitoring this risk (as described in the RMP).

The CHMP considers the following measures necessary to address issues related to safety:

- A Long-term, Open-label Study with Teduglutide for Subjects with Parenteral Nutrition Dependent Short Bowel Syndrome. The applicant should submit the final study report of a Long-term, Open-label Study with Teduglutide for Subjects with Parenteral Nutrition Dependent Short Bowel Syndrome. Due date: Q4 2013
- International Short Bowel Syndrome Registry: The MAH shall perform a non-interventional study (NIS) to gather further safety data based on a CHMP approved protocol. Focus will primarily be on disease characteristics, treatment and progression and will include real-life use and safety of teduglutide in those patients receiving teduglutide. Simple treatment outcome measures will be collected. Due date: The study is planned to start Q1 2013 and will continue until Q1 2022. Interim data for the NIS should be provided every second year within the PSURs.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The applicant has provided documents that set out a detailed description of the system of pharmacovigilance. The CHMP considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan

The applicant submitted a risk management plan, which included a risk minimisation plan

Summary of the risk management plan

Important identified risks

Safety concern	**Proposed pharmacovigilance activities (routine and additional)**	**Proposed risk minimisation activities (routine only)**

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine only)
Biliary adverse events such as cholecystitis	1) routine PV; 2) separate presentation of respective case reports in a special section of the PSUR; 3) recording of relevant enzymes in NIS.	SmPC, Section 4.4 Cases of cholecystitis, cholangitis, and cholelithiasis have been reported in clinical studies. In case of gallbladder or bile duct-related symptoms, the need for continued Revestive treatment should be reassessed. 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. SmPC, Section 4.8 lists 'Cholestasis and Cholecystitis' as undesirable effect.
Pancreatic adverse events such as chronic and acute pancreatitis, pancreatic duct stenosis, pancreas infection and increased blood amylase and lipase	1) routine PV; 2) separate presentation of respective case reports in a special section of the PSUR; 3) recording of relevant enzymes in NIS.	SmPC, Section 4.4 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. In case of pancreatic adverse events, the need for continued Revestive 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. SmPC, Section 4.8 lists 'Pancreatitis' as undesirable effect.
Cardiovascular Adverse Events associated with fluid overload	1) routine PV; 2) separate presentation of respective case reports in a special section of the PSUR; 3) recording and assessment of relevant AEs in NIS.	SmPC, Section 4.4 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. In general, fluid overload can be prevented by appropriate and timely assessment of parenteral nutrition needs. This assessment should be conducted more frequently within the first months of treatment. In case of a significant deterioration of the cardiovascular disease, the need for continued Revestive treatment should be reassessed.
Gastrointestinal stenosis and obstruction	1) routine PV; 2) separate presentation of respective case reports in a special section of the PSUR; 3) recording of cases of intestinal obstructions in NIS.	SmPC, Section 4.4 Cases of intestinal obstruction have been reported in clinical studies. In case of recurrent intestinal obstructions, the need for continued Revestive treatment should be reassessed. 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. SmPC, Section 4.8 lists '' Intestinal Obstruction' as undesirable effect.
Gastrointestinal Stoma Complications	1) routine PV	SmPC, Section 4.8 lists 'Gastrointestinal stoma complication' as undesirable effect and describes the nature of the complication (i.e., swelling of the stoma)

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine only)
Pre-exising moderate or severe renal impairment, or end-stage renal disease	1) routine PV;	SmPC, Section 4.2 No dose adjustment is necessary for patients with mild renal impairment. In 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% (see section 5.2).
Growth of pre-existing polyps of the colon	1) routine PV; 2) obligatory expedited reporting independent of seriousness; 3) separate presentation of respective case reports in a special section of the PSUR; 4) recording of colonoscopy results in NIS.	SmPC, Section 4.3 Revestive is contraindicated in patients with active or suspected malignancy. Revestive is contraindicated in patients with a history of malignancies in the gastrointestinal tract including the hepatobiliary system within the last five years. SmPC, Section 4.4 A colonoscopy with removal of polyps should be performed at the time of starting treatment with Revestive. 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). See also section 5.1. If a polyp is found, adherence to current polyp follow up guidelines is recommended. In case of malignancy, Revestive therapy should be discontinued (see section 4.3). 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 (see section 4.3). Caution should be exercised when prescribing Revestive. SmPC, Section 5.1 Based on the concerns derived from pre clinical studies (see section 5.3) 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. Several cases of benign colonic polyps occurred during the course of the trials, however, the frequency was not increased compared to placebo treated patients. In addition to the need for a colonoscopy with removal of polyps by the time of the initiation of the treatment (see section 4.4.), every patient should be assessed for the need of an enhanced surveillance schedule based on the patient characteristics (e.g. age and underlying disease, previous occurrence of polyps etc.).
Benign neoplasia of the gastrointestinal tract including the hepatobiliary system	1) routine PV; 2) obligatory expedited reporting independent of seriousness; 3) separate presentation of respective case reports in a special section of the PSUR; 4) NIS (ADR reporting – neoplasias of the small bowel).	SmPC, Section 4.3 Revestive is contraindicated in patients with active or suspected malignancy. Revestive is contraindicated in patients with a history of malignancies in the gastrointestinal tract including the hepatobiliary system within the last five years. SmPC, Section 4.4 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 one year duration. If a neoplasia is detected, it should be removed. In case of malignancy, Revestive therapy should be discontinued (see sections 4.3 and 5.3). SBS patients are to be kept under close surveillance according to clinical treatment guidelines. This usually

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine only)
		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. 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 (see section 4.3). Caution should be exercised when prescribing Revestive. SmPC, Section 5.1 Based on the concerns derived from pre clinical studies (see section 5.3) 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. Several cases of benign colonic polyps occurred during the course of the trials, however, the frequency was not increased compared to placebo treated patients. In addition to the need for a colonoscopy with removal of polyps by the time of the initiation of the treatment (see section 4.4.), every patient should be assessed for the need of an enhanced surveillance schedule based on the patient characteristics (e.g. age and underlying disease, previous occurrence of polyps etc.).
Tumour promoting ability	1) routine PV; 2) obligatory expedited reporting independent of seriousness; 3) separate presentation of respective case reports in a special section of the PSUR; 4) NIS (ADR reporting – benign and malignant neoplasias).	SmPC, Section 4.3 Revestive is contraindicated in patients with active or suspected malignancy. Revestive is contraindicated in patients with a history of malignancies in the gastrointestinal tract including the hepatobiliary system within the last five years. SmPC, Section 4.4 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 one year duration. If a neoplasia is detected, it should be removed. In case of malignancy, Revestive therapy should be discontinued (see sections 4.3 and 5.3). 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. 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 (see section 4.3). Caution should be exercised when prescribing Revestive. SmPC, Section 5.1 Based on the concerns derived from pre clinical studies (see section 5.3) 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. Several cases of benign colonic polyps occurred during the course of the trials, however, the frequency was not increased compared to placebo treated

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine only)
		patients. In addition to the need for a colonoscopy with removal of polyps by the time of the initiation of the treatment (see section 4.4.), every patient should be assessed for the need of an enhanced surveillance schedule based on the patient characteristics (e.g. age and underlying disease, previous occurrence of polyps etc.).
Occurrence of anti-teduglutide antibodies, cross reactivity with GLP 2, and occurrence of anti-ECP antibodies (and associated clinical immunogenicity reactions)	1) routine PV; 2) additional antibody and safety data from ongoing study CL0600-021. 3.) separate presentation of respective case reports in a special section of the PSUR	SmPC, Section 4.8 Consistent with the potentially immunogenic properties of medicinal products containing peptides, administration of Revestive may potentially trigger the development of antibodies. In phase 3 studies with SBS patients who received Revestive for up to one year, 30% of patients developed anti teduglutide antibodies and 40% of patients developed antibodies against E.coli proteins (residual host cell proteins from the manufacture). The antibody formation has not been associated with clinically relevant safety findings, reduced efficacy or changed pharmacokinetics of Revestive.
Anxiety	1) routine PV; 2) separate presentation of respective case reports in a special section of the PSUR;	SmPC Section 4.8 lists Anxiety as common

Important potential risks

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine only)
Adverse events associated with increased absorption of oral concomitant medications	1) routine PV; 2) NIS (concomitant medications - ADR reporting); 3) separate presentation of respective case reports in a special section of the PSUR.	SmPC, Section 4.4 Patients receiving oral concomitant medicinal products requiring titration or with a narrow therapeutic index should be monitored closely due to potential increased absorption (see section 4.5). SmPC, Section 4.5 No clinical drug-drug interaction studies have been performed. An in vitro study indicates that teduglutide did not inhibit cytochrome P450 drug metabolising enzymes. Based upon the pharmacodynamic effect of teduglutide, there is a potential for increased absorption of concomitant medicinal products (see section 4.4).
Increased C-Reactive Protein	1) routine PV; 2) separate presentation of respective case reports in a special section of the PSUR; 3) recording and assessment of relevant AEs in NIS.	SmPC, Section 4.8 “C-reactive protein increased” is labelled under SOC Investigations Modest increases of C reactive protein of approximately 25 mg/l have been observed within the first seven days of Revestive treatment, which decreased continuously under ongoing daily injections. After 24 weeks of Revestive treatment, patients showed small overall increase in C reactive protein 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.
Local Skin Reactions	1) routine PV.	SmPC Section 4.8 Injection site reactions occurred in 21% of patients treated with teduglutide. The reactions appeared to be dose dependent and occurred with the same frequency in patients given the recommended dose of 0.05 mg/kg/day teduglutide and in patients given placebo (injection site reactions were experienced by 12% of the placebo treated patients, by 12% of the patients who received 0.05 mg/kg/day teduglutide and by 41% of the patients who received 0.10 mg/kg/day teduglutide). The reactions included injection site erythema, injection site haematoma and injection site pain (see also section 5.3). SmPC, Section 5.3 In pre clinical studies, severe granulomatous inflammations were found associated with the injection sites.
Potential for off-label use in patients with active Crohn’s Disease	1) routine PV	SmPC, section 4.1 Revestive is indicated for the treatment of adult patients with Short Bowel Syndrome. Patients should be stable following a period of adaptation after surgery. SmPC, section 4.2 Treatment should be initiated under the supervision of a medical professional with experience in the treatment of Short Bowel Syndrome (SBS).

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine only)
Medication Errors	1) routine PV	SmPC section 4.2 Treatment should be initiated under the supervision of a medical professional experienced in the treatment of Short Bowel Syndrome. Instructions for Use Section of the PIL The Instructions for Use section of the Package Information Leaflet (PIL) describe in detail the general use and the correct technique for the drug usage process of Revestive. User testing indicates that the IFU and PIL are well structured and organised, easy to understand and written in a comprehensible manner. The test shows that the leaflets are readable and patients/users are able to act upon the information that it contains. The proposed brand name “Revestive” is considered to be unique with a very low potential for reading or branding errors or confusion in terms of the pharmaceutical form, the route of administration, the strength, or the setting for dispensing and use. SmPC Section 6.6 provides a table with injection volume per bodyweight

Important missing information

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine only)
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)	1) routine PV	SmPC, Section 4.4 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 (see section 4.3). Caution should be exercised when prescribing Revestive.
Lack of experience in pregnant or lactating women	1) routine PV	SmPC, Section 4.6 **Pregnancy:** There are no data from the use of Revestive in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Revestive during pregnancy. **Breastfeeding:** 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 subcutaneous 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.

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine only)
Lack of experience in paediatric population	1) routine PV; 2) paediatric investigation plan (PIP).	SmPC, Section 4.2 Teduglutide should not be used in children below 18 years old because of safety concerns (vulnerability to fluid overload) (see section 5.1).
Limited longer-term safety data over one year of exposure	1) routine PV; 2) additional safety data from ongoing study CL0600-021; 3) additional safety data from the NIS.	No risk minimisation activities are proposed at this time. Additional safety data will be available following completion and analysis of the ongoing long-term study CL0600-021 and of the NIS.
Lack of data in patients with pre-exising severe hepatic impairment	1) routine PV;	SmPC, Section 4.2 No dose adjustment is necessary for patients with mild and moderate hepatic impairment based on a study conducted in Child-Pugh grade B subjects. Revestive has not been studied in patients with severe hepatic impairment (see sections 4.4 and 5.2).

The CHMP, having considered the data submitted, was of the opinion that the below pharmacovigilance activities in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Description	Due date
Study CL0600-021. This is an on-going Long-term, Open-label Study with Teduglutide for Subjects with Parenteral Nutrition Dependent Short Bowel Syndrome. So far only an interim report of the study could be submitted, the study will be finalised about Dec. 2012, and thereafter there is the need to assess the final study report. This measure has been included as an annex II commitment since both efficacy (reduction in PN/i.v. volume) and safety results will be generated from this study which could affect the B/R.	Q4 2013
International Short Bowel Syndrome Registry Prospective: a long-term observational cohort study of patients with Short Bowel Syndrome. Focus will primarily be on disease characteristics, treatment and progression and will include real-life use and safety of teduglutide in those patients receiving teduglutide. Simple treatment outcome measures will be collected.	Planned to start Q1 2013 and will continue until Q1 2022. Interim data for the NIS will be provided every second year.

2.8. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Short bowel syndrome is a state of intestinal failure following major intestinal resection. Currently limited treatment options are available restricted to pharmacological therapy aiming at reduction of secretory losses and parenteral nutrition (PN: fluid/energy). PN is associated with a significant impact on quality of life in addition to risk of serious complications (e.g. central catheter sepsis and thrombosis, complications related to bacterial overgrowth of the small intestine, significant liver toxicity and biliary disease). Therefore, a continual effort to advance enteral feeding must be considered for these patients. Based on these considerations an unmet medical need exists for this rare and debilitating condition of intestinal failure. Due to the capacity of the intestine to undergo adaptation after surgical resection, PN requirements may not be permanent. Based on the mechanism of action, teduglutide could have the potential to improve/accelerate this adaptive process thereby providing a potential valuable additional treatment option to these patients with limited possibilities.

Study CL0600-004 failed to meet its primary objective and was only considered hypothesis generating. Based on exploratory analyses of this study, the applicant identified a dose of teduglutide (0.05 mg/kg/day) which seemed efficacious. Subsequently a new study was performed (study CL0600-020) intended to provide confirmatory evidence of the efficacy and safety of teduglutide 0.05 mg/kg/day. This study demonstrated that compared to placebo, teduglutide statistically significantly reduces the volume of PN/i.v. in SBS. The results showed that compared to placebo, teduglutide had statistically significant effect on the primary efficacy parameter, 20% or greater reduction in volume of PN/i.v. at weeks 20 and 24. The effect was seen both in terms of absolute and relative reductions in the volume of PN/i.v. The results were robust and confirmed in a number of sensitivity analyses. The effect was observed across a number of subgroups such as male/female, age groups, stoma/no stoma and colon-in-continuity/colon-not-in-continuity. The secondary endpoints generally supported the primary endpoint. Compared to placebo, teduglutide had superior effect after 8 to 12 weeks. Duration of effect was also superior in teduglutide treated patients compared to placebo treated patients. Data from the long-term extension trial indicated that the beneficial effects mentioned after 6 months treatment could be maintained, or even improved after 12 months of treatment, and that the beneficial effects shown in the placebo-controlled phase with active treatment could also be achieved when the substance was given to previously placebo-treated patients.

In fact the interim report from the long term follow up study CL0600-021 indicates a high frequency of subjects being able to reduce number of days on PN/i.v. by at least 1 day (a clinically relevant benefit for the patient) and even a few patients being able to discontinue PN/I.V. altogether (the ultimate goal of treatment). This seemingly provides evidence of the clinical relevance of the observed effect. The submission of the final study report has been made a condition in Annex II.

Uncertainty in the knowledge about the beneficial effects.

As stated above, the pivotal placebo controlled study (CL0600-020) has demonstrated that teduglutide can reduce the volume of PN/i.v. needed to maintain homeostasis in SBS. Whereas the long term study CL0600-021 is still ongoingnone of the subjects in the short term study could be weaned off PN/i.v. fluid completely which could constitute to a clear clinically relevant effect. As complete weaning of might only be realistic in a less severe population it may be more appropriate to show clinical relevance in the present setting with patients with a very short segment of remaining intestine and a

substantial requirement for PN/i.v. in the reduction in number of days on PN/i.v. Another way of supporting the clinical relevance of the observed effect is to demonstrate that patient satisfaction/QoL is improved. Unfortunately, in the present study with the instrument applied (SBS-QoL™) it was not possible to demonstrate any significant difference in QoL between placebo and teduglutide treated patients. The lack of effect on this secondary endpoint was considered to be related to the heterogeneity of the study population as well as the lack of sensitivity of the QoL instrument used. Thus the lack of effect on this endpoint was not considered to seriously question the clinical relevance of the observed effect on reduction in PN/i.v. volume. However further Data on Quality of Live will be generated within the NIS and the long term study CL0600-021, (as described in Annex II and RMP).

The extrapolation of data on long term non responders from the on-going long term study CL0600-021 indicates the basis for discontinuation of the Teduglutide treatment if no effects are visible after a defined period of time from the beginning of the treatment. The number of patients showing a PN volume response (defined as at least 20% reduction in PN volume from baseline) is continuously increasing over time, reaching more then 70% of patients after 6 months in trial CL0600-020. Thereafter, only a small increase is seen in the open extension trial CL0600-021. It seems therefore appropriate to evaluate the treatment effect after 6 months, because only very few patients with potential PN volume response might stop treatment inappropriately after this point in time.

On the other hand, due to the unknown long-term risks associated with teduglutide treatment, a life-long treatment without clear signs of efficacy is not justified. The CHMP considers that defining a general realistic goal for treatment applicable to all patients is neither realistic nor desirable. Thus a more general assessment by the physician should consider individual treatment objective and patient preferences. Treatment should be stopped after 6 months if no overall improvement of the patient condition is achieved (as reflected in the SmPC). Results of Study CL0600-021 (as described in Annex II) will provide further information on the long-term effects of teduglutide treatment.

Risks

Unfavourable effects

Most of the adverse events observed following administration of teduglutide were mild and moderate in severity; one third of the adverse events were considered to be severe.

The most frequently reported adverse events (AEs) were reported from the GI system. This finding is not surprising in view of the PD profile of teduglutide and the patient characteristics. The most commonly reported GI AEs for teduglutide vs. placebo were abdominal pain; nausea; vomiting; abdominal distension and constipation. While these events are important, the risk is well known (and described in the RMP).

Hepatobiliary and pancreatic events were only reported in teduglutide patients. In this respect, it is a concern that a considerable part of the reports were serious. That these events most probably represent the PD-action of teduglutide is further supported by the non-clinical studies which revealed hyperplastic and/or hypertrophic effects of teduglutide on intrahepatic and extrahepatic bile ducts, the gallbladder and pancreatic ducts. These risks are addressed in the RMP and the SmPC. In addition, the non-interventional study (NIS; described in Annex II)) will provide further safety data on these events.

Uncertainty in the knowledge about the unfavourable effects

There were 3 reports of cancer during teduglutide treatment (including open label treatment). Two of these subsequently died of their cancers. While it is agreed that one of the fatal cases (non-small lung cell cancer in a heavy smoker having received teduglutide for only 85 days) most certainly is not

related to teduglutide treatment, the causality assessment is more uncertain for the two other cases. Even though the number of events is small and it is not possible to determine if this rate of events during teduglutide is higher than what can be expected in a similar population, these reports give cause for concern. From the theoretical point of view, due to its character of being a growth factor inducer and inducing epithelial hyperplasia, there is some concern of induction and/or promotion of benign and/or malignant tumours. In addition to the above, the concerns are corroborated by the data derived in animals, where benign biliary tumours have been induced by high doses. The applicant has evaluated the occurrence of tumours and its precursors during the clinical studies and has found some colonic adenomatous changes, one being dysplastic in nature. Although from a theoretical point of view, the induction of colonic neoplasia appears to be more remote than in the small intestine, it is on the other hand known that small intestine neoplasia is in general a much rarer event compared to colonic neoplasia. Adequate warnings and recommendations regarding screening for intestinal neoplasia have been included in the SmPC. Furthermore, the applicant will design and implement a registry of teduglutide treated patients specifically aiming at monitoring the risk of neoplasia (as described in Annex II).Furthermore the recording of colonoscopy results will be performed in the planned NIS and respective case reports should be presented in a special section of the PSUR.

The combined analyses of data from the placebo controlled SBS studies CL0600-004 and CL0600-020 showed a small overall increase in average CRP during teduglutide treatment (1.43 mg/L above baseline at end of study) compared placebo treatment. Increased CRP values are a known predictor for an increased cardiovascular risk. In the SBS population an increased rate of cardiovascular AEs has not been observed in clinical trials with teduglutide however it is considered appropriate to address this observed modest increase in CRP in the RMP and in the SmPC. Furthermore it is considered relevant to monitor CRP/cardiovascular events in the proposed registry study (as described in Annex II).

Benefit-risk balance

Importance of favourable and unfavourable effects

The aim of teduglutide induced reductions in weekly PN or weaning off PN is to significantly improve the condition of intestinal failure in addition to improve quality of life and reduce frequency of severe potentially life-threatening complication related to PN.

The primary efficacy endpoint (percentage of patients who achieve a 20% or greater reduction in weekly PN/i.v. volume at week 20 and 24) was considered clinically relevant by a group of experts in the field. The clinical relevance of the observed effect was, also backed by the positive effect on the exploratory endpoint “reduction in number of days with PN/i.v.”. One or more days without having to be chained to an i.v. line constitutes a real benefit for the patient.

Teduglutide has an acceptable safety profile for treatment duration of up to 1 year. The CHMP noted that, effects obviously directly related to the pharmacodynamic action of the compound may lead to a relatively high burden of treatment withdrawals, and serious, and sometimes severe adverse events. Considering the serious and disabling nature of condition with a considerable impact on QoL and only limited symptomatic treatment options, this AE-profile is considered acceptable.

Benefit-risk balance

The results from the pivotal study showed that compared to placebo, teduglutide had statistically significant effect on the primary efficacy parameter, 20% or greater reduction in volume of PN/i.v. at weeks 20 and 24. The results were robust and confirmed in a number of sensitivity analyses. Data from the long-term extension trial indicated that the beneficial effects mentioned after 6 months

treatment could be maintained, or even improved after 12 months of treatment. The clinical relevance of the observed effects was confirmed by a number of experts in this field.

Most of the adverse events observed following administration of teduglutide were mild and moderate in severity; one third of the adverse events were considered to be severe. Adequate measures (as descibed in Annex II) have been identified to generate additional data in this rare condition to further elucidate particularly the safety profile. The SmPC is adequately describing the currently available information and provides appropriate guidance on the use of teduglutide.

Considering the serious and disabling nature of the condition with a considerable impact on QoL and only limited symptomatic treatment options, the demonstrated effect of clinical relevance clearly outweighs the safety concerns. Therefore, the benefit-risk balance for teduglutide for the treatment of adult patients with Short Bowel Syndrome, who should be stable following a period of intestinal adaptation after surgery, is demeed positive.

4. Recommendations

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Revestive in the treatment of adult patients with Short Bowel Syndrome is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

Risk Management System and PSUR cycle

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in {insert version reference} of the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA>

The PSUR cycle for the product will follow the standard requirements until otherwise agreed by the CHMP.

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

Not applicable

Obligation to complete post-authorisation measures

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

Description	Due date
Study CL0600-021 A Long-term, Open-label Study with Teduglutide for Subjects with Parenteral Nutrition Dependent Short Bowel Syndrome. The study is designed to monitor the safety, tolerability and efficacy for PN/i.v. dependent SBS subjects taking Teduglutide. The applicant should submit the final study report of a Long-term, Open-label Study with Teduglutide for Subjects with Parenteral Nutrition Dependent Short Bowel Syndrome.	Q4 2013
International Short Bowel Syndrome Registry The applicant will perform a non-interventional study (NIS) to gather further safety data. The study is planned to start Q1 2013 and will continue until Q1 2022. Interim data for the NIS should be provided every second year. The applicant should provide the protocol of the planned NIS.	 Four interim reports will be provided within six months after the data lock points (i.e., Q3 2015, Q3 2017, Q3, 2019, and Q3 2021). Before marketing of the product for assessment.

New Active Substance Status

Based on the CHMP review of the data and the Applicant's response to the CHMP LoQ, the CHMP considers that the active substance teduglutide is to be qualified as a new active substance.