Teduglutide for treating short bowel syndrome

Produced by Aberdeen HTA Group

Authors

Graham Scotland[1,2]
Daniel Kopasker[1]
Neil Scott[3]
Moira Cruickshank[1]
Rodolfo Hernández [1]
Cynthia Fraser[1]
Mairi McLean[4]
Alistair McKinlay[5]
Miriam Brazzelli[2]

1 Health Economics Research Unit, University of Aberdeen
2 Health Services Research Unit, University of Aberdeen
3 Medical Statistics Team, University of Aberdeen
4 School of Medicine, Medical Sciences & Nutrition, University of Aberdeen
5 Consultant Gastroenterologist, NHS Grampian

Correspondence to Graham Scotland
Senior Research Fellow
University of Aberdeen
Health Economics Research Unit
Foresterhill, Aberdeen, AB25 2ZD
Email: g.scotland@abdn.ac.uk

Date completed 20 September 2017

Version 1

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 15/07/04.

Declared competing interests of the authors

Alistair McKinley reports that he previously acted in a brief advisory capacity for Shire, through participation in an expert advisory meeting on short bowel syndrome in Scotland. All other authors have no competing interests to declare.

Acknowledgements

The authors are grateful to Lara Kemp for her administrative support.

Rider on responsibility for report

The view expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows: Scotland G, Kopasker D, Scott N, Cruickshank M, Hernández R, Fraser C, McLean M, McKinlay A, Brazzelli M. Teduglutide for treating short bowel syndrome. Aberdeen HTA Group, 2017.

Contribution of authors

Graham Scotland, Daniel Kopasker and Rodolfo Hernandez acted as health economists; critiqued and reviewed the cost-effectiveness evidence, checked and re-analysed the economic model, and carried out further sensitivity analyses. Neil Scott acted as statistician; critiqued the statistical methods presented in the submission, checked the numerical results, tables, and figures related to the review of the clinical effectiveness evidence, and ran the ERGs exploratory statistical analyses. Moira Cruickshank acted as the systematic reviewer; wrote the background chapter, critiqued the company's definition of the decision problem, and clinical effectiveness methods. Cynthia Fraser acted as information scientist; critiqued the methods used for identifying relevant studies and conducted additional searches. Alistair McKinlay and Mairi McLean acted as clinical experts; provided clinical advice and general

guidance. Miriam Brazzelli acted as project lead for this appraisal; contributed to the critique and review of the clinical effectiveness methods, and supervised the work throughout the project.

Table of contents

List of tables

List of figures

List of abbreviations

AE	Adverse event
AIC	Akaike information criterion
AWMSG	All Wales Medicines Strategy Group
BANS	British Artificial Nutrition Survey
BIC	Bayesian information criterion
BMI	Body mass index
BSG	British Society of Gastroenterology
CADTH	Canadian Agency for Drugs and Technologies in Health
CHMP	Committee for Medicinal Products for Human Use
CKD	Chronic kidney disease
CI	Confidence Interval
CRD	Centre for Reviews and Dissemination
CS	Company's submission
CSR	Clinical study report
DPP-IV	Dipeptidyl peptidase-IV
DSU	(NICE) decision support unit
EQ-5D	EuroQol 5 dimensions
ERG	Evidence review group
ESPEN	European Society for Parenteral and Enteral Nutrition
GLP-1/2	Glucagon-like peptide-1/2
HD	Haemodialysis
HPN	Home parenteral nutrition
HRQoL	Health-related quality of life
HSUV	Health state utility values
ICER	Incremental cost effectiveness ratio
IF	Intestinal failure
IFALD	Intestinal failure related liver disease
ITx	Intestinal transplantation
IV	Intravenous
LD	Liver disease

LY	Life years
NICE	National Institute for Health and Care Excellence
NMB	Net monetary benefit
NR	Not reported
PAS	Patient access scheme
PD	Peritoneal dialysis
PN	Parenteral nutrition
PS	Parenteral support
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
QALY	Quality adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
SA	Sensitivity analysis
SAE	Serious adverse event
SBS	Short bowel syndrome
SBS-IF	Short bowel syndrome with chronic type III intestinal failure
SD	Standard deviation
SE	Standard error
SF-36	36-item short form questionnaire
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
SOC	Standard of care
STA	Single technology appraisal
TEAE	Treatment emergent adverse event
TESAE	Treatment emergent serious adverse event
TPN	Total parenteral nutrition
TSD	(NICE) technical support document
TTO	Time trade off

1 Summary

Short bowel syndrome (SBS) is a rare and potentially life-threatening malabsorptive condition resulting from loss of significant mass of functional bowel or physical bowel. There are many reasons for loss of bowel mass, including congenital defects, disease (e.g. Crohn's disease) and intestinal resection. Short bowel syndrome can affect both adults and children. People with SBS may also develop chronic Type III intestinal failure (SBS-IF), and require long-term parenteral support (PS), consisting of parenteral nutrition and/or intravenous fluids. Issues related to PS include catheter-related bloodstream infections, venous thrombosis, metabolic bone disease, liver damage and psychosocial and financial problems. Treatments for SBS-IF have generally focused on optimising dietary interventions, and antisecretory and antidiarrhoea medication, with surgery an option for a small number of patients. More recently, emphasis has been on promotion of intestinal rehabilitation and improvement of absorption, including the use of the recombinant analogue of glucagon-like peptide 2 (GLP-2).

Teduglutide (Revestive®, Shire Pharmaceuticals Ireland Limited, Dublin, Ireland) is a recombinant GLP-2 analogue that differs from naturally-occurring GLP-2 by a single amino acid substitution, resulting in a longer elimination half-life. Teduglutide improves the structure and function of the remaining intestine, thus enhancing fluid and nutrient absorption. Teduglutide was granted European marketing authorisation for use in the adult population in August 2012 and for use in the paediatric population in September 2016. Since September 2014, teduglutide has been commercially available in the UK for treating short bowel syndrome, but not in Scotland or Wales.

1.1 Critique of the decision problem in the company submission

The NICE scope for this appraisal considered the clinical and cost-effectiveness of teduglutide within its licensed indication for the treatment of short bowel syndrome. The decision problem addressed in the company's submission was consistent with the NICE final scope.

1.2 Summary of clinical effectiveness evidence submitted by the company

The company's systematic review identified three RCTs and three non-randomised extension studies relating to the adult population and one non-randomised study for the paediatric population.

Adult population

The company's clinical effective evidence focused upon one of the three randomised studies: the Phase III, double-blind, placebo-controlled, randomised, multi-centre STEPS trial, which examined whether 0.05mg/kg/day teduglutide reduced PS in patients with SBS-IF. The second RCT (CL0600-004) compared two doses of teduglutide (0.05 and 0.1mg/kg/day) and placebo. The primary outcome in both studies was the percentage of patients who demonstrated a response at week 20 and maintained that response at week 24. A response was defined as achieving a 20% to 100% reduction from baseline in weekly PS volume. The third RCT (NCT02099084) was a small crossover study that examined only short-term physiological outcomes.

In STEPS, there was a statistically significantly higher proportion of responders in the teduglutide 0.05mg/kg/day group (27/43; 63%) than in the placebo group (13/43; 30%) (p=0.002). The CL0600-004 trial reported that 16/35 (46%) responded in the teduglutide 0.05mg/kg/day group, 8/32 (25%) in the teduglutide 0.10mg/kg/day group and 1/16 (6.3%) in the placebo group (p=0.005, 0.05mg/kg/day vs placebo; p=0.17, 0.1mg/kg/day vs placebo). Other PS outcomes also suggested a benefit for teduglutide 0.05mg/kg/day.

Treatment-emergent adverse events (TEAEs) were common in teduglutide and placebo groups in both STEPS and CL0600-004; around one-half of TEAEs in teduglutide-treated participants were related to treatment with teduglutide. The most frequently reported AEs in the teduglutide groups were gastrointestinal disorders (e.g. abdominal pain, nausea, abdominal distension, flatulence, vomiting, diarrhoea and gastrointestinal stoma change) and general disorders (e.g. catheter-related complications, fatigue and injection site bruising, erythema or pain). Around one-third of participants in STEPS and CL0600-004 experienced a serious adverse event (SAE), but these were generally not related to treatment.

Paediatric population

In the paediatric non-randomised study (TED-C13-003), a reduction in parenteral nutrition volume was reported in all three teduglutide groups (between 10% and 39%) but the volume increased in the standard care group by 7%. All participants experienced at least one AE. Serious AEs were reported in up to around half of participants treated with teduglutide and over half of the placebo group. None of the SAEs were related to teduglutide or led to its discontinuation.

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

Although the clinical effectiveness section was generally well-conducted, the ERG found some aspects of the company's search difficult to follow. The results of various RCTs and non-RCTs were reported throughout the main submission and Appendices in an inconsistent manner.

For the adult population, the company's narrative focused on the STEPS study and the results of the other two eligible RCTs, CL0600-004 and NCT02099084, were not considered as major sources of evidence. The ERG disagreed with this approach. In particular, it thought that the CL0600-004 study was equally as relevant as STEPS as a source of evidence and that a meta-analysis of these two studies could have been conducted.

The evidence for the paediatric population came from one small non-randomised study (TED-C13-003). Despite the uncertainty from using this source of evidence, the ERG believes this was a reasonable approach, given that the condition is rare.

1.4 Summary of cost effectiveness submitted evidence by the company

The company's economic case considered the cost-effectiveness of teduglutide plus established clinical management versus established clinical management alone, for patients with SBS-IF on PS who are stable following a period of adaptation following surgery.

The company submitted two economic models, one for the adult population and one for the paediatric population. The models were structured around a set of mutually exclusive health states defined by the level of PS dependence (i.e. number of days of

PS required per week). The adult model used a full range of eight PS health states from PS seven days per week through to PS independence (zero days). The paediatric model utilised a smaller number of composite states, reflecting the more limited data available to populate the model; low-PS (1-3 days per week), mid-PS (4-5 days per week), high-PS (6-7 days per week). The data to inform transition probabilities between the PS health states were derived from the STEPS and STEPS2 studies for the adult population, and from TED-C13-003 for the paediatric cohort. Beyond the observed follow-up periods for the teduglutide and standard care arms of the respective studies, extrapolation assumptions were required.

Health state utility values (HSUVs) for patients and carers, by level of PS dependence (days per week), were available form a number of different sources. The base case models applied patient HSUVs derived from an ad-hoc study which utilised lead-time time trade-off methods to elicit UK general population values for PS dependence states described using vignettes. Carer utilities, by level of PS dependence, were also included in the base case models. These were parametrised using the mid-point between a set of EQ-5D utility values derived from a small survey UK carers, and a set of values elicited from a panel of experts participating in a Delphi process. Rather than apply only the utility decrements associated with caring for patients on parenteral support, the company applied full health state utilities for carers up to the time of death of the patient.

Both models also allowed for the inclusion of intestinal transplant as a downstream event in the model. This was included in the paediatric base case but was only implemented as a scenario analysis in the adult model. The model also simulated the proportion of patients with intestinal failure associated liver disease and stage 5 CKD (requiring dialysis) by level of PS dependence, allowing health service costs and utility decrements associated with these events to be modelled. Further adverse events associated with teduglutide treatment and/or parenteral support, were included in the models as cycle specific incidence rates, with associated costs and utility decrements applied per cycle. Survival of the cohorts was modelled based on the parametric extrapolation of published observational data for patients requiring any PS (1-7 days per week) and for patients able to ween off PS.

Given the structural relationships embedded in the model, the incremental benefits of teduglutide are driven by improvements in health status (for patients and carers) associated with lower PS requirements, a lower adverse event burden, a reduced incidence of IFALD and CKD, and a modest survival gain resulting from a higher proportion of patients achieving PS independence. The incremental costs are driven primarily by the teduglutide acquisition costs, which are partly offset by the reduction in PS achieved, a lower modelled adverse event burden, a reduction in IFALD and stage 5 CKD, and, when applicable, lower intestinal transplant requirements.

The company's base case analysis for the adult cohort generated an ICER £193,548 per QALY gained over standard practice. The probabilistic base case analysis ICER increases to £222,971, due to the Bayesian approach used to specify the distribution assigned to the model transition probabilities. The incremental cost in the probabilistic analysis is [redacted] (95% CI: [redacted]), for a corresponding QALY gain of 2.25 (95% CI: 1.26 – 3.52).

The company base case deterministic ICER for the paediatric cohort was somewhat lower at £111,045. The company base case probabilistic ICER for the paediatric cohort was £143,851; corresponding to an incremental cost of £[redacted] (95% CI: [redacted]), for an incremental QALY gain of 1.83 (95% CI: -0.186 – 5.342). A range of one way sensitivity analyses and scenario analyses were performed for both the adult and paediatric models.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG identified a number of key issues and assumptions in the company base models that did not appear well justified:

- The ERG identified an error in the adverse event rates applied in the teduglutide and standard care arms of the model. This appears to result from the adverse event rates observed in respective arms of STEPS, being applied to the wrong arms in the model (i.e. the event rates being switched).
- An assumption is made that patients in the standard care arm of the model (and those modelled to stop teduglutide treatment) revert back to their baseline PS state beyond the period informed by the observed trial data. Conversely,

- patients on-treatment in the teduglutide arm are assumed to maintain their last observed PS state over the remaining time horizon of the model. This assumes that any observed PS reductions in the placebo arm of STEPS represent a temporary trial effect, while all of the observed PS reductions in the teduglutide arm represent real improvement. Given a lack of data to validate this assumption, the ERG believe that the same extrapolation assumptions should be applied to both arms.
- The utilities applied in the model are derived from an *ad-hoc* study commissioned by the company, in which TTO values were elicited for health state vignettes describing levels of dependence on parenteral support. These vignettes used some disease specific and potentially leading language, and may have created undue focus on the number of PS days as a driver of health related quality of life in SBS-IF patients. The elicited values show a steep negative relationship with increasing number of PS days. However, the actual observed utility data available from the trials shows a much flatter relationship with level of PS dependence. Use of the former (vignette) values results in substantially greater QALY gains for teduglutide compared with the application of values derived from the trial data.
- Carer health state utilities have been applied in the company models over the lifetime of SBS-IF patients. Rather than applying carer utility decrements for surviving SBS-IF patients, the company apply whole HSUVs for carers. This approach may exaggerate carer QALY gains associated with teduglutide, since it appears to attribute all of the carers QALYS to the SBS-IF patient while they are alive. Thus, in periods of extended survival with teduglutide, the carers entire QALYs are credited to teduglutide with no counterfactual applied in the standard care arm.
- Health state costs by level of PS dependence have been worked up using resource use scenarios that have not been well justified. In particular, the scenarios assume significant correlation between certain types of resource use by level of PS dependence, which do not appear well justified by the clinical advice the company received. For example, line sepsis, a high cost complication, is focussed exclusively in the highest PS dependence state, when the clinical advice received by the company suggests that such infections

- are not driven by number of days on PS, but on how well a patient looks after their line. The resource use assumptions serve to create a steep relationship between increasing levels of PS dependence (in days) and increasing health state costs. The ERG believe this relationship may be exaggerated, and it is a key driver of downstream cost savings for teduglutide in the model.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The systematic review was generally well conducted. The economic models were of good quality and were clearly described. The modelling was implemented as described in the company submission. The company models also provided the flexibility to explore many alternative assumptions, which were provided as scenario analyses in the company submission.

1.6.2 Weaknesses and areas of uncertainty

The submission focused on only one of two eligible RCTs with long-term data on PS outcomes for the adult population and did not perform any meta-analyses. The ERG recognises, however, that there was no advantage to the company in doing this, since both studies found results in favour of teduglutide 0.05mg/kg/day of a similar magnitude.

The economic models are informed by limited short term clinical effectiveness data based on relatively small numbers of patients. The paediatric model in particularly is reliant on non-randomised data. This reflects the rarity of the condition. Data to support many further assumptions was hampered by a lack of available published data. Therefore, the modelling relied quite heavily on expert opinion to support assumptions and to generate plausible valuables for various input parameters. The issues identified in 1.5 above in particular, give rise to significant upward uncertainty in the company reported ICERs for both the adult and paediatric populations

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG conducted meta-analyses of STEPS and CL0600-004 using the binary definition of PS. The results are similar to those obtained when only the data from STEPS were considered.

The ERG first of all corrected the identified adverse event rate bug in the company models, and then re-ran the company's reported scenario analyses. This raised the company's reported base case deterministic ICER to £206,690 for the adult population and to £120,766 for the paediatric population. Under the alternative scenarios explored by the company, the ICERs now ranged from £161,344 per QALY gained (with a 1.5% discount rate applied to QALYs) to £352,600 per QALY gained (with the omission of carer utilities) in the adult model. The lowest company scenario ICER in the paediatric model was revised upward to £75,177 (with the last observed transitions probabilities carried forward for teduglutide over the remaining time horizon). The highest company scenario ICER was revised upward to £538,451 per QALY gained (occurring when no stopping rule was applied for teduglutide).

The ERG further explored the impact of changing some of the assumptions underpinning the PS health state costs in the model, and the applying several alternative assumptions in combination. These combined changes pushed the deterministic ICER in the adult cohort as high as £709,847 - with patient utilities derived from STEPS; last observed health state carried forward for standard care in the extrapolation phase; application of carer utility decrements rather than whole HSUVs; and application of the ERGs alternative health state cost assumptions. The same combined scenario in the paediatric model pushed the ICER to £412,201.

In conclusion, given the limitations in the evidence base to inform the economic case, it is difficult to pinpoint the most plausible ICER. However, application of several alternative plausible modelling assumptions generates significant upward movement of the ICERs for both the adult and paediatric cohorts.

2 Background

2.1 Critique of company's description of underlying health problems

The company's description of short bowel syndrome with chronic Type III intestinal failure (SBS-IF) in terms of prevalence, symptoms and complications is accurate and appropriate to the decision problem. The company describes SBS-IF as an ultra-rare, serious, highly debilitating and life threatening condition that leaves patients unable to absorb sufficient nutrition/fluids without parenteral support. The company's description of the condition is consistent with a proposed consensus definition of SBS-IF ("*Short-bowel syndrome-intestinal failure results from surgical resection, congenital defect or disease-associated loss of absorption and is characterised by the inability to maintain protein-energy , fluid, electrolyte or micronutrient balances when on a conventionally accepted, normal diet*").[1] Common reasons for surgical resection of the intestine in adults are malignancy, Crohn's disease, vascular insufficiency or radiation.[2] In children, the main causes of SBS can be prenatal (such as atresia or gastroschisis), neonatal (such as necrotising enterocolitis) or postnatal (such as midgut volvulus, arterial thrombosis or inflammatory bowel disease).[3, 4] It has been estimated that having less than 200cm of small bowel can result in intestinal failure.[1]

Patients with SBS are a heterogeneous population due to differences in the anatomy and function of the remaining bowel.[5] The three main classes of patients with a short bowel are: (i) jejunum-colon (a jejunoileal resection and a jejunocolic anastomosis); these patients generally appear well after resection but may subsequently lose weight and become severely undernourished; (ii) jejunum-ileum (predominantly jejunal resection, with more than 10cm of terminal ileum and colon remaining); this is uncommon and patients rarely have undernutrition issues or need nutritional support; (iii) jejunostomy (a jejunoileal resection, colectomy and stoma formation); these patients have dehydration problems immediately after surgery due to large stomal water and sodium losses.[6]

Following extensive resection of the small bowel, some intestinal adaptation occurs, with the intestine experiencing structural changes which deliver an increase in the

absorptive surface area.[7, 8] In adults with SBS, the extent of intestinal adaptation by the remnant bowel is one aspect underlying whether permanent intestinal failure occurs and parenteral support (PS) is required.[8] Parenteral support maintains fluid, electrolytes, trace elements, vitamins and nutrient balances and consist of parenteral nutrition and/or intravenous fluid.[1, 5] Most patients with SBS can be fed with standard polymeric formulation by mouth or with high-caloric low-sodium products through medically placed feeding devices.[9] People who require PS are at risk of catheter-related bloodstream infections, venous thrombosis, metabolic bone disease and liver damage. Further issues related to PS include psychosocial and financial problems.[10-13] The goals of treatments for SBS-IF are to: optimise the absorptive capacity of the remnant bowel; minimise the symptoms of malabsorption; and avoid, minimise or remove the need for PS. Treatments for SBS have traditionally focused on optimising dietary interventions, and antisecretory and antidiarrhoea medication, with surgery a further option for some patients.[14, 15] In recent years, promotion of intestinal rehabilitation and improvement of absorption has become a prominent focus for the treatment of this population, including the use of recombinant human growth hormone and the recombinant analogue of glucagon-like peptide 2 (GLP-2).[8, 14]

Glucagon-like peptide 2 is a peptide which is secreted from the intestinal L cells after ingesting food and improves the pathophysiologic consequences of SBS.[5, 14] Teduglutide (Revestive®, Shire Pharmaceuticals Ireland Limited, Dublin, Ireland) is a recombinant GLP-2 analogue that differs from naturally-occurring GLP-2 by a single amino acid substitution, resulting in a longer elimination half-life.[16, 17] Teduglutide improves the structure and function of the remaining intestine, thus enhancing fluid and nutrient absorption.[16, 18] It has been reported that teduglutide reduces PS volume requirements which may be associated with a reduction in PS burden.[16]

Teduglutide was granted European marketing authorisation in August 2012. Initially, the licensed indication was for “the treatment of adult patients with short bowel syndrome. Patients should be stable following a period of intestinal adaptation after surgery”. Since September 2016, the licensed indication has been for “the treatment of patients aged 1 year and above with short bowel syndrome. Patients should be stable following a period of intestinal adaptation after surgery”.[19] Teduglutide has been commercially available for treating short bowel syndrome in the

UK since September 2014.[20] Teduglutide has not been assessed for use in Scotland or Wales and notices of non-submission have been issued by the SMC and AWMSG, respectively. Teduglutide is, therefore, not currently recommended for treatment of people with SBS in these countries.

The company's submission states that the only existing management option in England for adults and children with SBS-IF is PS in conjunction with pharmacological agents to manage SBS: to reduce gastric acid secretion (antisecretory agents, such as H2-receptor antagonists and proton pump inhibitors); to reduce motility and diarrhoea (antimotility agents, such as loperamide, diphenoxylate and codeine); and to reduce bacterial overgrowth (for example, antibiotics). The company's submission further states that there are three options for adults who are stabilised on PS: continue on PS; intestinal lengthening surgeries; or teduglutide in conjunction with PS. In addition, the company notes that intestinal transplantation may be recommended for the small number of adults whose disease is unstable or progresses. The ERG's clinical experts agree with the company's description of the currently available management options.

The quality of life of people with SBS is impaired due to the nature of the condition and the associated issues with PS. Alongside pain, the need to constantly eat, the effects of fistula and high-output stomas and a central venous line, and the daily struggle with PN, people with SBS can experience severe fatigue and gastrointestinal symptoms, all of which can affect QoL.[21] Overall QoL is also affected by previous experience, hopes, expectations, and ability to cope and adapt to the situation. In addition, people with SBS have reported concerns about being a burden on family, friends and hospital staff.[21]

It is difficult to estimate the incidence of SBS-IF due to the lack of an ICD-9 or ICD-10 code and the absence of relevant disease registries.[9] Prevalence of SBS in Europe has been reported to be three per million of population in Europe.[22] Data collected by the British Artificial Nutrition Survey (BANS) in the UK showed that there were 420 new home parenteral nutrition (HPN) adult registrations in 2015 and that short bowel was the most common indication for establishing HPN (34% of new cases in 2015).[23] The largest proportion of new registrations was in England (95%) Short bowel

syndrome is around twice as common in women as in men, possibly because the small intestine is shorter in women.[6, 24] According to NHS England[25] prevalence of Type III IF is around 15 patients per million (based on data from Scotland). Incidence of new patients with Type III IF is around 2 patients per million per annum.[25]

2.2 Critique of company's overview of current service provision

The company appropriately refers to the relevant guidelines for the management of SBS. The company states that the clinical guidelines for SBS most widely followed in the UK are those of British Society of Gastroenterology (BSG) and the European Society for Clinical Nutrition and Metabolism (ESPEN).

The BSG guidelines for management of patients with a short bowel[6] relate to adults only, with no separate guidance for children. In brief, the guidelines state:

- Patients with a short bowel and intact ileum and colon rarely need long term enteral or parenteral nutrition.
- Patients with a short bowel (due to loss of ileum) and a retained colon:
    - Gradual undernutrition is dominant. Due to adaptation, nutritional requirements may reduce with time
    - May need parenteral nutrition if less than 50cm small intestine remains
    - Need a high carbohydrate oxalate diet. The volume of food may increase diarrhoea.
- Patients with a jejunostomy:
    - Fluid and electrolyte losses are dominant. Adaptation does not occur so nutritional and fluid requirements do not reduce with time
    - If <75cm of jejunum remains, parenteral saline, and, if <75cm, parenteral nutrition and saline are likely to be needed in the long term
    - If <200cm of jejunum remains, oral hypotonic fluids may need to be restricted and a glucose-saline supplement is sipped to reduce stomal losses of sodium
    - Hypomagnesaemia is common and is treated by correcting sodium depletion, oral or intravenous magnesium supplements, and occasionally with oral 1 hydroxycholecalciferol

- Jejunal output may be further reduced by drugs that reduce motility or, if the bowel is <100cm, drugs that reduce gastric acid secretion

The ESPEN guidelines[26] relate to chronic intestinal failure in adults and involve a series of specific recommendations relating to diet/feeding, drug treatments and surgical options (intestinal transplant or non-transplant surgery). ESPEN specifically recommend that teduglutide be the first choice of treatment for carefully selected patients who are candidates for growth factor treatment.

The relevant NICE guidance relates to nutritional support for adults[27, 28] or intravenous fluid therapy in adults in.[29] These documents provide general guidelines only and none report specific guidelines for managing adults with short bowel syndrome.

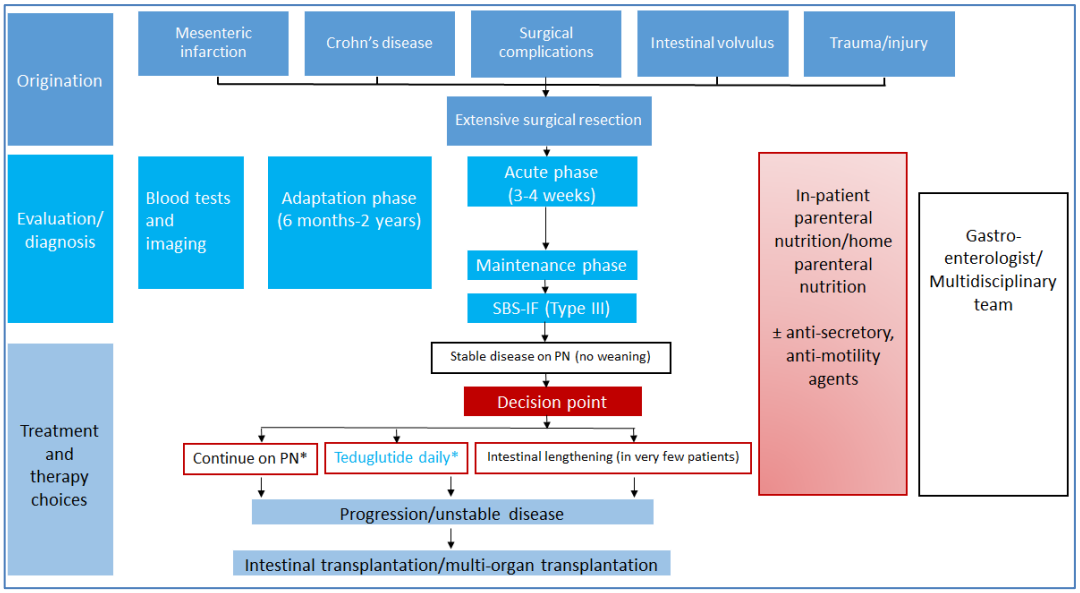


Figure 1 Company's anticipated positioning of teduglutide in clinical practice: adult indication (reproduced from Figure 1 of thecompany's submission)

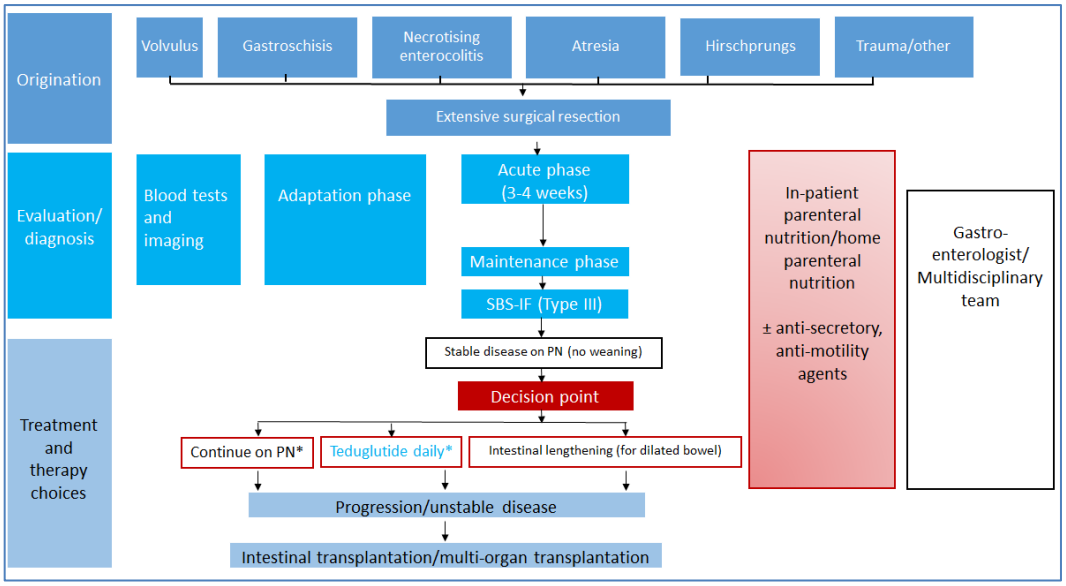


Figure 2 Company's anticipated positioning of teduglutide in clinical practice: paediatric indication (reproduced from Figure 2 of the company's submission)

Figures 1 and 2 present the company's anticipated positioning of teduglutide in practice for adults and children, respectively. The company's pathways show that it anticipates teduglutide becoming an option in adult and paediatric patients, respectively, once the disease is stable on PS, at which point the three treatment options would be: continue on PS; intestinal lengthening; or teduglutide plus PS. For both indications, the company noted that patients continuing to receive PN (with or without teduglutide) would be at risk of complications that also require management. For the paediatric indication, the company further recommended that teduglutide should be stopped where complications occur. The ERG agrees that the company's anticipated pathways are representative of current clinical practice and the anticipated positioning of teduglutide is within its licensed indication.

The company's submission highlights special warnings and precautions for use specified in the summary of product characteristics, relating to colorectal polyps; gastrointestinal neoplasia including hepatobiliary tract; gallbladder and bile ducts; monitoring of small bowel, gallbladder, bile ducts and pancreas; intestinal obstruction; fluid overload; fluid management; concomitant medicinal products; special clinical conditions; hepatic impairment; and discontinuation of treatment. The company states that "*no changes to the way services are organised or delivered are anticipated. However, additional monitoring will be required (as detailed in Section*

2.4.1) when eligible patients are initiated on teduglutide. To support this, a home care service will be provided and paid for by Shire". The company further states that "*Shire will be providing training to the homecare nurses and specialist centre nurses so that subsequently, they can train the patients on how to administer teduglutide themselves. As such, it is not anticipated that there will be a disruption in administration*".

3 Critique of company's definition of decision problem

3.1 Population

The NICE final scope specified the population for this appraisal as "people with SBS who are stable following a period of intestinal adaptation after surgery". The company's submission specified the population as "patients (adults and children aged 1 year and above) with SBS. Patients had been stable following a period of intestinal adaptation after surgery". The company's specification of the population is consistent with the indication specified on the UK marketing authorisation and the ERG agrees that it is appropriate.

3.2 Intervention

The NICE final scope specifies the intervention as "teduglutide in addition to established clinical management". The decision problem addressed in the company's submission is specified as "*teduglutide (Revestive®) will be given to patients with SBS-IF (those receiving chronic PS) in addition to best supportive care, including PS"*. The ERG considers this to be consistent with the NICE final scope.

Teduglutide is a recombinant analogue of human glucagon-like peptide 2 (GLP-2), which is a naturally-occurring intestinotrophic hormone secreted by L cells in the intestine after ingestion of food.[5, 10, 18, 30] Naturally occurring GLP-2 increases intestinal and portal blood flow, inhibits gastric acid secretion, reduces intestinal motility and improves the transport, absorption and utilisation of nutrients.[18, 30-34] Naturally-occurring GLP-2 has a half-life of around 7 minutes as a result of enzymatic degradation by dipeptidyl peptidase-IV (DPP-IV).[30] In contrast, the much longer half-life of teduglutide (2 hours) is enabled by a single amino acid substitution (alanine is substituted by glycine at the second position at the N-terminus) that allows some resistance to in vivo degradation by DPP-IV.[16, 17, 31, 35]

Teduglutide (Revestive®, Shire Pharmaceuticals Ireland Limited, Dublin, Ireland) is indicated for the treatment of patients aged 1 year and above with short bowel syndrome. Patients should be stable following a period of intestinal adaptation after surgery.[19]

Revestive® is formulated as a 1.25mg (for paediatric patients weighing <20kg) or 5mg (for adults and paediatric patients) powder and solvent for solution for injection. The reconstituted solution should be administered by subcutaneous injection once daily, alternating between 1 of the 4 quadrants of the abdomen. The thigh can also be used if injecting into the abdomen is hampered by pain, scarring or hardening of the tissue. Revestive® should not be administered intravenously or intramuscularly.[19]

For adults and children aged 1 to 17 years, the recommended dose of Revestive® is 0.05mg/kg body weight once daily. Due to the heterogeneity of the SBS population, a carefully monitored down-titration of the daily dose may be considered for some patients to optimise tolerability of the treatment. If a dose is missed, that dose should be taken as soon as possible on that day. Treatment effect should be evaluated after 6 months in adults or 12 weeks in the paediatric population. Continued treatment is recommended for patients who have weaned off parenteral nutrition. For the paediatric population, treatment should be initiated under the supervision of a medical professional with experience in treating paediatric SBS.[19]

A tabulated list of adverse reactions to Revestive® is presented in Table 1. Adverse reactions are listed by MedDRA system organ class and by frequency. Frequencies are defined as very common (≥1/10), common (≥1/100 to < 1/10), uncommon (≥1/1000 to < 1/100), rare (≥1/10000 to <1/1000), very rare (<1/10000), and not known (cannot be estimated from the available data). Within each frequency group, adverse reactions are presented in order of decreasing seriousness. All adverse reactions identified in post-marketing experience are presented in *italics*.

Table 1 Adverse reactions to Revestive® (reproduced from Summary of Product Characteristics)[19]

Frequency **System organ class**	**Very common**	**Common**	**Uncommon**	**Not known**
Infections and infestations	Respiratory tract infection*	*Influenza-like illness*		
Immune system disorders				*Hypersensitivity*
Metabolism and nutrition disorders		Decreased appetite Fluid overload		
Psychiatric disorders		Anxiety Insomnia		
Nervous system disorders	Headache			
Cardiac disorders		Congestive heart failure		
Vascular disorders			Syncope	
Respiratory, thoracic and mediastinal disorders		Cough Dyspnoea		
Gastrointestinal disorders	Abdominal distension Abdominal pain Nausea Vomiting	Colorectal polyp Colonic stenosis Flatulence Intestinal obstruction Pancreatic duct stenosis Pancreatitis†	Duodenal polyp	*Gastric polyp*

Frequency **System organ class**	**Very common**	**Common**	**Uncommon**	**Not known**
		Small intestinal stenosis		
Hepatobiliary disorders		Cholecystitis Cholecystitis acute		
General disorders and administration site conditions	Injection-site reaction‡	Oedema peripheral		*Fluid retention*
Injury, poisoning and procedural complications	Gastrointestinal stoma complication			

*Includes the following preferred terms: Nasopharyngitis, Influenza, Upper respiratory tract infection, and Lower respiratory tract infection.

†Includes the following preferred terms: Pancreatitis, Pancreatitis acute, and Pancreatitis chronic.

‡Includes the following preferred terms: Injection site haematoma, Injection site erythema, Injection site pain, Injection site swelling and Injection site haemorrhage.

3.3 Comparators

In line with the NICE final scope, the company's submission specifies as the comparator "best supportive care, including PS, antimotility and antisecretory agents, fluid restriction and dietary optimisation". The company acknowledged that intestinal lengthening and intestinal transplantation are further options for management of SBS-IF in the UK. However, these procedures are carried out in small numbers of patients only and are not currently considered standard treatment. The ERG agrees that the decision problem addressed by the company reflects current clinical practice in the NHS.

3.4 Outcomes

The outcomes specified in the NICE final scope were reduction in PS requirements (volume and frequency), adverse effects of treatment and health-related quality of life. The outcomes addressed in the company's submission were consistent with these, with the company further specifying the first outcome as "reduction in PS requirements (volume and frequency in terms of days)". The ERG agrees with the company's specification of this outcome.

3.5 Economic analysis

The NICE final scope specified that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The company's decision problem addressed a cost utility analysis conducted separately for both the eligible adult and paediatric population.

3.6 Other relevant factors

No subgroups were specified in the NICE final scope. The company stated that "*for adults, the eligible patient group for this submission could be considered a subgroup of the SBS population as a whole; teduglutide is only intended for SBS patients with Type III chronic intestinal failure (SBS-IF patients; as previously discussed with NICE, this is estimated to be approximately 391 adult patients), with Crohn's disease ischaemia, UC or any aetiology leading to SBS and no planned distal intestinal reconnective surgery"*.

"For paediatric patients, teduglutide is only intended for SBS-IF patients who weigh at least 10kg, and do not have active or suspected malignancy, and do not have a history of gastrointestinal/hepatobiliary malignancies within the last 5 years. Also, patients must be unable to wean from PN with minimal progression in EN for ≥3 consecutive months (estimated to be approximately 57 patients)".

Table 2 presents the NICE final scope and the decision problem addressed by the company and includes both the company's and the ERG's comments.

Table 2 Comparison of NICE final scope and decision problem addressed by the company

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
Population	People with SBS who are stable following a period of intestinal adaptation after surgery	Patients (adults and children aged 1 year and above) with SBS. Patients had been stable following a period of intestinal adaptation after surgery	None	None
Intervention	Teduglutide in addition to established clinical management	Teduglutide will be given to patients with SBS-IF (those receiving chronic PS) in addition to 'best supportive care, including PS'	None	None
Comparators	Established clinical management without teduglutide (including PS, antimotility and antisecretory agents, fluid restriction and dietary optimisation)	Best supportive care, including PS, antimotility and antisecretory agents, fluid restriction and dietary optimisation	None	None
Outcomes	• Reduction in PS requirements (volume and frequency) • Adverse effects of treatment • HRQoL	• Reduction in PS requirements (volume and frequency in terms of days) • Adverse effects of treatments and the consequences of morbidity and mortality	The reduction in number of days on PS is an important outcome and has been measured in the teduglutide trials as a	The ERG agrees with the company's comments

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
		• HRQoL	representative measure of frequency of PS use	
Economic analysis	Cost utility analysis	Cost utility analysis (to be conducted separately for the eligible adult and paediatric populations)	None	None
Subgroups	Not applicable	No subgroups will be considered for the adult or paediatric population. However, for adults, the eligible patient group for this submission could be considered a subgroup of the SBS population as a whole; teduglutide is only intended for SBS patients with Type III chronic intestinal failure (SBS-IF patients; as previously discussed with NICE, this is estimated to be approximately 391 adult patients), with Crohn's disease ischaemia, UC or any aetiology leading to SBS and no planned distal intestinal reconnective surgery. For paediatric patients, teduglutide is only intended	None	None

	Final scope issued by NICE	Decision problem addressed in the submission	Comments from the company	Comments from the ERG
		for SBS-IF patients who weigh at least 10kg, and do not have active or suspected malignancy, and do not have a history of gastrointestinal/hepatobiliary malignancies within the last 5 years. Also, patients must be unable to wean from PN with minimal progression in EN for ≥3 consecutive months (estimated to be approximately 57 patients)		

4 Clinical effectiveness

4.1 Critique of the methods of review(s)

4.1.1 Searches

The company submission provides full details of the searches that were undertaken to identify the included studies for the clinical effectiveness review. The major relevant databases were searched: MEDLINE and EMBASE for RCTs, observational studies and systematic reviews; CENTRAL for RCTs; and the Cochrane Database for Systematic Reviews (CDSR) and DARE for systematic reviews. The searches for the adult population were undertaken on 4-5 August 2015 and updated on 12th December 2016, while, for the paediatric population, the searches were undertaken on 10th November 2016. No language restrictions were applied. The submission, however, does not provide the date range for any database so it is unclear if the searches included an appropriate date range.

In addition, the company searched the disease-specific conference proceedings for the ESPEN Congress for 2012-2015 while including only conference abstracts identified through searching EMBASE for the most recent 2 years. The reason why an exception was made to include earlier abstracts for the ESPEN conferences was not clarified by the company and the ERG continues to question this disparity.

The search strategies are documented in full in Appendix 3 and are reproducible however the company conducted the searches using the EMBASE.com platform which is not accessible to the ERG. The MEDLINE and EMBASE searches combine three search facets using the Boolean operator AND: short bowel syndrome; tedglutide or any of the comparators (as detailed in Table 8 of the company submission); and study design. Separate searches were undertaken for RCTs, observational studies and reviews. The search in the Cochrane Library for CENTRAL, CDSR and DARE excluded the study design facet which was appropriate.

The strategies include an exhaustive list of text word terms for each facet but some key MeSH and EMTREE terms appear to have been omitted, most notably the MeSH and EMTREE term *Short Bowel Syndrome/;* the Emtree term *Teduglutide/;* and the MeSH and EMTREE *Glucagon Like Peptide(s)/.* The extensive range of text terms used may have mitigated against failing to retrieve important studies but the use of the appropriate subject headings in both databases would have ensured a sensitive search. The search in the Cochrane Library did, however, use the MeSH term *Short Bowel Syndrome/* along with the same text terms. There were no separate searches for adverse events or quality of life outcomes. Relevant data were obtained from the included trials.

4.1.2 Inclusion criteria

The inclusion and exclusion criteria used in the company's systematic review of clinical evidence are presented in Table 3.

Table 3 Inclusion and exclusion criteria used in the company's systematic review of clinical effectiveness (reproduced from Table 8 of company's submission)

	Inclusion criteria	Exclusion criteria
Population (adult indication SLR)	• Adult patients with SBS (IF Type III)[a]	• Children[a] with SBS (IF Type III) • Healthy volunteers
Population (paediatric indication SLR)	• Paediatric patients with SBS-IF (IF Type III) who are dependent on PN (including TPN, PS and HPN)[a]	• Adults[a] with SBS (IF Type III) • Healthy volunteers
Interventions	• Teduglutide • PN (including TPN, HPN and PS) • Human growth hormone • Glucagon-like peptide-1 o Exenatide o Liraglutide	

	• **Inclusion criteria**	**Exclusion criteria**
	• Surgical lengthening procedures o The Longitudinal Intestinal Lengthening and Tailoring procedure • The Serial Transverse Enteroplasty procedure	
Outcomes	• All outcomes included	• No restrictions
Study design	• Randomised controlled studies • Non-randomised trials[b] • Single-arm studies[b] • Cohort studies[b] • Long-term follow-up studies • Systematic reviews/meta-analyses[c]	• Retrospective studies[b] • Non-systematic reviews • In-vitro studies • Preclinical studies • Studies in animals • Comments • Letters • Editorials • Case reports
Language restrictions	No restrictions	No restrictions

Note: HPN: home parenteral nutrition, IF: intestinal failure, PN: parenteral nutrition, PS: parenteral support, SBS: short bowel syndrome, TPN: total parenteral nutrition
[a]Searches were not restricted to adult or paediatric populations. Relevant studies in adults or children were screened for the appropriate SLR at the inclusion/exclusion stage;
[b]Retrospective studies were excluded from the adult SLR but included in the paediatric SLR;
[c]Systematic reviews and meta-analyses were included at level 1 screening and used to cross-check for any randomised trials that may not have been identified in the primary searches but not included in their own right

The ERG questioned the apparent inconsistency of including retrospective studies in the paediatric systematic review but not in the adult version. At clarification, the company explained that the marketing authorisations for teduglutide for the adult and paediatric populations were granted at different times (i.e. August 2012 and

September 2016, respectively). The company anticipated that the nature of the paediatric population would result in a limited evidence base as compared to the adult population and, therefore, included retrospective studies to provide a broader evidence base for the appraisal. The ERG agreed that the evidence base for the paediatric population is likely to be limited but questioned the methodological integrity of utilising inconsistent inclusion criteria across the two populations.

The number of included studies listed in Table 10 of the company's submission did not match the details reported in the text of the company's submission (Section 4.1.3). Moreover, the ERG found that the company's presentation of four PRISMA flow diagrams for the adult population searches (Figures 1 to 4, company's appendices) hampered cross-checking the numbers reported in Table 10 with the relevant text. At clarification, the company agreed that there were issues with the referencing in the original submission and provided a full list of references for the included studies in the adult and paediatric indications. In general, the ERG found the company's description of its systematic literature review difficult to follow, both due to some inaccuracies in the text and its fragmentation throughout the submission.

Although the company had searched for studies that included the pharmaceutical and surgical comparators (parenteral nutrition, human growth hormone, exnatide, liraglutide, the longitudinal intestinal lengthening and tailoring procedure and the serial transverse enteroplasty procedures), the ERG could find no further reference to studies involving these interventions in the company's submission and it was unclear whether any such studies were identified with the search strategy. At clarification, the company explained that the specified interventions were included as potential comparators in a systematic literature review prior to the NICE scoping exercise. As these comparators were subsequently not relevant to the submission, any studies were excluded at the Level 2 screening stage. The ERG accepts the company's explanation.

The company's systematic review ultimately included three RCTs in the adult systematic review (STEPS, CL0600-004, NCT02099084) and one non-randomised study in the paediatric review (TED-C13-003).[5, 36-38] The company also reported that nine reports of three non-RCTs were included in the adult systematic review. The ERG could find no further information regarding these studies in the company's

submission. At clarification, the company explained that the three non-RCTs identified were the three extension studies to STEPS (i.e. STEPS 2 and STEPS 3)[10, 39] and CL0600-004 (i.e. CL0600-005).[40] The company further explained that there had been some inaccurate referencing in the original submission and listed 13 references relating to these three extension studies. The ERG is satisfied with the company's explanation regarding the three non-RCTs.

The company's submission also included three studies described as "presenting long-term, real-world evidence for teduglutide".[41-43] These three studies were all retrospective in design and, therefore, not eligible for inclusion in the review, according to the inclusion/exclusion criteria presented in Table 3 above (and Table 8 of the company's submission). Furthermore, two of the studies were published after the date of the company's last searches.[41, 42] and only one involved patients with SBS.[41] At clarification, the company stated that the Kochar et al. and Micic et al. studies had been identified by the search strategies but had been excluded due to their study design. The company also agreed that the Joly et al. study had been published after the last search dates but did not account for the Kochar et al. study, which was also published in 2017 (having been incorrectly referenced by the company as published in 2016). The company's justification for presenting these three studies was for completeness and to satisfy the template structure for STA submissions, which includes a section for non-randomised or non-controlled evidence. In the ERG's opinion, it is likely there is further non-randomised evidence in the published literature and therefore limiting inclusion to only three "real world" studies does not appear to comply with the standard principles and methods of conducting systematic reviews. For this reason, and for the fact that the results of these "real world" studies were not used in the economic model, the ERG has not provided further details of these studies in this report.

In brief, the company's systematic review focused on three RCTs and three non-randomised extension studies with regard to the adult population and one non-randomised study with regard to the paediatric population.

4.1.3 Critique of data extraction

The company reported that the systematic review was conducted in accordance with the NICE STA template user guide.[44] Two reviewers independently screened the titles and abstracts identified by the search criteria. Any disagreements were resolved by a third senior researcher. The company states that full-text versions of potentially relevant articles were "*independently reviewed against each eligibility criterion*". The number of reviewers involved at this stage is not reported in the company's submission. Data were extracted from included studies by one reviewer and cross-checked by a second independent reviewer. These methods are considered appropriate by the ERG.

4.1.4 Quality assessment

The number of reviewers involved in the quality assessment process is not reported in the company's submission. The company reported risk of bias assessment for the included RCTs (STEPS, CL0600-004 and NCT02099084) using the criteria recommended by the CRD.[45] These criteria involve assessment of selection bias, performance bias, detection bias, attrition bias and reporting bias, and are considered appropriate by the ERG. In general, the ERG agreed with the company's critical appraisals of STEPS (Table 16 of company's submission, Table 11 of company's appendices), CL0600-004 (Table 12 of company's appendices) and NCT02099084 (Table 8 of company's appendices).

Quality assessment of the non-randomised TED-C13-003 cohort study in paediatric patients was based on the Downs and Black checklist, which the ERG considers appropriate.[46] The ERG largely agrees with the company's appraisal of the study.

The ERG conducted a broad assessment of the methods used by the company for the systematic review of clinical effectiveness evidence using the CRD criteria. Results are shown in Table 4.

Table 4 Quality assessment of the company's systematic review of clinical effectiveness evidence

CRD quality item	Yes/No/Unclear
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes
2. Is there evidence of a substantial effort to search for all of the relevant research?	Yes
3. Is the validity of included studies adequately assessed?	Yes
4. Are sufficient details of the individual studies presented?	Yes
5. Are the primary studies summarised appropriately?	Yes

4.1.5 Evidence synthesis

The company's submission identified three RCTs for the adult indication (STEPS, CL0600-004, NCT02099084)[5, 37, 38] and one non-randomised study for the paediatric indication (TED-C13-003).[36]

Adult population

The main focus of the submission was the Phase III prospective, multinational, multicentre, randomised, placebo controlled double-blind STEPS study (86 participants in total) plus its extension studies, STEPS 2 (2-year open-label extension study to STEPS; 88 participants in total) and STEPS 3 (additional 1-year open-label extension to STEPS 2; 14 participants in total). The company also included a further randomised, double-blind, placebo controlled study, CL0600-004 (83 participants in total), plus its 12-month extension study, CL0600-005 (65 participants in total) and a double-blind, randomised, crossover pilot study (NCT02099084; 8 participants in total).

Table 5 presents study characteristics of the three included RCTs involving adult populations. Funding by NPS Pharmaceuticals was reported by two studies (STEPS, NCT02099084). The third study (CL0600-004) reported the study sponsor as the Mayo Clinic and other links to NPS Pharmaceuticals. Two studies reported having study sites in the UK (STEPS, CL0600-004).

Table 5 Characteristics of the three RCTs involving adults included in the company submission

Study ID	Country (no of centres)	Main inclusion criteria	Main exclusion criteria	Intervention	Comparator	Primary outcome reported	Other outcomes reported
STEPS[5]	27 centres in 10 countries (USA 6, Canada 4, Poland 4, Italy 3, Germany 2, France 2, Spain 2, UK 2, Denmark 1, Netherlands 1)	• Age ≥18y • Intestinal failure resulting in SBS due to major intestinal resection (e.g. injury, cancer Crohn's disease, vascular disease volvulus) • Minimum 12 continuous months of PN dependency	• Cancer within last 5 years • BMI<15kg/m^2 • IBD on immunosuppressant therapy introduced in last 3mo or biologic treatment in last 6mo • Previous use of teduglutide • Use of native GLP-2 or HGH in last 6mo	Teduglutide 0.05mg/kg/day (once daily subcutaneously into abdomen, thigh or arm) (n=43)	Placebo (n=43)	% patients who demonstrated a response at week 20 and maintained that response at week 24. A response was defined as the achievement of a 20% to 100% reduction from	% change in PS, absolute change in PS, no of patients who stopped PS, time of discontinuation of patients who stopped PS, duration of response, proportion of patients with a ≥20% or ≥2L reduction in PS at week 20, an ordered graded

Study ID	Country (no of centres)	Main inclusion criteria	Main exclusion criteria	Intervention	Comparator	Primary outcome reported	Other outcomes reported
		• PS required at least 3 times/ week to meet caloric, fluid or electrolyte needs • People with Crohn's disease had to be in clinical remission for at least 12 weeks prior to dosing	• More than 4 SBS-related hospital admissions in last 12mo • Unscheduled hospital admission in last 1mo			baseline in weekly PS volume	response that accounted for intensity and duration of response at week 24, SBS-QoL
CL0600-004[38]	32 centres in 9 countries (USA,	• Age ≥18y • SBS due to major intestinal resection, e.g.	• Cancer in last 5 years • Active Crohn's disease	Teduglutide 0.05mg/kg/ day (n=35) or	Placebo (n=16)	Graded response score that accounts for	% patients with a response at week 20 maintained to week 24

Study ID	Country (no of centres)	Main inclusion criteria	Main exclusion criteria	Intervention	Comparator	Primary outcome reported	Other outcomes reported
	Canada, Denmark, France, Poland, Germany, Netherlands, UK, Belgium)	injury, volvulus, vascular disease, cancer, Crohn's disease • PS dependency of at least 12mo duration • Dependent of PS (fluid, electrolytes or nutrients) at least 3 times/ week for at least 12mo • Stable for at least 4w based	• Radiation enteritis, scleroderma, coeliac disease, refractory or tropical sprue, pseudo-obstruction, other specified gastrointestinal, immune or systemic disease • Previous use of teduglutide • Use of GLP-2 within last 3mo	teduglutide 0.1mg/kg/ day (n=32)		both intensity and duration of response at 24 weeks. Intensity relied on reduction from baseline in weekly PN volume. Duration took account of responses at weeks 16 to 20 and	(response defined as ≥20% reduction from baseline in weekly PN volume), absolute reduction from baseline in parenteral volume and parenteral kilojoules, achievement of at least 1 day reduction in parenteral administration, total weaning

Study ID	Country (no of centres)	Main inclusion criteria	Main exclusion criteria	Intervention	Comparator	Primary outcome reported	Other outcomes reported
		on specified clinical criteria	• Hospital admission within prior 1mo			weeks 20 to 24	from PS, SF-36, EQ-5D, IBDQ
NCT02099084[37]	USA (no of centres NR)	• Adults with SBS • Dependent on home PN	• Active Crohn's disease • Previous use of teduglutide • Hospitalisation within previous 1mo • Use of octreotide, IV glutamine, growth hormone or growth factors within last 12w	Teduglutide 0.05mg/kg (once a day, subcutaneous, for 7 days) (n=8, crossover design)	Placebo (n=8, crossover design)	Gastric emptying half-time at 2h after ingestion of radiolabelled meal, overall gut transit at 6h after ingestion of radiolabelled meal	Change in small intestinal and colonic permeability as measured by urinary excretion of mannitol, lactulose or mannitol/lactulose ratio at 2h after ingestion of radiolabelled meal

Study ID	Country (no of centres)	Main inclusion criteria	Main exclusion criteria	Intervention	Comparator	Primary outcome reported	Other outcomes reported
			• History of pancreatitis, primary renal impairment, radiation enteritis, scleroderma, coeliac disease, tropical sprue, diabetes, chronic pseudo-obstruction, active malignancy				

Note: PN, parenteral nutrition; PS, parenteral support; HGH, human growth hormone; SBS, short bowel syndrome; IBD, inflammatory bowel disease; IV, intravenous; NR, not reported; mo, months; h, hours; w, weeks

Table 6 reports baseline demographics and disease characteristics of participants in the three RCTs included in the company's review of clinical effectiveness in adult populations. Within and across the three trials, age, sex and BMI were fairly consistent (STEPS, CL0600-004, NCT02099084).

Across the trials, the most common causes of the major intestinal resection were vascular disease, Crohn's disease (STEPS, CL0600-004) or Crohn's disease-related complications (NCT02099084).

Time receiving parenteral support varied across, and within, trials; for example, median time on parenteral nutrition was 2.95 years in the NCT02099084 trial. In contrast, mean time receiving PS was 7.9 years in the placebo group of the CL0600-004 trial, as compared to 5.9 years in the teduglutide 0.10mg/kg/day group. Overall, remnant small bowel length was also variable across, and within, trials, for example, mean 68.7cm and 84.4cm in the 0.05mg/kg/day and placebo groups, respectively, of the STEPS trial.

In the CL0600-004 trial, mean baseline parenteral volume tended to be higher in the teduglutide 0.10mg/kg/day group than the teduglutide 0.05mg/kg/day or placebo groups (1816mL/day, 1374mL/day, 1531mL/day, respectively).

Table 6 Baseline demographics and disease characteristics of the three included adult population RCTs

	STEPS		CL0600-004			NCT02099084	
	TED 0.05mg/kg/day (n=43)	**Placebo (n=43)**	**TED 0.10mg/ kg/day (n=32)**	**TED 0.05mg/ kg/day (n=35)**	**Placebo (n=16)**	**TED 0.05mg/kg/day (n=8)**	**Placebo (n=8)**
Participant characteristics							
Age, years, mean (SD) [range]	50.9 (12.6) [22-78]	49.7 (15.6) [18-82]	50.3 (14) [19-79]	47.1 (14.2) [20-68]	49.4 (15.1) [20-72]	54 (13)[NR]	
Sex, F/M, n (%)	22/21 (51/49)	24/19 (56/44)	19/13 (59/41)	18/17 (51/49)	9/7 (56/44)	4/4 (50/50)	
BMI, kg/m^2, mean (SD) [range]	22.5 (3.2) [17.6-29.8]	22.3 (3.1) [17.5-28.6]	21.7 (2.6) [17-26.4]	21.2 (3) [15.6-26.7]	22 (2.9) [17.4-28.4]	25 (4) [NR]	
Disease characteristics							
Cause of major intestinal resection, n (%)							
Vascular disease	13 (30)	16 (37)	8 (25)	14 (40)	3 (19)	NR	
Crohn's disease	10 (23)	8 (19)	13 (41)	10 (29)	7 (44)	NR	
Volvulus	3 (7)	6 (14)	4 (13)	5 (14)	2 (13)	NR	
Injury	4 (9)	4 (9)	2 (6)	3 (9)	1 (6)	NR	
Cancer	1 (2)	2 (5)	0	0	0	NR	
Other	12 (28)	7 (16)	5 (16)	3 (9)	3 (19)	NR	
Crohn's disease related complications	NR	NR	NR	NR	NR	4 (50)	
Adhesive SB obstruction with complication	NR	NR	NR	NR	NR	1 (20)	
Desmoid tumour	NR	NR	NR	NR	NR	1 (20)	
Intestinal ischaemia	NR	NR	NR	NR	NR	1 (20)	

	STEPS		**CL0600-004**			**NCT02099084**	
	TED 0.05mg/kg/day (n=43)	**Placebo (n=43)**	**TED 0.10mg/ kg/day (n=32)**	**TED 0.05mg/ kg/day (n=35)**	**Placebo (n=16)**	**TED 0.05mg/kg/day (n=8)**	**Placebo (n=8)**
Trauma	NR	NR	NR	NR	NR	1 (20)	
Stoma, n (%) Yes No	(n=42) 21 (50) 21 (50)	(n=43) 17 (39.5) 26 (60.5)	NR	NR	NR	NR	NR
Type of stoma, n (%) Jejunostomy Ileostomy Colostomy Other	(n=21) 11 (52.4) 6 (28.6) 4 (19) 0	(n=17) 5 (29.4) 9 (52.9) 1 (5.9) 2 (11.8)	 7 4 NR NR	 2 6 NR NR	 1 4 NR NR	NR	NR
Colon in continuity, n (%)	26 (60.5)	23 (53.5)	19 (59.4)	26 (74.3)	11 (68.8)	NR	NR
Remnant colon, n (%) >25%-50% >50%-75% >75%-100%	 14 (33) 6 (14) 3 (7)	 5 (12) 8 (19) 10 (23)	 8 (25) 4 (12.5) 7 (21.9)	 7 (20) 9 (25.7) 10 (28.6)	 4 (25) 4 (25) 3 (18.8)	% of colon remaining, mean (SD): 25 (15)	
Overall remnant small bowel length, mean (SD), cm	(n=40) 84.4 (64.6)	(n=40) 68.7 (63.9)	(n=27) 68 (43)	(n=31) 58 (44)	(n=15) 77 (53)	Residual small intestine length, mean (SD), cm: 63 (12)	
Time receiving PS, mean (SD), y	6.8 (6.3)	5.9 (5.7)	(n=32) 7.3 (5.9)	(n=35) 6.6 (6.5)	(n=16) 7.9 (7.5)	Time on PN, median (IQR), y: 2.95 (2.4-27.3)	
Parenteral volume, mean (SD), mL/d	1844 (1057)	1929 (1026)	(n=32) 1816 (1008)	(n=34) 1374 (639)	(n=16) 1531 (874)	NR	NR

Note: TED, teduglutide; BMI, body mass index; NR, not reported; PS, parenteral support; PN, parenteral nutrition; NR, not reported; F, female; M, male; SD, standard deviation; SB, short bowel; d, days; y, years; IQR, inter-quartile range

Table 7 presents the relevant PS results reported by the adult population RCTs included in the company's submission.

Table 7 Relevant PS results reported by included adult population RCTs

	STEPS		**CL0600-004**			**NCT02099084**	
	TED 0.05mg/kg/day (n=43)	**Placebo (n=43)**	**TED 0.10mg/kg/ day (n=32)**	**TED 0.05mg/kg/ day (n=35)**	**Placebo (n=16)**	**TED 0.05mg/kg/day (n=8)**	**Placebo (n=8)**
Number with response (20-100% PS reduction from baseline) at week 20 and week 24, n (%)	27 (62.8) *p=0.002 vs placebo*	13 (30.2)	8 (25) *p=0.17 vs placebo*	16 (45.7) *p=0.005 vs placebo*	1 (6.3)	NR	NR
PS volume, L/wk, mean (SD)						NR	NR
Baseline	12.92 (7.8)	13.20 (7.4)	12.71 (7.06)	9.62 (4.47)	10.72 (6.12)		
Change from baseline	-4.37 (3.81)	-2.29 (2.74)	-2.47 (3.33)	-2.48 (2.34)	-0.90 (1.41)		
% reduction in PS volume	32.42 (18.86)	21.33 (25.43)	NR	NR	NR		
Number completely weaned from PS, n (%)	0	0	1 (3)	2 (6)	0	NR	NR
Number with a 1-day or more reduction in weekly PS use, n (%)	(n=39) 21 (53.8)	(n=39) 9 (23.1)	3 (9.4)	11 (31.4)	4 (25)	NR	NR
1-day reduction	13 (33.3)	6 (15.4)	NR	NR	NR		
≥2-day reduction	8 (20.5) *p=0.005 vs placebo*	3 (7.7)	NR *p=0.120 vs placebo*	NR *p=0.684 vs placebo*	NR		
Graded response scores, n (%)[a]						NR	NR
Criterion value 0[b]	16 (37.2)	30 (69.8)	24 (75)	19 (54.3)	15 (93.8)		
Criterion value 1	3 (7)	1 (2.3)	2 (6.3)	6 (17.1)	0		
Criterion value 2	13 (30.2)	6 (14)	4 (12.5)	6 (17.1)	1 (6.3)		

	STEPS		**CL0600-004**			**NCT02099084**	
	TED 0.05mg/kg/day (n=43)	**Placebo (n=43)**	**TED 0.10mg/kg/ day (n=32)**	**TED 0.05mg/kg/ day (n=35)**	**Placebo (n=16)**	**TED 0.05mg/kg/day (n=8)**	**Placebo (n=8)**
Criterion value 3	4 (9.3)	2 (4.7)	0	0	0		
Criterion value 4	7 (16.3)	4 (9.3)	2 (6.3)	2 (5.7)	0		
Criterion value 5[c]	0 *p=0.004 vs placebo*[d]	0	0[e] *p=0.16 vs placebo*	2 (5.7) *p=0.007 vs placebo*	0		

Note: [a]Criterion values for the graded response score; values for STEPS are as reported in company's submission; [b]<20% reduction in PS; [c]Off PS; [d]comparison between the graded response categories for the two groups used extended CMH test statistics (with standardised mid-ranks) adjusted for the randomisation stratification variable; [e]One participant weaned off PS at week 24 with a score of 4; TED, teduglutide; PS, parenteral support; NR, not reported

Both STEPS and CL0600-004 reported the following outcome, which was the primary outcome in STEPS: the proportion of participants with a response at week 20 and sustained until week 24. Response was defined as a reduction in PS volume from baseline of 20-100%. A reduction in PS volume of ≥20% was considered to be equivalent to a patient being able to have one day off from receiving PS. In the STEPS trial, response was achieved by 27/43 (63%) participants in the teduglutide 0.05mg/kg/day group and 13/43 (30%) in the placebo group. This difference was statistically significant (p=0.002). In the CL0600-004 trial, 8/32 (25%), 16/35 (46%) and 1/16 (6%) participants in the 0.1mg/kg/day, 0.05mg/kg/day and placebo groups, respectively, achieved a response. Compared with placebo, there was a significant difference in favour of the 0.05mg/kg/day regimen (p=0.005), but not for the 0.1mg/kg/day one (p=0.17).

Adverse events - adult population

Table 8 presents adverse events summary information and adverse events reported in at least 10% of any single group, in the three adult population trials included in the company's submission.

Table 8 Summary of adverse events and adverse events reported in at least 10% of participants from the three adult population studies included in the company's submission

	STEPS		**CL0600-004**			**NCT02099084**	
	TED 0.05mg/kg/day (n=42)	**Placebo (n=43)**	**TED 0.10mg/kg/day (n=32)**	**TED 0.05mg/kg/day (n=35)**	**Placebo (n=16)**	**TED 0.05mg/kg/day (n=8)**	**Placebo (n=8)**
Any TEAE, n (%) total events	35 (83.3) 247	34 (79.1) 274	31 (96.9) 250	33 (94.3) 279	15 (93.8) 91	2 (25)[a] 3	1 (12.5)[a] 2
TEAE related to treatment, n (%) total events	23 (54.8) 91	19 (44.2) 54	19 (59.4) 63	15 (42.9) 45	2 (12.5) 7	NR	NR
TEAE severity, n (%) total events						NR	NR
Mild	31 (73.8) 111	32 (74.4) 133	26 (81.3) 157	26 (74.3) 172	13 (81.3) 50		
Moderate	27 (64.3) 105	25 (58.1) 112	24 (75) 86	23 (65.7) 75	9 (56.3) 30		
Severe	16 (38.1) 31	12 (27.9) 29	6 (18.8) 7	9 (25.7) 32	3 (18.8) 11		
TEAE leading to study discontinuation, n (%) total events	2 (4.8) 2	3 (7) 3	2 (6.3) 3	6 (17.1) 12	1 (6.3) 1	NR	NR
TESAE, n (%) total events	15 (35.7) 22	12 (27.9) 20	11 (34.4) 16	13 (37.1) 43	5 (31.3) 12	0	0
TESAE related to treatment, n (%) total events	2 (2.8) 2	0	2 (6.3) 2	6 (17.1) 10	0	0	0
TESAE severity, n (%) total events							
Mild	3 (7.1) 3	3 (7) 4	7 (21.7) 9	3 (8.6) 5	2 (12.5) 2	0	0
Moderate	9 (21.4) 11	6 (14) 7	2 (6.3) 3	8 (22.9) 14	1 (6.3) 2	0	0
Severe	5 (11.9) 8	6 (14) 9	4 (12.5) 4	7 (20) 24	2 (12.5) 8	0	0
Deaths	0	0	0	0	0	0	0

	STEPS		CL0600-004			NCT02099084	
	TED 0.05mg/kg/day (n=42)	**Placebo (n=43)**	**TED 0.10mg/kg/day (n=32)**	**TED 0.05mg/kg/day (n=35)**	**Placebo (n=16)**	**TED 0.05mg/kg/day (n=8)**	**Placebo (n=8)**
TEAEs in ≥10% participants in any group, n (%)							
Abdominal distension	9 (21.4)	1 (2.3)	3 (9.4)	6 (17.1)	0	NR	NR
Abdominal pain	13 (31)	10 (23.3)	9 (28.1)	7 (20)	2 (12.5)	NR	NR
Catheter-related infection	5 (11.9)	1 (2.3)	1 (3.1)	3 (8.6)	0	NR	NR
Catheter-related complication	NR	NR	3 (9.4)	1 (2.9)	3 (18.8)	NR	NR
Catheter sepsis	NR	NR	4 (12.5)	4 (11.4)	2 (12.5)	NR	NR
Central line systemic infection[b]	7 (16.7)	7 (16.3)	NR	NR	NR	NR	NR
Diarrhoea	3 (7.1)	5 (11.6)	3 (9.4)	0	0	NR	NR
Fatigue	4 (9.5)	3 (7)	5 (15.6)	1 (2.9)	2 (12.5)	NR	NR
Flatulence	5 (12)	3 (7)	NR	NR	NR	NR	NR
Gastrointestinal stoma change	10 (23.8)	3 (7)	5 (15.6)[c]	3 (8.6)[c]	3 (18.8)[c]	NR	NR
Headache	2 (4.8)	7 (16.3)	7 (21.9)	9 (25.7)	1 (6.3)	1 (25)[c]	0
Influenza	NR	NR	4 (12.5)	3 (8.6)	1 (6.3)	NR	NR
Injection site bruising	NR	NR	7 (21.9)	1 (2.9)	0	NR	NR
Injection site erythema	NR	NR	6 (18.8)	1 (2.9)	0	NR	NR
Injection site pain	NR	NR	4 (12.5)	0	0	NR	NR
Mild increase in size of stoma	NR	NR	NR	NR	NR	2 (50)[d]	0
Moderate abdominal discomfort	NR	NR	NR	NR	NR	0	1 (25)
Nasopharyngitis	3 (7.1)	0	5 (15.6)	6 (17.1)	2 (12.5)		
Nausea	12 (28.6)	8 (18.6)	10 (31.3)	5 (14.3)	4 (25)	1 (25)[d]	0

	STEPS		CL0600-004			NCT02099084	
	TED 0.05mg/kg/day (n=42)	**Placebo (n=43)**	**TED 0.10mg/kg/day (n=32)**	**TED 0.05mg/kg/day (n=35)**	**Placebo (n=16)**	**TED 0.05mg/kg/day (n=8)**	**Placebo (n=8)**
Pain	NR	NR	4 (12.5)	0	1 (6.3)	NR	NR
Peripheral oedema	7 (16.7)	2 (4.7)	NR	NR	NR	NR	NR
Urinary tract infection	6 (14.3)	4 (9.3)	5 (15.6)	3 (8.6)	3 (18.8)	NR	NR
Vascular disorders	8 (19)	4 (9.3)	NR	NR	NR	NR	NR
Vomiting	5 (11.9)	4 (9.3)	6 (18.8)	4 (11.4)	2 (12.5)	NR	NR
Weight decreased	1 (2.4)	6 (14)	NR	NR	NR	NR	NR

Note: [a]Reported as "transient side effects"; [b]includes catheter-related infection, central line infection, catheter sepsis, infective thrombosis, bacteraemia; [c]these data taken from company's submission; [d]one participant reported headache, nausea and increased size of stoma; TED, teduglutide; NR, not reported; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event

In the STEPS trial, 83.3% and 79.1% of participants in the teduglutide and placebo groups, respectively, experienced a TEAE compared with 96.9% in the teduglutide 0.10mg/kg/day group, 94.3% in the teduglutide 0.05mg/kg/day and 93.8% in the placebo group in the CL0600-004 trial. However, the number of TEAEs related to treatment were broadly consistent across the teduglutide groups in the two trials (54.8% in STEPS; 59.4% and 42.9% in the 0.05mg/kg/day and 0.10mg/kg/day teduglutide groups, respectively, in CL0600-004). There was a discrepancy in the number of treatment-related TEAEs in the placebo groups across the trials, with 44.2% reported in STEPS and 12.5% in CL0600-004. Discontinuations due to AEs were infrequent across the majority of groups in the two RCTs, with the exception of the teduglutide 0.05mg/kg/day group in CL0600-004, with six participants (17.1%) discontinuing the study due to AEs (as compared to 4.8% in the equivalent group in STEPS).

The most frequently reported AEs in participants in the teduglutide groups were gastrointestinal disorders, such as abdominal pain, nausea, abdominal distension, flatulence, vomiting, diarrhoea and gastrointestinal stoma change (64.3% in STEPS; 60% and 59.4% in the 0.05mg/kg/day and 0.10mg/kg/day teduglutide groups, respectively, in CL0600-004) and general disorders and administrative site conditions, such as catheter-related complications, fatigue and injection site bruising, erythema or pain (40.5% in STEPS; 37.1% and 71.9% in the 0.05mg/kg/day and 0.10mg/kg/day teduglutide groups, respectively, in CL0600-004).

Serious AEs were reported in greater proportions of participants treated with teduglutide than with placebo (35.7% in the teduglutide group and 27.9% in the placebo group in STEPS; 34.4% in the teduglutide 0.10mg/kg/day group, 37.1% in the teduglutide 0.05mg/kg/day group, and 31.1% in the placebo group in CL0600-004). Serious AEs related to treatment were generally infrequent across the two studies, the exception being the 0.05mg/kg/day teduglutide group in CL0600-004, with six participants (17.1%) reporting 10 serious AEs related to treatment, as compared to two participants (4.8%) reporting two events in the teduglutide group in STEPS.

In the NCT02099084 study, a total of five adverse events described as “transient” were reported in three participants. Whether they were treatment-related adverse events was not specified.

No participants died in any of the three included adult population trials.

Extensions to the STEPS and CL0600-004 studies provided long-term safety data for teduglutide in the relevant population. STEPS 2 (n=88) was a 24-month extension to STEPS and STEPS 3 (n=14) was a 12-month extension to STEPS 2. The intervention in both STEPS 2 and STEPS 3 was teduglutide 0.05mg/kg/day/kg/day. CL0600-005 (n=65) was a 28-week extension to CL0600-004. The intervention was either teduglutide 0.1mg/kg/day/kg/day or teduglutide 0.05mg/kg/day/kg/day.

In all three extension studies, the vast majority of participants experienced at least one AE (95.5% in STEPS 2, 100% in STEPS 3, 93.8% in CL0600-005). Proportions of adverse events related to treatment varied: 52.3% in STEPS 2, 21.4% in STEPS 3, and 38.5% in CL0600-005. Similarly, rates of SAEs varied across studies; 63.6% in STEPS 2, 35.7% in STEPS 3, and 41.5% in CL0600-005. Of these, 10.2% in STEPS 2 were considered to be treatment related adverse events, and 1.5% in CL0600-005, but no serious AEs in STEPS 3 were attributed to teduglutide. No adverse events in STEPS 3 led to discontinuation of the study. In STEPS 2, 15 participants (17%) discontinued and eight participants (12.3%) in CL0600-005 discontinued.

The most frequently reported adverse events across the three extension studies were broadly similar to the original trials (percentages reported for STEPS 2, STEPS 3, CL0600-005, respectively): abdominal pain (34.1%, 14.3%, 13.8%), asthenic conditions (22.7%, 21.4%, 4.6%), catheter sepsis (28.4%, 14.3%, 10.8%), diarrhoea (14.8%, 21.4%, 6.2%), nausea (19.3%, 14.3%, 12.3%), upper respiratory tract infection (17%, 14.3%, 10.8%), weight decreased (25%, 14.3%, NR).

Three participants in STEPS 2 died, of which one was reported as treatment related (a 48 year old male who was diagnosed with metastatic adenocarcinoma of the liver 11 months after starting teduglutide treatment. The investigator considered the patient’s prior Hodgkin’s disease and chemotherapy and radiotherapy treatment to be risk

factors for neoplasm but the event was reported as treatment related). There were no deaths in STEPS 3 or CL0600-005.

Evidence synthesis- adult population

The company did not conduct any meta-analyses. The rationale was that the CL0600-004 trial did not meet its primary endpoint and was considered by the CHMP to be suitable for hypothesis generation only.

Paediatric population

The company's submission also included one non-randomised study in a paediatric population (TED-C13-003), a 12-week, open-label, multi-centre, phase III study with the objective of determining safety and pharmacodynamics/efficacy of teduglutide in children with intestinal failure associated with SBS. The study recruited 42 participants aged 1 to 17 years in the USA (16 sites) and UK (1 site). Participants were enrolled sequentially into three teduglutide cohorts (0.0125mg/kg/day [n=8], 0.025mg/kg/day [n=14], 0.05mg/kg/day[n=15]) or received standard of care (n=5). The main pharmacodynamics/efficacy endpoints were change in PN requirements (including the number of patients achieving complete PN independence), change in enteral nutrition tolerance and changes in plasma citrulline.

A reduction in PN volume was observed in all three teduglutide groups (-9.95% in 0.0125mg/kg/day group, -37.34% in 0.025mg/kg/day group, -39.11% in 0.05mg/kg/day group) while an increase of 7.38% was observed in the standard of care group.

Based on physician-prescribed data, 4/34 (10.8%) teduglutide-treated participants were completely weaned off of PN at 12 weeks, while none of the five participants in the standard of care group were completely weaned. According to both physician-prescribed and subject diary data, two participants in the teduglutide group and none in the standard of care group were completely weaned off PN at the end of the study.

Compared to baseline (and using physician prescribed data), a reduction of at least 20% in PN volume was achieved in 12.5%, 71.4% and 53.3% of participants in the

teduglutide 0.0125, 0.025 and 0.05mg/kg/day groups, respectively. None of those in the standard of care group showed a reduction in PN volume.

All participants experienced at least one AE during the conduct of the study. Serious AEs were observed in 37.5% of the teduglutide 0.0125mg/kg/day group, 42.8% of teduglutide 0.025mg/kg/day group, 53.3% of the teduglutide 0.05mg/kg/day group, and 60% of the standard of care group. None of the serious AEs were related to teduglutide or led to its discontinuation. Adverse events experienced by at least 10% of teduglutide-treated participants were: vomiting (32%), upper respiratory tract infection (27%), catheter-related complication (24%), pyrexia (24%), cough (19%), abdominal pain (16%), headache (14%), nausea (14%), fatigue (14%), blood bicarbonate decreased (14%), diarrhoea (11%), faecal volume increased (11%), central line infection (11%).

TED-C13-003 was the only study assessing a paediatric population included in the submission and no meta-analysis was, therefore, feasible.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

Adult population

For adults, the company's search identified three randomised controlled trials, two of which had associated non-randomised extension studies:

- STEPS (with extension studies STEPS 2 and STEPS 3),
- CL0600-004 (with extension study CL0600-005)
- NCT02099084.

Three non-RCTs were also identified; all three were long-term extension studies relating to the STEPS and CL0600-004 studies. Many of the identified studies were described in more than one publication.

Although the methodology and results of all three adult RCTs were presented in the submission, there was a difference in prominence and emphasis. STEPS was fully

reported in the main text of the submission, whereas CL0600-004 and NCT02099084 were mainly reported in the Appendices. While this is in line with the company's narrative that STEPS was the key piece of evidence for the submission, it is unclear why some non-RCTs,[41-43] which did not meet the company's inclusion criteria, were reported in detail in the main submission. The ERG found the scattering of randomised and non-randomised evidence throughout the main submission and the Appendices inconsistent and unstructured.

No meta-analysis of the included three trials was conducted by the company. The reason given for not combining the results of CL0600-004 with those of STEPS was that CL0600-004 did not meet its primary endpoint and was only considered hypothesis generating by the CHMP. The reason given for not including NCT02099084 was that, as it only contained eight patients, data from this study are not presented as a major source of evidence for this submission. The company, therefore, based the economic model only on the results of the STEPS trial.

The ERG believes that the company's choice to focus on only one of the three available RCTs was not entirely justified and not in line with the principles and methods for conducting systematic reviews. All three studies met the criteria specified by the NICE final scope and should have been reported in the main submission. The ERG is not convinced by the reasons given for the exclusion of these trials.

The ERG accepts, however, that NCT02099084 could not have been included in a meta-analysis of all included trials due to its cross-over design and to the fact that it does not share common outcomes with either of the other trials (but not because of its sample size).

CL0600-004 could, however, have been included in a meta-analysis with STEPS. The studies appear to share the same definition for the primary outcome. Although it was considered hypothesis generating by the EMA, this was because its primary endpoint related to the 0.1mg/kg/day dose and this was found not to be statistically significant when compared with placebo. As CL0600-004 is a three-arm trial, it would mean either excluding the 0.1mg/kg/day teduglutide dose or pooling the 0.1mg/kg/day

and 0.05mg/kg/day doses. Meta-analyses were conducted by the ERG using both of these assumptions (see section 4.5 below).

Paediatric population

No paediatric RCTs were identified by the company, and only one non-RCT: TED-C13-003. The information on the literature searches was not particularly clear.

The company considered the paediatric population separately to the adult population. The company had to decide between generalising evidence from adult randomised trials to children, or relying on the results of a small non-randomised study, which could be prone to bias. Considering that the condition of interest (SBS-IF) is very rare, the ERG agrees with the company's approach.

4.3 Critique of trials identified and included in the indirect comparison and/ or multiple treatment comparison

No such analysis was conducted by the company.

4.4 Critique of the indirect comparison and/ or multiple treatment comparison

No such analysis was conducted by the company.

4.5 Additional work on clinical effectiveness undertaken by the ERG

The ERG has conducted two additional meta-analyses using data from both the STEPS and CL0600-004 trials, which shared the same clinical outcomes.

Both RCTs assessed participants at 24 weeks, compared teduglutide 0.05mg/kg/day versus placebo and included PS outcomes, even though these were not always measured identically. CL0600-004 contained an additional teduglutide arm (0.1mg/kg/day).

Two meta-analyses were conducted by the ERG (Figures 3 and 4). Both analyses pooled odds ratios using the Mantel-Haenszel approach and a fixed effect model. The first meta-analysis examined only the 0.05mg/kg/day dose of teduglutide versus placebo. The second analysis used data from all doses of teduglutide. For this meta-

analysis, data from the two active arms from the CL0600-004 study were first combined.

Both meta-analyses confirmed a statistically significant benefit of teduglutide versus placebo. The pooled odds ratio for the 0.05mg/kg/day dose versus placebo was 5.06 (95% CI 2.25 to 11.39). The pooled odds ratio for any dose of teduglutide versus placebo was 4.68 (95% CI 2.06 to 10.65). In both meta-analyses, the odds ratio for CL0600-004 was slightly more favourable to teduglutide than that of STEPS.

However, it is worth pointing out that the results of these meta-analyses could not be directly incorporated into the company's economic model as this used an ordinal definition of PS. Any meta-analysis of the ordinal definition of PS would have been complicated by the low cell counts, particularly for the CL0600-004 trial.

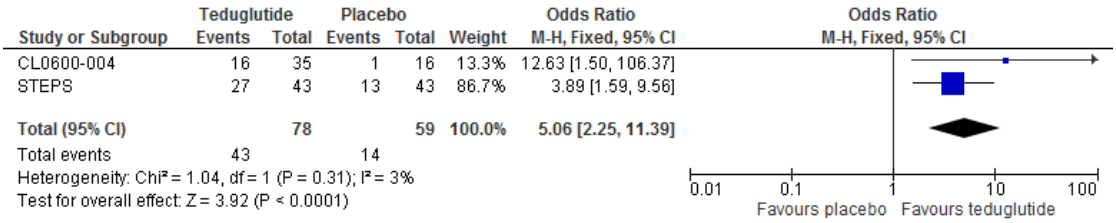


Figure 3 Fixed effect meta-analysis of teduglutide (0.5mg/kg/day) versus placebo

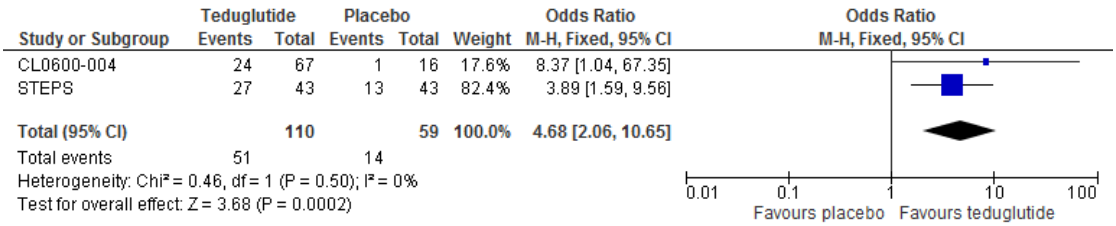


Figure 4 Fixed effect meta-analysis of teduglutide (any dose) versus placebo

4.6 Conclusions of the clinical effectiveness section

The ERG thought that the clinical effectiveness section was generally well conducted but there were some concerns about the systematic review methodology used. The ERG did not find the reporting of the results of the literature searches particularly clear. In particular, it was difficult to work out which studies were being referred to in the text and match these to the list of references.

The ERG did not understand why information on two of the three identified RCTs was mainly presented in the Appendices, while results for three non-RCTs were given prominence in the main submission even though they did not meet the pre-specified inclusion criteria.

The company referred to STEPS as the key piece of evidence for the submission. The ERG believes that data from CL0600-004 should also have been considered. Meta-analysis of these two studies would have been possible for the primary binary definition of PS. The ERG recognises, however, that a meta-analysis based on the ordinal definition of PS, suitable for the economic model, would have been challenging.

5 Cost effectiveness

5.1 ERG comment on company's review of cost-effectiveness evidence

5.1.1 State objectives of cost effectiveness review. Provide description of companys search strategy and comment on whether the search strategy was appropriate. If the company did not perform a systematic review, was this appropriate?

The company conducted separate SLRs to identify and summarise the economic evidence (i.e. cost-effectiveness, resource use and cost, and HRQoL studies) on the use of Teduglutide in adult and paediatric patients with SBS-IF.

Reports of cost effectiveness and utilities were sought by the company by searching MEDLINE AND EMBASE (vis Embase.com), NHS Economics Evaluation Database (NHS EED) and HTA Database (vis Cochrane Library) and Econlit (via Ebsco) in July 2015 and updated in December 2016. The search strategies are documented in full in Appendix 12 and are reproducible however the company conducted the MEDLINE and EMBASE searches using the EMBASE.com platform which is not accessible to the ERG.

The MEDLINE and EMBASE searches combined two search facets using the Boolean operator AND: short bowel syndrome combined with either economic / cost terms or utility/HRQL terms. These searches were run separately. The search strategy for the Cochrane Library and Econlit included only short bowel syndrome terms which was appropriate.

The strategies included an exhaustive list of text word terms for each facet however the MeSH and EMTREE term Short Bowel Syndrome/ was absent from the MEDLINE and Embase searches although the MeSH was included in the Cochrane Library search. While the text terms used should have retrieved the most important articles, inclusion of the MESH and Emtree term may have enhanced sensitivity.

5.1.2 State the inclusion/ exclusion criteria used in the study selection and comment on whether they were appropriate

The company's inclusion and exclusion criteria for the SLR is reproduced in Table 9. The review included full economic evaluations of teduglutide and/or PS that considered individuals with SBS-IF. Outcomes of interest were the incremental cost-effectiveness ratio (ICER), QALYs, resource use and costs. The ERG believes this inclusion criteria is adequate and reflects the focus of the submission.

Table 9 Inclusion/exclusion criteria (cost-effectiveness studies) – (Source: Table 34 of the company submission)

Inclusion criteria	Exclusion criteria
*Population**	*Population**
• Studies that include patients with SBS-IF. The disease is also known as short gut syndrome or simply short gut.	• Healthy volunteers • Diseases other than SBS-IF • Studies with children only
Interventions	*Interventions*
• Teduglutide and PS	• Interventions other than teduglutide and PS will be excluded
Comparator	*Comparator*
• Any treatment for SBS-IF	• No exclusion on comparator
Outcomes	*Outcomes*
• ICER, QALYs, costs, resource use • Results should include either incremental QALYs (or another measure of health outcome/clinical effectiveness) or be structured with a cost-minimisation argument	• Studies assessing or giving the results for cost-only outcomes without using an economic model (e.g. burden-of-illness studies)
Study design	*Study design*
• Full economic evaluations, in terms of: o Cost-effectiveness o Cost-minimisation o Cost-utility o Cost-benefit	• Reviews, letters and comment articles • Burden of illness studies
Budget impact	*Systematic reviews will be flagged.*

Key: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; PS, parenteral support; SBS-IF, short bowel syndrome with intestinal failure.

Note: *For the adult search, paediatric populations were excluded, and *vice versa*.

5.1.3 What studies were included in the cost effectiveness review and what were excluded? Where appropriate, provide a table of identified studies. Please identify the most important cost effectiveness studies

Adult population

The company submission reports the number of studies retrieved from the literature in a PRISMA diagram (Figure 9 of the company submission). From the 255 studies retrieved as full text, 227 were excluded with the reasons stated in the PRISMA diagram. The remaining 28 studies corresponded to 23 independent studies (five cost studies, two full economic evaluations, and 16 utility and HRQoL studies). An update of these searches resulted in the inclusion of a further full economic evaluation (three in total) and two HRQoL studies (18 in total). Table 35 of the company submission summarises the characteristics of the three economic evaluations included.

A study by Roskott[47] used a discrete event simulation approach to compare home parenteral nutrition with scenarios involving intestinal transplantation (ITx) for individuals with less than 12 months life-expectancy. The model considered HPN, intestinal transplant, graft failure after intestinal transplantation and death as possible health states. The ITx pathways differed with respect to the proportion of the eligible individuals going on to receive ITx. The model did not captured differences in quality of life or costs driven by number of days of PS required per week, and was therefore not considered suitable for assessing the cost-effectiveness of teduglutide.

A further study by Migliaccio-Walle et al[48] also used a discrete event simulation approach to model the economic implications of growth hormone (somatropin) use in patients with short bowel syndrome on PS compared to PS alone. The model considered time to partial PS reduction and full PS independence (no PS requirement), and also a number of clinical outcome measures such as occurrence of sepsis and superficial infections, but focused primarily on resource use and cost. The company note that the model structure was not utilised in their submission due to a lack of granularity in the health states for capturing changes in PS requirements, combined with a short time horizon. The ERG are satisfied that the model structure appears insufficient for capturing the demonstrated and potential benefits of teduglutide.

The third study identified in the SLR was an economic evaluation based on a Markov model developed by the company to support their submission to the Canadian Agency

for Drugs and Technologies in Health .[49] The model was structured around the number of days of PS required (per week), and also simulated complications associated with PS dependence. It is a Canadian specific version of the model used in the current Teduglutide submission. This is the most relevant published economic evaluation related to the adult population for the current submission. However, it was developed for the Canadian payer and the results will reflect differences in patterns of resource use, pricing structures and health state utilities. The reported ICER for teduglutide versus standard care was $1,600,145 per QALY gained.

Paediatric population

Figure 10 of the company submission provides the PRISMA diagram related to economic studies retrieved by the literature searches for the paediatric population. From an original 220, 412 and 594 possible economic evaluations, cost and resource use studies, and HRQoL studies, respectively, 14, 99 and 140 papers were retrieved for full text screening. One, 10 and three of these studies were finally included in the respective study categories. The main reason for rejecting studies was the disease area not being relevant.

The single included economic evaluation, reported by Lopushinsky et al,[50] considered the optimal timing of intestinal transplantation for children dependent on total PN. Using a Markov model to determine life-expectancy, two strategies were compared: (1) standard care consisting of PN and referral to transplantation according to accepted guidelines and (2) early listing for isolated small intestine transplantation. Further details on the study are presented in Table 36 of the company submission. The study is not a full economic evaluation as no costs were estimated. The ERG understands that the study was included because a Markov modelling approach was used. The ERG agrees with the company that the decision problem addressed by Lopushinsky et al[50] is inconsistent with the decision problem for teduglutide in the UK setting, where the focus is on reductions in PS requirements compared with established clinical management without teduglutide.

5.1.4 What does the review conclude from the data available? Does the ERG agree with the conclusions of the cost effectiveness review? If not, provide details.

The company review of economic evaluations does not draw any conclusions regarding cost-effectiveness, but notes that the only directly relevant cost-effectiveness model corresponds to the previous HTA submission for teduglutide to CADTH.[49] The decision model used in the current submission is a modified version of the model developed to support the Canadian submission. The ERG generally agrees with the company that the structure of this model is suitable for informing the decision problem in the current NICE submission. A detailed critique of this model follows below.

5.2 Summary and critique of company's submitted economic evaluation by the ERG Suggested research priorities

5.2.1 NICE reference case checklist (Table only)

Table 10 presents the ERG's review of the company submission (CS) against the NICE reference case checklist. Major issues are highlighted in the table and discussed in more detail throughout the report.

Table 10 NICE reference case checklist (Table only)

Attribute	Reference case and TA Methods guidance	Does the *de novo* economic evaluation match the reference case
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice.	Yes. Comparator is standard care which includes parenteral support, antimotility and antisecretory agents, fluid restriction and dietary optimisation.
Patient group	As per NICE scope. "*people with relapsed or refractory systemic anaplastic large cell lymphoma*"	Yes. The company note that the submission focusses on those who are stable on permanent parenteral support following a period of intestinal adaptation following surgery.
Perspective costs	NHS & Personal Social Services	Partly, the submission focusses on health service costs, including treatment costs, parenteral support costs, adverse event costs, and costs associated with intestinal failure related liver disease and chronic kidney disease. The paediatric base case also includes costs of intestinal transplant, which are only applied in a scenario analysis in the adult model.
Perspective benefits	All health effects on individuals	Yes. The company note that the health effects (measured as QALYs) for patients and their carer's are included in the base case analysis.
Form of economic evaluation	Cost-effectiveness analysis	Yes
Time horizon	Sufficient to capture differences in costs and outcomes	Yes. A 40 year time horizon is modelled from a start age of 50 in the adult model. Approximately 5% of the standard care cohort

Attribute	Reference case and TA Methods guidance	Does the *de novo* economic evaluation match the reference case
		and ~6% of the teduglutide cohort remain alive at this time point. The Paediatric model adopts a time horizon of 96 years from a starting age of 4. Less than 1% of the cohort remain alive by this time point.
Synthesis of evidence on outcomes	Systematic review	Yes, systematic reviews were undertaken to inform clinical effectiveness, cost and utility parameters.
Outcome measure	Quality adjusted life years	Yes
Health states for QALY	Described using a standardised and validated instrument	No, health state vignettes were used to describe the model health states. The vignette descriptors were based partly on dimensions of the EQ-5D, but included information on the number of days (per week) of parenteral support required and further disease specific impacts. Further utility decrements associated with adverse events, and utilities associated with chronic complications, were derived from the systematic literature review. Health state utilities for carers, by number of days of PS required, were based on a combination of EQ-5D data from a carer survey and the values elicited from clinical experts through a Delphi process.
Benefit valuation	Time-trade off or standard gamble	Partly. The TTO was used to value the main health state vignettes. However, the carer utilities, by number of days of PS required, were based on a combination of TTO valued EQ-5D status and expert opinion.

Attribute	Reference case and TA Methods guidance	Does the *de novo* economic evaluation match the reference case
Source of preference data for valuation of changes in HRQL	Representative sample of the public	Partly. The health state vignettes were valued by a sample of 100 members of the UK general public. The EQ-5D data for carers were valued using the appropriate general population TTO tariff, but these values were combined with expert opinion in the model. Sources of preference data for other complications come primarily from samples of the general public. In the absence of paediatric specific utility data for patients and carers, the same values were applied in the paediatric model.
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes.
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Probabilistic modelling	Probabilistic modelling	Yes. All relevant parameters were included in the PSA. Probabilistic results were only presented for the base case analysis.
Sensitivity analysis		Yes. A range of one-way sensitivity analysis and scenario analyses were undertaken. Most of these illustrated the impact of single changes to parameters and assumptions. The ERG note that combined changes to several key but uncertain assumptions may better illustrate the uncertainty in the ICERs.

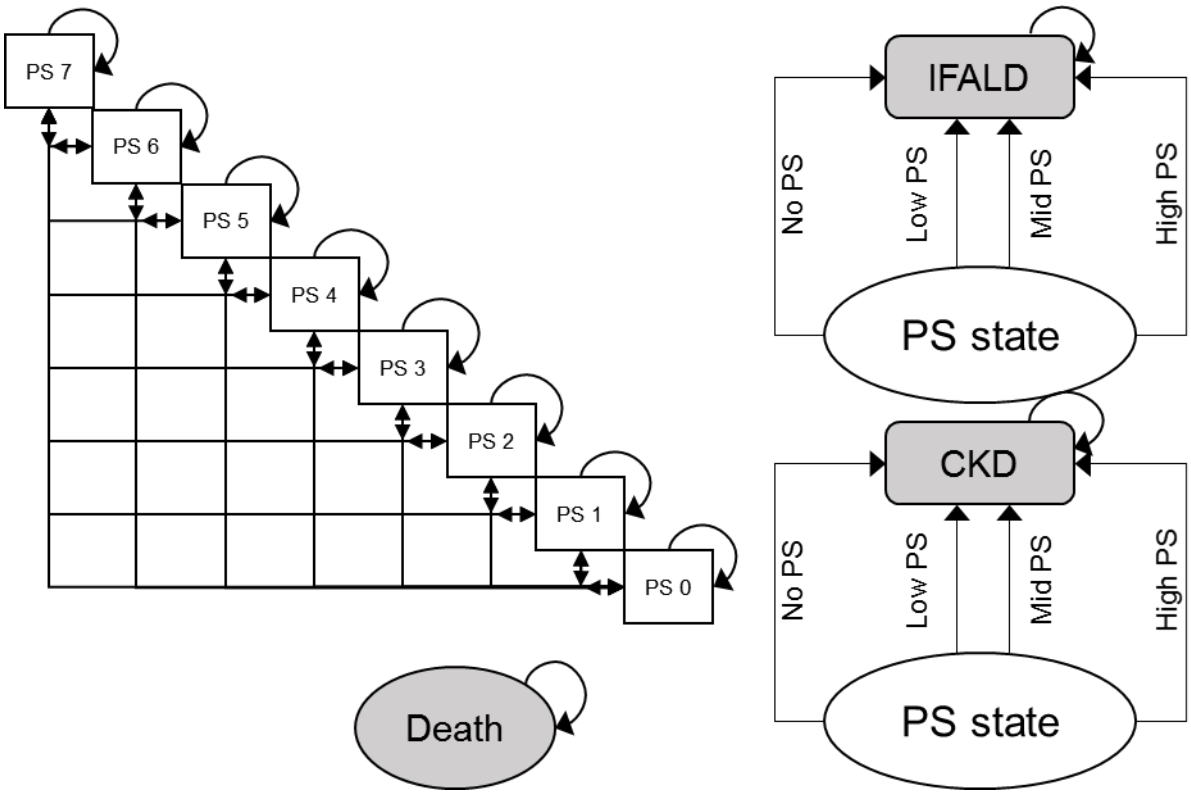
Key: CS: Company submission; HRQoL: health related quality of life; PSS: personal social services; QALY: quality adjusted life year; SLR: systematic literature review; TTO: time trade off

5.2.2 Models structure

The company submission describes two Markov cohort models, one for adults (Figure 5) and one for children (Figure 6), structured around the number of days of parenteral support (PS) required (per week) for patients with short bowel syndrome with chronic type III intestinal failure (SBS-IF). The standard care arm of the adult model incorporates eight core PS states; from a requirement for PS seven days per week (PS7) through to no requirement for PS (PS0). The Paediatric model is described as a variation of the adult model, with a reduced number of PS health states: No PS; low-PS (1-3 days per week); mid-PS (4-5 days per week); and high-PS (6-7 days per week). The models use matrices of transition probabilities to govern the flow of the respective cohorts through the specified health states on a fixed 28-day Markov cycle. The 28-day Markov cycle was chosen to be in keeping with the STEPS trial monthly assessment schedule.[5] The teduglutide treatment arms of the adult and paediatric models contain double the number of PS states to reflect the expected costs and transitions for those on and off treatment. Patients are allowed to transition from any PS state to any other PS state during each 28-day model cycle, or remain in the same PS states. Patient can also die from any cause from any PS state. The transition probabilities for the adult model are derived directly from the STEPS studies,[5, 39:Iyer, 2016 #42] while transition probabilities in the paediatric model are derived primarily from TED-C13-003.[36]

In addition to transitions between the PS states, the clinical trial evidence base is used to model the per cycle incidence of adverse events. Further, the incidence of key SBS-IF associated complications (by level of PS dependence) is modelled per cycle, based on a combination of available literature and expert opinion elicited through a number of meetings and surveys. The associated complications included in the adult and paediatric base cases are intestinal failure related liver disease (IFALD) and stage 5 chronic kidney disease (CKD). These complications are modelled as cumulative proportions of the cohort affected, with associated costs and utilities applied. Finally, the models allows for incident intestinal transplantation to be modelled. This event is included in the paediatric base case but its impact is only assessed in a scenario analysis in the adult model. It is generally modelled using a series of 13 tunnel states to reflect the number of months since transplant, and a final post-transplant state where patients remain until they die. The paediatric model also incorporates an option

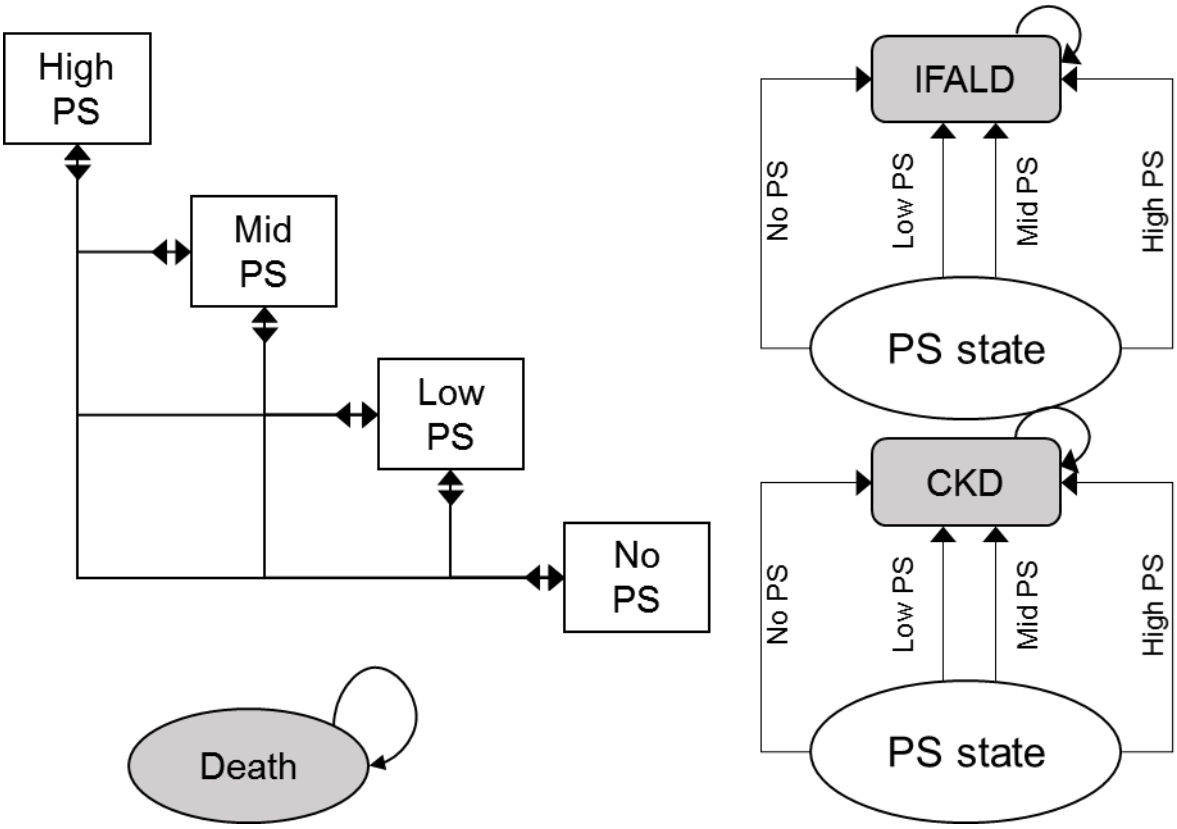
to utilise a series of tunnel states to reflect increased risks of mortality for patients on the waiting list for transplant. However, the company note a lack of data to inform all the required parameters for this component, and therefore only apply it in scenario analysis. Further details on the model structure for intestinal transplantation are provided in section 5.3.6 of the company submission.



Key: PS, parenteral support.

Note: The death health state is an absorbing state and can be entered from any state. IFALD and CKD states are not mutually exclusive to PS state. Upon discontinuation from teduglutide, the transition probabilities for each PS state switch to those for the standard of care arm.

Figure 5 Model diagram (adult) (Source: company submission Figure 11, p.166)



Key: PS, parenteral support.

Note: The death health state is an absorbing state and can be entered from any state. The IFALD and CKD states are not mutually exclusive to the PS states. Upon discontinuation from teduglutide, the transition probabilities for each PS state switch to those for the standard care arm.

Figure 6 Model diagram (paediatric) (Source: company submission Figure 12, p. 168)

Mortality is modelled by level of PS dependence - no requirement (zero days) versus any requirement (1-7 days) - using a combination of parametric survival curves fitted to observational cohort data[51] and general population life table data.

Costs are included in the models for teduglutide treatment and monitoring, parenteral support (by level of PS dependence), additional medications, catheter related complications, adverse events, SBS-IF related complications (IFALD and CKD), and intestinal transplant (scenario analysis in adult model; base case in paediatric model). Health state utilities for the parenteral support states are incorporated as multipliers. Per cycle utility decrements associated with adverse events are combined with data on the treatment arm specific incidence of each type of event (per cycle) and the assumed

duration of events (one cycle) to estimate a per cycle QALY decrement associated with adverse events in each treatment arm. Further, health state utilities associated with IFALD, CKD and (where applicable) intestinal transplant, are applied to the proportions of the cohorts modelled to have these ongoing complications. Thus the model tracks the cumulative costs to the health service and QALYs accruing to patients with teduglutide versus standard care. Furthermore, the model also incorporates health state utility weights for carers by the level of PS requirement of their dependents, such that QALYs accruing to care givers are also estimated and included in the base case ICER.

Given the structural relationships built into the model, modelled incremental benefits of teduglutide in the company model are driven by improvements in health status (for patients and carers) associated with lower PS requirements, a lower adverse event health burden, a reduced incidence of IFALD and CKD, and a modest survival gain resulting from a higher proportion of patients achieving PS independence. Teduglutide acquisition and monitoring costs are partly offset by lower PS requirements, a lower modelled adverse event cost burden, a reduction in IFALD and stage 5 CKD, and, where applicable, lower intestinal transplant requirements.

In general, the ERG believe the model structure adequately represents the disease process and captures the demonstrated/potential benefits of teduglutide in relation to a reduced need for PS and a reduced incidence of complications associated with PS. However, the ERG have some concerns regarding some of the assumptions underpinning the company's approach to parameterising the model.

5.2.3 Population

Within the company submission two cost-effectiveness models for teduglutide were compiled – one for an adult population and one for a paediatric population. Characteristics for the modelled adult cohort are sourced from the Phase III STEPS study (24-week), with additional 2-year follow up from the STEPS 2 study (Table 11). The characteristics of a separate paediatric (aged 1-17) cohort (starting age 4) are based on the 3-month open-label cohort study, TED-C13-003 (Table 12). As such, the models consider patients (adults, and children aged 4 years and above) with SBS-IF. The company submission notes that patients should be stable following a period of

intestinal adaptation post-surgery and on permanent parenteral support (PS). In the adult model, the starting cohort has a minimum level of PS dependence of at least 3 days per week, reflecting the inclusion criteria of STEPS. Paediatric subjects must have stable levels of PS which supplies at least 30% of calorific and/or fluid/electrolyte needs. The paediatric model differs from the adult model in the number of health states and the time horizon considered.

Table 11 Baseline adult patient characteristics (Source: company submission Table 37; Page 163)

Patient characteristic	**Value**
Mean age (yrs)	50
Proportion of female patients	53.5%
Proportion of patients by PS distribution at baseline	
7 PS days per week	52%
6 PS days per week	18%
5 PS days per week	6%
4 PS days per week	13%
3 PS days per week	11%
2 PS days per week	0%
1 PS day per week	0%
0 PS days per week (independent of PS)	0%
Key: PS, parenteral support.	

Table 12 Baseline paediatric patient characteristics

Patient characteristic	**Value**
Mean age (yrs)	4
Proportion of female patients	14%
Proportion of patients by PS distribution at baseline	
6-7 PS days per week	90%
4-5 PS days per week	10%
1-3 PS days per week	0%
0 PS days per week (independent of PS)	0%
Key: PS, parenteral support.	

Table 11 and Table 12 above provide the baseline characteristics of each cohort and the baseline distribution across the PS health states. The baseline levels of PS are based upon the average number of days on PS in the 14 day period prior to the relevant trial commencing. It can be noted that the majority of both samples begin with 6 or 7 days per week of PS. This pattern suggests that the relevant trials from which these figures are taken involved relatively severe cases of SBS-IF. This is consistent with the baseline characteristics presented in Table 14 and Table 15 within the company submission. Severity of the condition, and PS requirement, is broadly related to the remnant small bowel length. Within the adult population a remnant small bowel of less than 100cm could be considered to be a severe case (ERG clinical advice), which would be likely to require high levels of PS. The overall median remnant bowel length in the STEPS trial was 57.5 cm. This indicates that the sample is made up of predominantly severe or very severe SBS-IF cases, and is consistent with the PS distribution in Table 3. An equivalent comparison for the paediatric population is more difficult to make. However, based on expert advice received from the ERGs clinical advisor, it appears that the TED-C13-003 study also included many severe cases of SBS-IF.

A key feature of treatment with teduglutide is that patients can transition to a lower level of PS dependence, with associated gains in their health-related quality of life (HRQL). As is evident from the tables above, a large proportion of the baseline sample are in the highest band of PS, and consequently the model offers significant scope for HRQL gains from treatment with teduglutide. However, the largest HRQL gains might be expected for patients moving from a situation of PS dependence to being independent of PS. This transition may be more likely in less severe cases of SBS-IF - remnant bowel length in excess of 100cm in adults. Such cases would be likely to have a lower PS burden at baseline, and may be closer to the lower limit of 3 days PS per week outlined in the inclusion criteria for the STEPS study.

The representativeness of the samples used to inform the baseline characteristics is not readily verifiable given limited availability of data on the population affected by SBS-IF in the UK. The ERG agrees that informing the model baseline characteristics from observed data taken from relevant studies is a valid approach. It should be noted that this approach may have led to relatively severe cases of SBS-IF being modelled,

and that this may limit the scope for maximising the reductions in PS dependence and associated HRQL gains.

5.2.4 Interventions and comparators

The modelled intervention is teduglutide, as licensed for the treatment of patients aged 1 year and above with SBS-IF, in addition to established clinical management (including PS, antimotility antisecretory agents, fluid restriction and dietary optimisation). Patients should be stable following a period of intestinal adaptation after surgery to be considered for treatment.[19] The licenced dose of teduglutide is 0.05 mg/kg body weight once daily. Pharmaceutical formulation is one vial of powder containing 5mg of teduglutide. After reconstitution, each vial contains 5mg teduglutide in 0.5ml of solution, corresponding to a concentration of 10mg/ml.[19] A vial containing 1.25 mg of teduglutide is also available, which after reconstitution in 0.5 ml of solution corresponds to a concentration of 2.5 mg/ml. The company submission states that this lower dose vial will be available for paediatric patients with a body weight <20 kg. The mode of administration is by one subcutaneous injection per day. It should be noted that a single vial is sufficient for delivery of the licenced dose in patients weighing up to 100kg.

The modelled comparator for teduglutide in the adult and paediatric populations is established clinical management without teduglutide, which includes PS, antimotility and antisecretory agents, fluid restriction and dietary optimisation. PS is required to provide patients with sufficient critical nutrients and fluids, while the symptom-relieving medication aims to reduce gastric acid secretion (e.g. H2 receptor antagonists, proton pump inhibitors), motility and diarrhoea (e.g. loperamide, diphenoxylate) and bacterial overgrowth (e.g. antibiotics, probiotics). There are currently no other active treatments focused on achieving a reduction in the level of patient PS dependency.

Surgical interventions such as bowel lengthening and intestinal transplantation were not included as comparators in the model as these are currently considered as a ‘last resort’ for patients who fail on PS.

The modelled intervention and comparator are consistent with those in the pivotal clinical trials (STEPS for adults and TED-C13-003 for paediatric patients). The company submission states that the placebo arm of these respective trials is taken to be representative of standard care in the UK. The intervention and the comparators in the economic model are also consistent with NICE final scope for this technology appraisal.

5.2.5 Perspective, time horizon and discounting

The company submission focusses on health service costs, including treatment and monitoring costs, parenteral support costs, adverse event costs, and costs associated with intestinal failure related liver disease and chronic kidney disease. The paediatric base case also includes costs of intestinal transplant, which are only applied in scenario analysis in the adult model.

The perspective on benefits is all direct health effects on the individual and also direct health effects on carers through a reduced carer burden. This is in keeping with the NICE reference case.

A 40 year time horizon is modelled form a start age of 50 in the adult model. The paediatric model adopts a time horizon of 96 years from a starting age of 4. The ERG note that 5% of the standard care cohort and ~6% of the teduglutide cohort remain alive in the adult model at the end of the time horizon. However, extending the time horizon to 50 years has very little impact on results. Costs and benefits are appropriately discounted at a rate of 3.5% per annum in the base analyses.

5.2.6 Treatment effectiveness and extrapolation

Transition matrices

Treatment effectiveness in the company's economic model is based on reducing patient dependence on PS. Patients can transition to a higher or lower PS state, or remain in the same PS state, at the end of each 28-day cycle within the model. Each state is defined as the number of days needed on PS per week, ranging from zero to 7. Alternatively, patients can transition from any state to the absorbing state death.

For the first six 28-day cycles (24 weeks) in the adult model, the transition matrices for the teduglutide arm are derived from the observed transitions occurring between the 4-weekly assessments in the STEPS trial. The observed transitions in the placebo arm of STEPS are correspondingly applied to the standard care arm of the model. Beyond 24 weeks, transitions for patients who continue on teduglutide are derived from the observed transitions of patients who continued on teduglutide and were followed up in STEPS 2, the open label extension to STEPS. Assessments of PS dependence in STEPS 2 continued on a monthly basis from month 6 to month 9 of follow-up, and then moved to a 3-monthly schedule up to the final PS assessment at month 30. Because of the change in assessment pattern beyond 9 months, patients are held in the same state of the model for the three consecutive cycles between the observed assessment points. Thus, the model includes observed transition probabilities for patients on-treatment in the teduglutide arm up to cycle 30. Since there were no further observations on patients assigned to placebo beyond 24 weeks in STEPS, the model only contains transition probabilities for the comparator arm up to cycle 6.

The ERG notes that there appears a minor bug in the first cycle transition matrix for the teduglutide arm of the adult model, where the transitions from state PS2 do not sum to 1. This appears to be due to an incorrectly specified formulae ("Transition Probabilities", cell E16) but is also related to an absence of any observed transitions from this state in cycle 0-1. Since there is zero occupancy of state 2 in the first cycle of the model, this has no impact on the model results.

In the paediatric model, sets of transition probabilities are derived directly from the teduglutide (0.05mg/kg) and the placebo arms of TED-C13-003. This non-randomised study in a paediatric population only followed patients up for 12 weeks. As such, it only provides observed transitions up to cycle three in the model. Further, since no transitions were observed in the standard of care (SOC) arm of TED-C13-003, between the PS states included in the paediatric model, no transitions between PS states are applied in standard care arm of the paediatric model. The company acknowledge the limitations of TED-C13-003 for the purpose of informing the economic model. In particular, it was a non-randomised study with small sample size (n=5 in the SOC arm; n = 14 in the teduglutide 0.5mg/kg arm) and short follow-up

(12 weeks). Thus, it has severe limitations for informing a modelled lifetime comparison. Nevertheless, it appears to be the only available comparative data for the paediatric population, reflecting the rarity of the condition.

Stopping rule

Within the teduglutide arm of the adult model, a stopping rule is applied to the proportion of patients, initially on teduglutide, who do not attain at least a 20% reduction in PS volume by the end of 24 weeks follow-up. The same stopping rule is applied at the end of 12 weeks in the paediatric model. Under these circumstances patients are not permitted to continue treatment with teduglutide, and revert to the transition probabilities of the comparator arms of the respective models.

Table 13 below shows the proportion of patients, by level of PS dependence, modelled to stop teduglutide in the adult and paediatric models. The proportion stopping treatment does not show a consistent pattern across the PS states for adults at 24 weeks. However, in the opinion of the ERG, this is unavoidable due to the limited number of observations which are available, which in turn is partly attributable to the rare nature of the condition being treated. The company also explored the impact of removing the stopping rule or applying it at the later time points of 12 months and 24 months in the adult model, or 24 weeks in the paediatric model.

Table 13 Proportion of patients who discontinue teduglutide due to insufficient PS-volume response, by health state (Source: company submission Table 41; Page 176)

PS state	Proportion of patients			
	12 weeks	24 weeks	12 months	24 months
Adult model				
PS7	N/A	27%	23%	17%
PS6	N/A	17%	0%	0%
PS5	N/A	33%	0%	0%
PS4	N/A	0%	0%	0%
PS3	N/A	67%	0%	0%
PS2	N/A	0%	0%	0%
PS1	N/A	0%	0%	0%
PS0	N/A	0%	0%	0%
Paediatric model				
High PS	60%	N/A	N/A	N/A
Mid PS	0%	N/A	N/A	N/A
Low PS	0%	N/A	N/A	N/A
No PS	0%	N/A	N/A	N/A

Key: PS, parenteral support.

Note: For example, 27% of patients that are in the PS7 health state at Week 24 discontinue treatment with teduglutide.

Extrapolation

Transition probabilities in the models are initially based on the observed trial data. For the adult population, the observed data covers 24-weeks for the randomised comparison between teduglutide and placebo, with open label extension to 30 months for those who remain on teduglutide only. As previously mentioned, the paediatric model relies on non-randomised comparative data observed over 12 weeks of follow-up.

Beyond the observed periods the data are extrapolated out to a maximum of 40 years from baseline in the adult model and 96 years from baseline in the paediatric model. Within the adult model the extrapolation commences at 24-weeks in the standard care arm (and in those who stop treatment in the teduglutide arm). For those who remain

on-treatment in the teduglutide arm, the extrapolation period commences at 30 months. Extrapolation commences in the paediatric model following the initial 12 weeks of observed data for both teduglutide and standard care.

Both models apply the same approach to extrapolation beyond the observed period, although extrapolation is handled differently in each arm of the respective models. Those remaining on teduglutide at the end of the observed period are assumed to remain in the same PS state until death. Conversely, standard care patients are assumed to revert to the baseline PS state distribution. By default, patients who stop teduglutide will also revert to the baseline health state distribution. This inconsistency between the two arms of the model is justified in the company submission based on the assumption that improvements in the placebo arm during the trial period of STEPS resulted from increased monitoring and fluid intake. Additionally, it is argued that since reduced PS dependence is still observed despite lower monitoring levels of teduglutide patients during the extended follow-up period (STEPS 2 trial), this means that the same explanation is not valid in the teduglutide arm of the trial – i.e. reductions in PS dependence are observed with or without monitoring in the treatment arm. However, no evidence is presented to support the assumption of a relationship between monitoring and fluid intake. This controversial assumption also appears to assume that none of the reduction in PS dependence observed in the teduglutide arm of STEPS is attributable to increased monitoring and fluid intake, whereas all the observed reduction in the placebo arm is. The extrapolation assumption appears akin to stripping out the observed placebo effect at 24 weeks from the standard care arm but not from the teduglutide arm. The company acknowledges the uncertainty in this assumption, and also presents a scenario analysis where the last observed health state distribution of the placebo arm of STEPS is carried forward in the extrapolation.

The ERG prefers this latter scenario since the company have not presented any clear evidence to demonstrate a difference in non-specific trial or placebo effects between the randomisation arms of STEPS. In the absence of data to the contrary, the ERG believe that both arms of the model should be treated consistently with respect to the extrapolation assumptions.

Adverse events

Data on rates of adverse events (occurring in three or more patients) by treatment allocation were sourced from the STEPS trial and STEPS2 follow-up study. The STEPS trial is used to inform the event rates for the first 24 weeks (6 cycles) of the model in the teduglutide arm and for the entire duration of the model in the placebo arm. The longer term follow-up data from the STEPS2 open label extension is used to inform long term adverse event rates in the teduglutide arm of the model. This distinction results in a substantially lower adverse event rate being applied long-term in the teduglutide arm comapared to the standard care arm. The company justified this on the grounds that initial treatment can cause a number of adverse events which are associated with stimulation of the bowel. Such adverse events subside as treatment continues.

The ERG noted an apparent inconsistency between the adverse event probabilities presented in Table 26 of company submission and the modelled per cycle event rates presented in Table 50 of the company submission. Table 25 in the clinical effectiveness chapter of the company submission shows a higher burden of treatment emergent adverse events in the teduglutide arm during the 24-week randomised phase of STEPS. Conversely, the modelled event rates place a higher cost and health burden on patients in the standard care arm during the same time period; i.e. a cost burden of £451 per cycle versus £292 per cycle and a utility decrement of -0.39 per cycle versus -0.026 per cycle respectively.

Upon closer inspection of the source documents for the adverse event rates included in the model ,(NPS Pharmaceuticals CSR CL0600-020, 2011) it is apparent that the teduglutide (0-6 months) and standard care adverse event rates have been entered the wrong way round in the model. The same issue applies to both the paediatric and the adult models, since the same rates are applied in both due to a lack of available safety data in the paediatric population.

A further limitation in the modelling of adverse events is the focus on adverse events that occur in three or more patients only. This results in the omission of a substantial proportion of serious treatment emergent adverse events which occurred in fewer than three patients in STEPS. That said, there was only a small difference in the proportion

of patients suffering a serious TEAE between the treatment arms of STEPS; 15 (35%) in the teduglutide arm versus 12 (27.9%) in placebo arm. The model provides a scenario that includes only serious adverse events, but this is restricted to include only those serious adverse events that occurred in three or more patients.

Intestinal transplant

As noted above in Section 5.2.2, the company model allows for incident intestinal transplant (ITx) to be incorporated in the models for the adult and paediatric cohorts. This event is only included as a scenario analysis in the adult model, but is included in the base case of the paediatric model. The company justify this on the grounds that it is used more frequently in the paediatric population, based on the views of clinical experts interviewed for a costing study carried out to support the company submission. The company submission also notes that very little data are available to inform the incidence of this complication. To inform the scenario in the adult model, the company used estimates of incidence (by PS dependence) elicited from a group of clinical experts attending a Delphi meeting organised to support model development and parametrisation. Within this process, the experts were asked to give an estimate of the prevalence of patients with intestinal transplants (by level of PS dependence) over time. From these cumulative prevalence estimates, time dependent incidence rates were derived for application in the model. These are presented in Table 44 (p. 179) of the company submission. Within the model, the rates (by cycle number and PS dependence) are applied to the proportion of patients in each PS state in each cycle. The proportion with ITx are entered into a series of 13 tunnel states which allow costs and mortality to vary over the first year following transplant. Following this, patients with ITx enter a final holding state where they remain until they die.

The paediatric model utilises the same general approach to model ITx, but the incidence rates are informed by data obtained from an NHS Blood and Transplant report.[52] The overall annual incidence rate (2.35%) is reweighted by level of PS dependence to maintain the ratios between the PS state specific rates elicited for the adult model. For example, the annual rate in the mid PS (4-5 days) state is two times the rate in the low PS (1-3 days) state. The final incidence rates used the in the model are presented in Table 45 of the company submission.

As mentioned in 5.2.2 the company paediatric model also allows for a scenario analysis whereby a series of tunnel states can be used to model time spent on the waiting list for ITx – to reflect higher mortality for these patients. However, the company submission notes that the data required for this scenario are not all available. Therefore, it is only applied in scenario analysis.

Intestinal failure associated liver disease (IFALD)

The company submission notes the potential for teduglutide to reduce the incidence of IFALD through reducing dependence on parenteral support. The company were able to find only limited data on the incidence of IFALD, and noted that the clinical experts believed the available estimates to be extremely high. Thus, the company have utilised estimated prevalence rates obtained from a Delphi meeting of clinical experts (Table 42 of the company submission). These rates were estimated by time for stable cohorts of adults requiring no PS, PS 1-3 days per week, PS 4-5 days per week, and PS 6-7 days per week. Since the company were not able to obtain estimates of IFALD development rates in children, the same rates are applied in the paediatric model. It should be noted that even if there is an association between level of PS dependence and the prevalence of IFALD, it doesn't necessarily follow that the relationship is causal; which is what the model assumes.

The proportion of the modelled cohorts with IFALD is calculated cycle by cycle by multiplying the proportion of the cohort in each PS health state (in each model cycle) by the expected prevalence of IFALD among patients stable in that state for the corresponding period of time. This methodology appears to decouple the incidence of IFALD from transitions between the PS states which may lead to inaccuracies in the estimated cumulative proportions with IFALD. For example, if a portion of the cohort spends 6 cycles in the PS3 state and then transits to the PS7 state, the cumulative proportion with IFALD (in this portion) will jump to the cumulative proportion expected for patients that have spent 6 cycles in the PS7 state. Conversely, for portions of the cohort who spend several cycles in high dependence states, and then transit to a lower dependence state, the cumulative proportion with liver disease would drop to the lower level. The impact of this can be seen the teduglutide arm of the model, where the cumulative proportion of patients with liver disease actually

drops on occasion compared to the previous cycle, despite the assumption that LD does not affect mortality based on level of PS dependence.

Further issues with assuming equal mortality in those with liver disease compared to those without liver disease, are: 1) it could lead to the model underestimating LY and QALY gains associated with teduglutide treatment (which may reduce liver disease); and 2) it could overestimate cycle specific prevalence of liver disease and the cumulative costs and utility decrements associated it. Given the limitations in the data inputs and methodology used to inform the burden of liver disease in the economic models, it is important to address its impact on the ICER. The company have done this through exploring scenarios where it is removed from the model.

Chronic kidney disease

The company submission notes that stage 5 CKD is another complication clinically believed to be associated with SBSIF and PS. The approach to incorporating this in the model is similar to that used for IFALD. The company submission states that due to a lack of other data, estimates of incidence in adults (by PS dependence) were derived from the Delphi meeting of clinical experts. The derived rates are presented in Table 43 of the company submission. Since the paediatric gastroenterologists could not give any estimate for CKD development rates, the company applied the same rates in the paediatric base case model. The same issue regarding the decoupling of the CKD incidence rates from the transitions between the PS dependence states applies as it does to the modelled incidence if IFLAD. Equal mortality is also assumed for those with comorbid CKD, which may in reality underestimate QALY gains associated with teduglutide (if it does reduce the incidence of CKD) but overestimate costs associated with CKD.

Survival analysis

Due to the limited data available from the STEPS trial, survival was modelled using 10-year published observational data from a French cohort.[51]The characteristics of the STEPS trial sample are broadly similar to those of the cohort reported by Amiot et al.[51] In the absence of randomised data on mortality, the ERG understands the need to use survival data from an alternative source. However, the approach of relying on

observational data to model mortality by PS dependence, requires the caveat that evidence of association in being used to drive treatment related effects in the model. Amiot et al. reported Kaplan Meier survival data for SBS-IF patients who remained PS dependent compared to those who became PS independent.[51] Individual patient data were reconstructed from the published Kaplan Maier curves, allowing various parametric survival curves to be fitted. The company submission states that an expert panel were unable to identify a survival curve which was most representative of actual patient outcomes, despite the curves varying significantly in the overall survival rates. Consequently, the parametric survival curve for the base case was selected on a statistical basis only, using information criterion.

Table 14 below provides statistics assessing the goodness of fit of each parametric survival curve. As can be seen, the values are within a small range in all cases. The base case results employ the log-normal distribution, which can be justified on the basis of these statistics. However, from approximately year 26-27 onwards the extrapolated curves, based on the log-normal survival distributions, predict a lower mortality rate for adults SBS-IF patients than the age matched background mortality rate of the general population. An adjustment is made within the cost effectiveness model to address this issue - the SBS mortality rate is set to equal the background mortality rate in cases where the survival curve predicts that the former will be lower than the latter.

Table 14 Statistical goodness of fit of parametric survival curves to the data – AIC and BIC (Source: company submission Table 47; Page 184)

Parametric model	PS-independent		PS-dependent		Total	
	AIC	BIC	AIC	BIC	AIC	BIC
Exponential	158.5	161.5	304.7	307.5	463.2	469.0
Gamma	154.6	163.5	301.3	309.8	456.0	473.3
Gompertz	159.2	165.1	305.8	311.4	465.0	476.6
Log-logistic	155.9	161.8	304.4	310.0	460.3	471.9
Log-normal	153.9	159.9	300.9	306.5	454.8	466.4
Weibull	156.7	162.6	306.7	312.3	463.4	475.0

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; PS, parenteral support.

In the opinion of the ERG, the assumption of SBS-IF and background mortality being equal after ~25 years of treatment is contentious. For this reason an argument could be made to base the choice of parametric survival curve on grounds beyond the information criterion. For example, the mortality rate associated with the Weibull survival curve remains higher than the background mortality rate for 35 of the 40 year time horizon in the adult model. However, scenario analysis provided by the company within the company submission indicates that such a change would have a negligible effect on the overall ICER. Consequently, the ERG does not propose to alter the current approach.

Clinical advice and available literature identified the company suggests that survival in paediatric SBS-IF patients is better than in adults. However, the company were unable identify paediatric survival data for patients that are weaned off PS versus those that are not. Consequently, the company calculated a hazard ratio between survival in the overall adult population reported by Amiot, and a paediatric population reported by Pironi et al.[26] The derived hazard ratio of 2.42 (adult versus paediatric) was applied to the chosed adult survival curves to estimate mortality by PS dependence in the paediatric model.

As mentioned previously, the proportion of patients with liver disease and CKD are assumed to have the same level of mortality corresponding to their PS dependence state. Mortality for those who have ITx is however modelled separately. This was estimated from data reported on NHS bowel transplant (Shire, Clinical interview, 2017) as presented in Table 49 of the company submission. The rates are time dependent based on the 90 day, 1 year and 5 year survival rates.

5.2.7 Health related quality of life

The company adult and paediatric models consider the health effects on patients as well as carers. While this is in line with NICE reference case, the instruments and weights used for valuation do not fully meet NICE reference case.

The company submission reports on a number of potential sources for quality of life data for the economic model. These include the relevant clinical trials reported in the company submission clinical effectiveness section, studies retrieved from an additional review of the literature and new studies commissioned by the company.

Utility data available from the trials

Three clinical trials, from the five included in the company submission effectiveness section, reported QoL data. The STEPS trial used the SBS-QoL instrument.[53] This is a disease specific QoL instrument but utilities can be derived from this instrument using a valuation algorithm reported in Lloyd et al.[54] In addition, study CL0600-005 included the SF-36 QoL questionnaire, while study CL0600-004 employed both the SF-36 and the EQ-5D-3L instruments. This offers potential for direct estimation of EQ-5D values by PS health states, or mapped EQ-5D values based on responses to the SF-36 using a published mapping algorithm. The company noted that direct calculation of utility weights from the EQ-5D matches the NICE Reference and are thus preferred over mapped SF-36 data. However, whilst the company submission did report EQ-5D health state values derived from trial CL0600-004, these were calculated using a USA tariff[55] rather than the recommended UK general population valuation tariff.[56] As such, the company reported EQ-5D based health state utility weights, reproduced in Table 15 below, do not fully match NICE reference case.

Table 15 EQ-5D utilities from CL0600-004 by number of PS days per week (Source: company submission Table 51, Page 194)

# of PS days	# of pts	# of obs	Utility mean	Utility median	Utility 5 percentile	Utility 95 percentile	Utility SD
PS0	5	50	0.941	1.000	0.691	1.000	0.108
PS1	9	30	0.812	0.796	0.585	1.000	0.164
PS2	14	135	0.836	0.796	0.620	1.000	0.158
PS3	27	499	0.877	1.000	0.620	1.000	0.165
PS4	38	598	0.844	0.850	0.620	1.000	0.190
PS5	28	448	0.829	0.848	0.516	1.000	0.218
PS6	22	241	0.648	0.760	(0.077)	1.000	0.381
PS7	32	1,057	0.813	0.848	0.364	1.000	0.223

Key: obs, observations; PS, parenteral support; pts, patients; SD, standard deviation.

The company also used a published algorithm reported by Lloyd et al. (2014) to derive health state utility values based on the SBS-QoL response data collected in STEPS. Lloyd et al. (2014) developed an algorithm to obtain six-dimension health states from the SBS-QoL items. They then developed a valuation tariff for this six dimension health state descriptor based on modelling of health states valuations obtained from a lead-time TTO survey in a sample of the UK general population (N=250). Table 16 below reproduces the mean health state utility values obtained for PS states 1 to 7 using the STEPS SBS-QoL data in combination with this published valuation algorithm. As the approach uses a standardised descriptor and TTO values elicited from a sample of UK general population, it could be seen to be in keeping with the NICE reference case if it can be argued that the EQ-5D is inappropriate for capturing health benefits resulting from reductions in PS dependence in the SBS-IF population. However, this argument has not been supported by evidence to show that EQ-5D performs poorly on tests of construct validity and responsiveness in the particular patient population.

Table 16 STEPS utilities mapped from SBS-QoL using the Lloyd algorithm[54] (by number of PS days per week (Source: company submission Table 52, page 196)

# of PS days	# of pts	# of obs	Utility mean	Utility median	Utility 5 percentile	Utility 95 percentile	Utility SD
PS1	2	2	0.814	0.814	0.628	1	0.263
PS2	7	17	0.79	0.733	0.608	1	0.127
PS3	19	62	0.812	0.808	0.635	0.971	0.109
PS4	20	54	0.861	0.873	0.613	0.991	0.106
PS5	21	47	0.782	0.797	0.589	0.976	0.117
PS6	31	88	0.762	0.764	0.559	0.949	0.112
PS7	42	228	0.745	0.743	0.58	0.933	0.105

Key: obs, observations; PS, parenteral support; pts, patients; SBS-QoL, short bowel syndrome-quality of life; SD, standard deviation.

Further studies indented in the literature

The company submission also included a SLR for adult and paediatric populations focused on health related quality of life studies in with SBS-IF. The search methodology used was commented on in section 5.1 above. Three studies from the original SLR were identified as potentially suitable for use in the economic model.[54, 57, 58] The study by Lloyd et al is a published algorithm for generating health state utilities from responses to the SBS-QoL and has already been discussed above.

The two further studies obtained from the original SLR[57, 58] were UK based and included EQ-5D data. Culkin et al[58]. analysed EQ-5D data on 48 individuals with intestinal failure to evaluate the effectiveness of nutrition advice. Chambers et al.[57] studied the longitudinal changes in EQ-5D scores following hospital discharge for individuals starting home parenteral nutrition. This was a randomised controlled study comparing telemedicine with standard contact with a nutrition nurse specialist by telephone (N=30). The EQ-5D based utility scores were not reported according to the number of days on PS in either of these studies and they were therefore not directly applicable to the company's decision model.

Two additional studies were identified from the update of the health state utilities search. One study, published as an abstract,[59] reported on a web-based TTO survey of the Canadian adult general population to estimate utility values for PS states defined by number of days/hours of PS required. No details of the survey questionnaire (or accompanying video) were reported and therefore the ERG cannot comment on the quality of the study. However, as the study was conducted on a sample of the Canadian general population, the ERG agrees with the company that these data do not meet NICE reference case.

The final study reported in the submission,(Ballinger, NPS Pharmaceuticals, 2016) is an *ad-hoc* study commissioned by the company. The study used TTO methods to elicit utility values for the PS dependency states (from zero days through to seven days per week) described using vignettes. These utility weights were obtained from a sample of the UK general population (N=100) and are the values used in the company's base case analyses for both the adult and paediatric population. Table 17 below provides the utility weights.

Table 17 Health state utility scores - n=100 (Source: company submission Table 56, page 207)

Health state	Mean (SD)	Minimum	Maximum
0 days on PS	0.82 (0.22)	-0.48*	1
1 day on PS	0.78 (0.23)	-0.48	1
2 days on PS	0.72 (0.23)	-0.48	1
3 days on PS	0.65 (0.27)	-1	0.98
4 days on PS	0.58 (0.31)	-1	1
5 days on PS	0.51 (0.33)	-1	0.98
6 days on PS	0.41 (0.34)	-1	0.98
7 days on PS	0.36 (0.35)	-1	1

Key: PS, parenteral support; SD, standard deviation.
Note: *One participant rated all states as worse than death. Also, three participants rated all health states the same.

The ERG notes the recommendation from the NICE Technical Support Document[60] on the use of vignettes: "*Vignettes not based on standardized and validated measures*

of HRQL and patient own health state valuations do not meet NICE Methods Guidance and have a limited role. These methods should only be used where there are no other data based on validated HRQL measures". While the Vignette descriptions were based around dimensions of the EQ-5D, the ERG understand that they were adapted to include disease specific descriptions (e.g. "*You have diarrhoea and a sudden need to have a bowel movement*") and in certain cases the descriptions may be considered leading (e.g. "*You would value having one day per week without having treatment*", and "*However you value having one day per week without having treatment*"). In addition, co-morbidities and complications regularly present in SBS-IF patients such as the use of a stoma were excluded from the vignette descriptions. Furthermore, while the study sample was selected from the UK general population, the ERG notes that the sample was on average slightly younger, more educated, with a higher proportion female, and a higher proportion single. The ERG believes that all the above factors create potential for bias towards exaggerated differences between the utility values elicited for the PS dependence states.

In summary, the company submission presents three possible utility sources for the adult population with SBS-IF. Only study CL0600-004 collected EQ-5D data which could have potentially satisfied the NICE reference case. However, the valuation of these EQ-5D health states in the company submission was conducted using a US tariff rather than the preferred UK tariff. No clear rationale for this was provided within the company submission. Unfortunately, meaningful differences do exist between US and UK population valuations for EQ-5D states.[61] Given this, it would inappropriate to apply the US based EQ-5D values presented in the company submission in the cost-effectiveness models.

Figure 7 plots the three sets of mean health state utility weights by level of PS dependence. It is clear that the vignette-based measure shows the steepest negative relationship between health state utility and increasing number of days dependent on PS. The other two sets of utility weights show a flatter relationship. While none of the three sets of weights appear fully justified with respect to NICE guidance, the company chose the vignettes study for their base case. The company model also includes a switch which allows for the use of the utility values derived from the SBS-QoL responses in STEPS, the results of which are presented as scenario analyses.

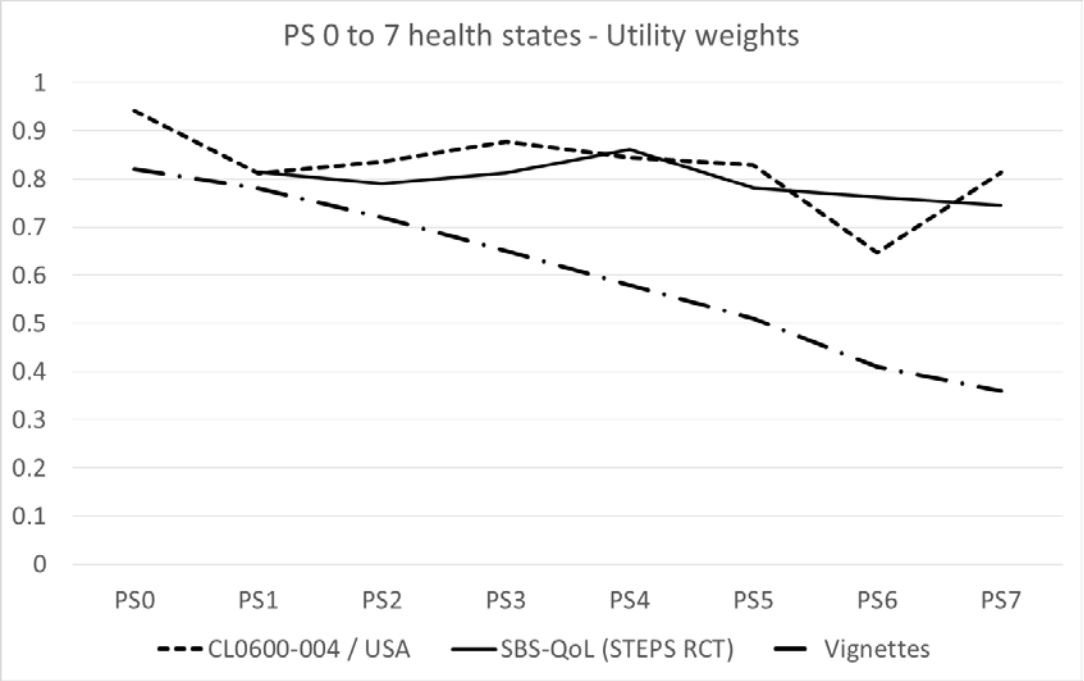


Figure 7 Alternative sets of health state utility values by level of PS dependence

Adverse events

Utility weights for adverse reactions were obtained from one of three sources: the catalogue of EQ-5D scores for the UK[62] the company submission for NICE TA342 (vedolizumab for treating moderate to severe active Crohn's disease after prior therapy),[63] and a systematic review of studies assessing the health related quality of life impact of urinary tract infections.[64] The catalogue of EQ-5D scores for the UK relies on regression modelling of EQ-5D data collected from various sources to obtain utility weight decrements (based on UK valuations) for different health conditions. Data from NICE TA352 were used to value the most severe adverse events; i.e. bacteraenemia, catheter-related infection, central line infection, bacterial overgrowth and upper respiratory tract infection. Utility decrements for all these severe adverse events were set at -0.52. The source of this utility weight is the study by Brown et al.[65] which elicited valuations from a sample of 30 oncology nurses in the UK using the standard gamble method. In Brown's study, an "infection without hospitalisation" was valued at 0.48. The company submission for NICE TA342 calculated the decrement of 0.52 the relative to full health (=1 - 0.48), which assumes individuals are in full health before they experience an infection without hospitalization - the maximum possible decrement.[63] The ERG note that NICE DSU TSD 12 states that "*it is inappropriate to assume that baseline is perfect health if an individual does not have*

a specific health condition". Therefore, the utility reduction should have been calculated from the mean utility weight for adult individuals with SBS-IF.[60]

Finally, it was not possible to marry the utility decrements for urinary tract infection in the current company submission with those reported in Bermingham et al.[64] Adverse event utility decrements in the model are applied for the entire duration of the cycle in which they occur. There is limited justification provided in the company submission for this assumption, but based on the ERGs clinical advice, it may overestimate QALY losses associated with some complications but potentially underestimate losses associated with other. On balance, it therefore appears reasonable.

Paediatric model

The company identified in their SLR three studies that reported potentially relevant quality of life data for the paediatric population. The earlier study was published in 1984[66] and was designed to capture changes in morbidity and mortality associated with PS; however, the study period was 1973 to 1983 and given the improvements in PS from the 1970s the study findings were deemed irrelevant and not incorporated in the de novo analysis. The second study identified was conducted in The Netherlands,[67] and did not include the EQ-5D and therefore did not meet the NICE reference case. Finally, a third study conducted in Manchester Royal Children's hospital had a small sample size (N=20) and used a modified version of an existing questionnaire[68] to assess the effect of anti-gastroesophageal reflux procedures on caregivers' perceptions of their child's and their own physical wellbeing and the QoL. As none of the study methods met the NICE reference case the same utility weights as used for the adult population were applied in the paediatric model.

Carer utilities

The company submission states that SBS-IF affects not only the patient but also the QoL of carers. To quantify this impact the company asked a panel of experts using a Delphi process, to give estimates of HSUVs of carers for patient with SBS-IF with low (1-2 days), medium (3-5 days) or high (6-7 days) PS requirements. Participants were instructed to give their valuations on the scale where zero represents death and one represents perfect health. The mean and range of the elicited values are

reproduced below in Table 18. While the Delphi process is a technique to reach consensus between a number of individuals, it is not a choice based preference elicitation technique. In addition, the Delphi was conducted with experts. This is not in line with the NICE reference case which stipulates that health state values should reflect the preferences of a representative sample of the public. The company also considered a scenario analysis where the values obtained from the Delphi process were adjusted by the age specific utility (0.85) for a person of 50 years. These values are also reported in Table 18 below.

Table 18 Carer health state utilities estimated by the Delphi panel (Source: company submission Table 58, page 209)

Health state	Mean	Range	With correction for general population applied (scenario analysis)
Carer/family member of a low-volume patient	0.89	0.85-0.98	0.757
Carer/family member of a mid-volume patient	0.77	0.70-0.90	0.655
Carer/family member of a high-volume patient	0.67	0.50-0.80	0.570

To help inform carer utilities in the model, the company also conducted a survey of carers of SBS-IF patients in the UK using the EQ-5D instrument. This survey was based on a small sample which may explain the inconsistent relationship observed between level of PS dependence and the mean EQ-5D scores (Table 19).

The final HSUVs applied for carers in the model were taken as the midpoint between those elicited from the Delphi process and mean EQ-5D values based on the carer survey. These final values are presented in the Table 20 below. The company produced a number of sensitivity analyses using alternative value sources as well as an age adjustment using the mean EQ-5D population norm for people aged 50 in the UK (i.e. 0.85).

Table 19 EQ-5D utilities from carer HRQL study (Source: company submission Table 59, page 209)

Days/Nights on PS	Mean	SD	With correction for general population applied (scenario analysis)
2 days (n=2)	1.00	0.00	0.850
3 days (n=10)	0.89	0.11	0.757
4 days (n=5)	0.77	0.26	0.655
5 days (n=9)	0.97	0.09	0.825
6 days (n=11)	0.89	0.11	0.757
7 days (n=10)	0.88	0.12	0.748
Key: HRQL, health-related quality of life; n, number; PS, parenteral support; SD, standard deviation			

Table 20 Carer utilities applied in the model base case (Source: company submission Table 60, page 210)

Health State	Carer utility study	Delphi panel	Midpoint
0 days on PS	Assumed 1	1	1
1 day on PS	Assumed 1	0.89	0.95
2 days on PS	1	0.89	0.95
3 days on PS	0.89	0.89	0.86
4 days on PS	0.77	0.77	0.72
5 days on PS	0.97	0.77	0.81
6 days on PS	0.89	0.67	0.75
7 days on PS	0.88	0.67	0.74
Key: PS, parenteral support			

Incorporation of carer utilities in the economic model

The company submission notes that carer utility weights were incorporated using a novel approach, where the absolute value was assumed up to time of the patients death, instead of the usual methods of applying a utility decrement up to the time of death. The company submission states that "*This new approach was adopted as to*

prevent the life-extending nature of teduglutide resulting in a negative relative impact on QALYs, as an extension of life would mean the inclusion of caregiver utility decrements for a longer duration". The company submission provides a hypothetical illustrative example reproduced in Table 21 below. The example shows how the standard approach applies a disutility to the intervention arm during the period of extended survival (year 3) when no disutility is applied to the comparator arm. The new method conversely applies a substantial QALY gain over the comparator arm during the period of extended survival. This seems somewhat counterintuitive to the ERG, because it appears to assume the carer's entire health state utility is attributable to the intervention during the period of extended survival when no carer utility is being counted in the comparator arm. There does not appear to be strong justification for this assumption and it will potentially exaggerate carer QALY gains associated with the intervention.

Table 21 Fictional example of different methods of including caregiver utilities (Source: company submission Table 57, page 208)

QALYs		**No carer utilities applied**			**'Standard' application of carer utilities**			**New method of applying carer utilities**		
		Year 1	**Year 2**	**Year 3**	**Year 1**	**Year 2**	**Year 3**	**Year 1**	**Year 2**	**Year 3**
Intervention	Patient	0.65	0.65	0.65	0.65	0.65	0.65	0.65	0.65	0.65
	Carer	0	0	0	-0.10	-0.10	-0.10	0.9	0.9	0.9
Comparator	Patient	0.60	0.60	0	0.60	0.60	0	0.60	0.60	0
	Carer	0	0	0	-0.20	-0.20	0	0.8	0.8	0
Sum of QALY difference between the arms		0.75			**0.85**			**1.85**		
Key: QALYs, quality-adjusted life years										

5.2.8 Resources and costs

The company submission describes a systematic review of the literature for costs and resource use associated with SBS-IF. The methods were discussed under 5.1. Five studies were included for the adult population, and eight were included for the

paediatric population. The company noted that of the studies identified in the adult population, two reported on the length of hospitalisation, two focussed on catheter days for patients on home parenteral nutrition, and one focused on post-transplant duration of parenteral and enteral nutrition. The ERG further note that two of the identified studies were only published in abstract from, providing limited details on methods and findings.

The company also reported that most of the studies identified for the paediatric population were conducted outside the UK, and were therefore not included in the de novo economic analysis. Details on all the identified studies are presented in Tables 62 and 63 on the company submission.

Treatment costs

The list price for teduglutide is £521.98 per vial containing 5mg of the drug. The recommended daily dose is 0.05mg/kg body weight, so a single vial can provide the recommended dose for patients weighing up to 100 kg. The model makes the assumption that one vial per day is sufficient to meet the daily dose requirement for all patients. A smaller vial containing 1.25mg of teduglutide is also available for paediatric patients weighing less than 20kg, at a list price of £260.99 per vial. The company report that all patients aged 6 years and over in CL13-003 weighed greater than 20kg, and so all patients aged 6 and over in the paediatric model are assumed to require the larger vial, while all patients less than 6 years are assumed to require the smaller vial. The ERG considered the potential for these assumptions to underestimate teduglutide costs in the paediatric population, since an increasing proportion of children under the age of 6 will be breaching the 20kg threshold as they age. However, consultation of UK population growth charts shows that ~40% of 6 year olds would still be expected to weigh less than <20kg, and not until approximately 9 years of age will 100% of children weigh greater than 20kg. Therefore, the company's assumptions are probably reasonable.

A simple PAS discount of [redacted] has been agreed with the department of health, making the cost per 5mg vial [redacted] and the cost per 1.25mg vial [redacted]. Using the company's dosing assumptions, the teduglutide acquisition cost per 28 days cycle in the model is [redacted] for children below the age of 6 and [redacted] for children

aged 6 years and over and adults. Scaling up, this equates to annual drug acquisition costs of [redacted] and [redacted] per year on treatment respectively. The drug acquisition costs assume zero wastage among those who stop treatment, which may be unrealistic. This could potentially reduce drug acquisition costs, particularly in the paediatric population.

Administration and monitoring

The company submission notes that administration of teduglutide is associated with no specific costs other than one initial nurse led appointment to instruct patients on how to administer the treatment. The once off hourly cost of a community nurse (£50) is applied for this purpose at the start of treatment. Regarding the administration arrangements for teduglutide, section 2.4.1 of the company submission states that: "*teduglutide is delivered as a subcutaneous injection. For this, Shire will be providing training to the homecare nurses and specialist centre nurses so that subsequently, they can train the patients on how to administer teduglutide themselves. As such, it is not anticipated that there will be a disruption in administration.*"

With respect to monitoring of patients on teduglutide, section 2.4.1 of the company submission outlines a number of additional tests, investigations and administration requirements that may be necessary for patients on teduglutide. These include: monitoring for colorectal polyps; monitoring for gastrointestinal neoplasia; monitoring of the small bowel, gallbladder, bile ducts, and pancreas; monitoring for intestinal obstruction; monitoring patients with cardiac insufficiency and hypertension for fluid overload, particularly during the initiation period; evaluation of fluid status following any reductions in PS; close monitoring of concomitant medications requiring titration or a narrow therapeutic window (due to potential for increased absorption); and advised caution when prescribing teduglutide to patients with severe concomitant diseases. The company submission (section 2.4.3) goes on to state that: "*No changes to the way services are organised or delivered are anticipated. However, additional monitoring will be required (as detailed in Section* ***Error! Reference source not found.****) when eligible patients are initiated on teduglutide. To support this, a home care service will be provided and paid for by Shire.*"

However, little detail is provided on the nature of this home care service, and to what extent it will be able to meet all of these additional monitoring demands. It is therefore unclear to the ERG whether the NHS may bear further monitoring costs that have not been included in the model. The only additional monitoring cost that has been included for teduglutide in the economic model is a colonoscopy at initiation of treatment, and again at 1 year, 2 years and then every 5 years thereafter.

Health state costs

The costs of providing parenteral support (by days per week) are one of the key cost drivers in the economic model. The provision of PS is resource intensive and results in significant costs to the health service. One of the key value propositions for teduglutide is a reduction in PS costs associated with a reduced level of dependence.

The company submission notes that the costs of PS were taken from costing studies undertaken to inform the submission; one for the adult population and one for the paediatric population. The adults study utilised data on key resources driving the cost of home PS, collected from four gastroenterologists, five nurses, one pharmacist and one dietician from specialised intestinal failure centres. The paediatric studies utilised data from six consultant gastroenterologists, two nurses, one pharmacist, and two dietitians. This allowed low (three days of PS per week), medium (five days PS per week) and high (seven days PS per week) cost PS scenarios to be constructed based on PS requirements, additional drug usage, and line complications other than those included as AEs in the economic model. In the adult model, health state costs for the remaining PS dependence states were derived by linear interpolation, assuming zero cost for the no PS state. The resultant annual costs and 28 day cycle cost are presented in Tables 66 to 69 of the company submission.

The company submission and the costing reports (Parexcel Access Consulting, 2017)[5] did not provide detailed information on the resource use estimates and unit costs used to work up the scenarios. In response to a clarification request, the company provided a more detailed breakdown of these data (replicated in Tables 22 and 23 below). Given the limited methodological detail provided in the SBS-IF costing study reports and the detailed data required for costing purposes, justification for some of the resource use estimates (by level of PS dependence) remains unclear to the ERG

(Parexcel Access Consulting, 2017).[5] For example, the costing report for adults clearly states that "*infections are not correlated with disease severity or PN nights; they are related to the patients thoroughness in taking care of the line*". It also states that 7-10% of patients would be expected to get this complication per year, with most patients likely to have one infection every few years. Yet the health state costing assumptions assume that only those in the high dependence group (PS seven days per week) incur this high cost complication, at a rate of 2 episodes per year, with 14 days per year in intensive care. Further variations in resource use by level of dependence (Tables 22 and 23), which have not been fully justified, are: 1) an approximately three times higher nursing hour requirement of those on PS seven days a week compared to those on PS five days a week; 2) the variable distribution of Taurolock use across the dependence states; 3) the additional medication costs in the mid to high dependence PS states but none in the lower dependence state; 4) the higher number of specialist visits assumed for the high dependence state in the adult population; and 5) the unequal incidence of suspected sepsis by level of PS dependence in the paediatric population.

Table 22 Breakdown of adult health state costs reported and applied by the company (Source: adapted from Table 7 of the company response to clarification)

				Resource use per time unit			Annual Costs		
Cost category	**Cost item**	**Units**	**Cost per unit**	**Low PS (3 days/ week)**	**Mid PS (5 days/ week)**	**High PS (7 days/ week)**	**Low PS (3 days/ week)**	**Mid PS (5 days/ week)**	**High PS (7 days/ week)**
PN cost	PN bag (≥8 ingredients) band A	day/week	£119.03	3	5	7	£18,569	£30,948	£43,327
	Delivery	delivery/month	£77.50	2	2	2	£1,860	£1,860	£1,860
	Nurse time	hour/week	£99.64	0	5	**14**	£0	£25,906	£72,538
	Taurolock	day/week	£12.52	**3**	**0**	**7**	£1,953	£0	£4,557
Additional drigs	PPIs	day	£8.81	0	**1**	**1**	£0	£3,218	£3,218
	Antimotility agents	day	£10.85	0	**1**	**1**	£0	£3,963	£3,963
	Fragmin 5----unit (0.2mL syringe)	day	£2.82	0	**1**	**1**	£0	£1,030	£1,030
	Ondansetron	day	£22.78	0	**1**	**1**	£0	£8,320	£8,320
Monitoring costs	Specialist visits	Visit/year	£189.79	3	3	**4**	£569	£569	£759
Complications	Line sepsis	episode/year	£5,668.10	0	0	**2**	£0	£0	£11,336
	Line sepsis requiring critical care	day/year	£1,516.50	0	0	**14**	£0	£0	£21,231
	Line fracture occlusion	episode/year	£354.00	1	1	1	£354	£354	£354
				ERG estimated Total			**£23,305**	**£76,169**	**£172,494**
				Company reported total			**£23,305**	**£76,169**	**£172,494**
				Company modelled values			**£23,305**	**£76,369**	**£172,949**
				Discrepancy			**£0**	**£200**	**£455**

Note: Company costs for the PS1 and PS2 states in the adult model were derived by interpolation between the cost for PS3 and zero cost assumed for PS0. Costs for PS4 were derived by linear interpolation between the PS3 and PS5 costs, and costs for PS6 were derived by linear interpolation between PS5 and PS7.

Table 23 Breakdown of paediatric health state costs reported and applied by the company (Source: adapted from Table 7 of the company response to clarification)

				Resource use per time unit			Annual Costs		
Cost category	**Cost item**	**Unit**	**Cost per unit**	**Low PS (3 days/ week)**	**Mid PS (5 days/ week)**	**High PS (7 days/ week)**	**Low PS (3 days/ week)**	**Mid PS (5 days/ week)**	**High PS (7 days/ week)**
PN cost	PN bag (≥8 ingredients) band A	day/week	£119.03	3	5	7	£18,569	£30,948	£43,327
	Delivery	delivery/month	£77.50	2	2	2	£1,860	£1,860	£1,860
	Taurolock	day/week	£12.52	3	0	**7**	£1,953	£0	£4,557
Additional drigs	PPIs + H2 receptor blocker	day	£10.64	0	**1**	**1**	£0	£3,886	£3,886
	Antimotility agents	day	£5.42	0	**1**	**1**	£0	£1,980	£1,980
	Fragmin 5----unit (0.2mL syringe)	day	£2.82	0	**1**	**1**	£0	£1,030	£1,030
	Ondansetron	day	£11.39	0	**1**	**1**	£0	£4,160	£4,160
Monitoring costs	Haematology tests	tests/year	£3.10	4	4	4	£12	£12	£12
	Inflammatory markers	tests/year	£6.42	4	4	4	£26	£26	£26
	Clinical biochemistry	tests/year	£1.18	4	4	4	£5	£5	£5
	Specialist visits	Visit/year	£268.41	4	4	4	£1,074	£1,074	£1,074
Complications	Line sepsis	episode/year	£5,668.10	0	0	**2**	£0	£0	£11,336
	Line sepsis requiring critical care	day/year	£3,306.50	0	0	**14**	£0	£0	£46,291
	Suspicion of sepsis	episode/year	£2,343.50	**1**	**1**	0	£2,344	£2,344	£0
	Line fracture occlusion	episode/year	£654.00	1	**2**	**2**	£654	£1,308	£1,308
				ERG estimated Total			**£26,496**	**£48,632**	**£120,852**
				Company reported total			**£26,495**	**£48,633**	**£120,852**

Notes: The costed scenarios were mapped directly to the health states utilised in the paediatric model: low PS (1-3 days per week), mid PS (4-5 days per week), and high PS (6-7 days per week).

A further problem with the annual health state costs relate to a slight mismatch between some of the annual estimated values reported for adults in the company submission and the costs actually applied in the model (discrepancies highlighted in Table 22 above). For example, based on the reported annual resource inputs and unit costs for health state PS7, the total annual cost comes to £172,494 as reported in the company submission and cross checked by the ERG. However, £172,949 is the value applied in the model. Similarly the annual cost of health state PS3 is £200 higher in the model compared with the company reported value and ERG cross checked value. While the ERG have not been able to clarify the reason for the discrepancy, we assume that that the total annual values reported in the company submission, and in response to clarification (replicated in Tables 22 and 14 above), are correct. Thus, the ERG uses the detailed data presented in Tables 22 and 23 to work up any further exploratory scenarios surrounding the costing assumptions by level of PS dependence.

Adverse event costs

Costs of the different types of adverse events are derived from a number of sources, and are combined with cycle specific incidence rates to estimate the total cost of adverse events per cycle (by the treatment arm). The unit costs applied to adverse events are presented in Table 71 of the company submission. Some minor events are assumed to have zero cost based on the opinions of experts attending a face to face Delphi meeting. The same adverse event unit costs were applied in both the adult and paediatric models. The ERG has no major issues with the general approach to estimating costs associated with adverse events but, as indicated above, do have concerns regarding the incidence rates applied in the respective arms of model, and the decision to include only those events occurring in 5% or more of the cohort.

Costs of associated complications

Further costs applied in the economic model include the cost of dialysis for the proportion of the cohorts modelled to have stage five CKD, and the cost of IFALD for the proportion modelled to suffer from this complication.

The applied costs of dialysis are reported to have been calculated by taking a weighted average of all the NHS reference costs for chronic dialysis (LD01A and LD13A). However, the reported costs are much higher than expected; £3,690 per 28 day cycle (£47,970 per year) in adults and £6,624 per cycle (£86,112 per year) in children. The ERG suspect that the reference costs for haemodialysis (HD) may have been treated as a daily cost rather than

costs per session, of which dialysis patients generally have three per week. Recalculating dialysis costs, assuming 3 sessions of HD per week, and daily peritoneal dialysis (PD) weighted by activity, the ERG generate average estimates of £1,870 per 28 day cycle (£24,399 per year) for adults and £4,229 per cycle (£54,971 per year) for children. The ERG explore the impact of applying these alternative values.

The unit cost (per cycle) associated with IFALD is a weighted average of costs per month, derived from a study by Crossan et al.[69] for those with non-progressed liver disease, fibrosis, and cirrhosis (see Table 70 of the company submission). The cycle costs for these three sub-states are weighted by the proportion of time that patients with liver disease would be expected to spend in each. The proportions of time in each sub-state are in turn derived from data on rates of LD progression calibrated on data reported by Cavicchi et al.[70] Of note, the methodology does not appear to account for correlations between disease severity and mortality, which may overestimate the average costs of IFALD, as those in the more costly end stage may not survive as long as those in the less severe states. The approach to costing IFALD is the same in both the adult and the paediatric models.

5.2.9 Cost effectiveness results

Adult model

Table 24 replicates the company cost-effectiveness results as shown in Table 74 of the company submission, with the confidential patient access scheme applied. Teduglutide generates 0.55 incremental life years and 2.6 incremental QALYs. The incremental QALY consists of a gain of 1.56 QALYs for patients and a gain of 1.04 for carers. The total incremental cost is [redacted], giving an incremental cost-effectiveness ratio of £193,548 (including patient and carer QALY gains).

Table 24 Company discounted base case results (Source: company submission Table 74, page 232)

		Standard care	Teduglutide
Costs		£1,173,684	[redacted]
LYs	**Patient**	8.76	9.31
	carer	8.76	9.31
QALYs	**Patient**	3.43	4.99
	Carer	6.66	7.69
Incremental	**Costs**	-	[redacted]
	LYs	-	0.55
	QALYs	-	2.60
ICER		-	£193,549
Key: ICER, incremental cost-effectiveness ratio; LYs life years; QALYs, quality-adjusted life years.			

The company submission provides further model outputs in terms of clinical outcomes (days on PS) at time points corresponding to the trial follow-up periods (Table 75 of the company submission), Markov traces (Figure 22 and 23 of the company submission), a breakdown of QALYs and life-years by health state (Tables 76 and 77 of the company submission), and a breakdown of costs by cost categories (Table 78 of the company submission) and health states (Table 79 of the company submission). The breakdown of QALYs by health state is reproduced below in Table 25. It can be noted that the greatest percentage of the QALY gain accrues to the proportion of patients in the teduglutide arm achieving PS independence (No PS).

Table 25 Summary of discounted QALY gain by health state for a 40-year time horizon (Source: company submission Table 76, page 235)

Health state	QALYs – Teduglutide	QALYs – Standard care	Increment	Absolute increment	% absolute increment
No PS	1.67	0.00	1.67	1.67	41%
PS 1 day per week	0.13	0.00	0.13	0.13	3%
PS 2 days per week	0.29	0.01	0.28	0.28	7%
PS 3 days per week	0.65	0.59	0.06	0.06	1%
PS 4 days per week	0.76	0.62	0.14	0.14	3%
PS 5 days per week	0.23	0.26	-0.03	0.03	1%
PS 6 days per week	0.26	0.59	-0.33	0.33	8%
PS 7 days per week	1.06	1.45	-0.39	0.39	9%
IFALD	-0.03	-0.04	0.01	0.01	0%
CKD	-0.03	-0.04	0.01	0.01	0%
Subtotal patient QALYs	**4.99**	**3.43**	**1.56**	**3.04**	**75%**
Carer QALYs	7.69	6.66	1.04	1.04	25%
Total	**12.68**	**10.09**	**2.60**	**4.08**	**100%**

Key: CKD, chronic kidney disease; IFALD, intestinal failure-associated liver disease; PS, parenteral support; QALY, quality-adjusted life year.

Table 26 reproduces the breakdown of costs by cost category, which reveals the key drivers of the incremental cost. It can be noted that drug acquisitions costs are the largest driver, followed by the PS health state costs (which favour teduglutide) and the adverse event costs (which also favour teduglutide). The model projects that over a 40 year time horizon, teduglutide will reduce PS costs by an average of £336,785 (net present value) per patient, partly offsetting the incremental cost of drug acquisition. The further substantial cost saving comes through the lower adverse event burden included for teduglutide in the model (-£25,313 per patient).

Table 26 Summary of incremental discounted costs by cost category for a 40-year time horizon (Source: company submission Table 78, page 236)

Cost category	Costs – Teduglutide	Costs – Standard care	Increment	Absolute increment	% absolute increment
Teduglutide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Teduglutide administration training	£50	£0	£50	£50	[redacted]
Colonoscopy	£1,852	£0	£1,852	£1,852	[redacted]
PS	£762,201	£1,098,986	-£336,785	£336,785	[redacted]
IFALD	£4,650	£6,538	-£1,887	£1,887	[redacted]
CKD	£11,800	£16,569	-£4,769	£4,769	[redacted]
Adverse events	£26,278	£51,591	-£25,313	£25,313	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: CKD, chronic kidney disease; IFALD, intestinal failure-associated liver disease; PS, parenteral support.

Paediatric model

Table 27 replicates the company base case cost-effectiveness results for the paediatric cohort as shown in Table 80 of the company submission, with the confidential patient access scheme applied. Teduglutide generates 0.27 incremental life years and 2.57 incremental QALYs and an incremental cost of [redacted] versus standard care. The corresponding ICER comes to £111,045 per QALY gained.

Table 27 Discounted paediatric base-case results for a lifetime time horizon (Source: company submission Table 80, page 237)

		Standard care	Teduglutide
Costs		£1,643,061	[redacted]
LYs	**Patient**	14.20	14.47
	carer	14.20	14.47
QALYs	**Patient**	5.35	7.11
	Carer	9.50	10.30
Incremental	**Costs**	-	[redacted]
	LYs	-	0.27
	QALYs	-	2.57
ICER		-	£111,045
Key: ICER, incremental cost-effectiveness ratio; LYs life years; QALYs, quality-adjusted life years.			

The further clinical outputs (days on PS), LY, QALY and cost breakdowns are provided in Tables 81-85 of the company submission. Figures 24 and 25 of the company submission provide the Markov traces for the teduglutide and standard care arms of the model respectively. Table 28 below reproduces the breakdown of the QALY gains by health state. As with the adult model, the greatest percentage of the absolute increment accrues to patients achieving PS independence (No PS).

Table 29 below reproduces the cost breakdown by cost category for the paediatric model. Again, this shows the teduglutide acquisition costs to account for the greatest proportion of the increment, followed by the PS health state costs and the adverse event costs, both of which favour teduglutide. The CKD costs also account for a slightly greater proportion of the incremental cost than they do in the adult model, which likely reflects the higher costs of dialysis in paediatric patients. Over the lifetime horizon, the model projects that teduglutide will generate PS cost savings of £384,703 per patient, adverse event cost savings of £25,820 per patient, and dialysis cost saving of £21,311 per patient, partly offsetting the teduglutide acquisition costs.

Table 28 Summary of discounted QALY gain by health state for a lifelong time horizon (Source: Table 82 of the company submission)

Health state	QALYs – Teduglutide	QALYs – Standard care	Increment	Absolute increment	% absolute increment
No PS	2.70	0.00	2.70	2.70	56%
Low PS	0.01	0.00	0.01	0.01	0%
Mid PS	0.48	0.64	-0.16	0.16	3%
High PS	2.96	3.94	-0.98	0.98	20%
ITx	0.00	0.00	0.00	0.00	0%
IFALD	1.12	0.93	0.19	0.19	4%
CKD	-0.07	-0.08	0.01	0.01	0%
Subtotal (patient QALYs)	**7.11**	**5.35**	**1.77**	**4.05**	**84%**
Carer QALYs	10.30	9.50	0.80	0.80	16%
Total	**17.41**	**14.84**	**2.57**	**4.85**	**100%**

Key: CKD, chronic kidney disease; IFALD, intestinal failure-associated liver disease; ITx, intestinal transplantation; L, Litre; PS, parenteral support; QALY, quality-adjusted life year.

Table 29 Summary of incremental discounted costs by cost category for a lifelong time horizon (Source: company submission Table 84, page 241)

Cost category	Costs – Teduglutide	Costs – Standard care	Increment	Absolute increment	% absolute increment
Teduglutide	[redacted]	£0	[redacted]	[redacted]	[redacted]
Teduglutide administration training	£50	£0	£50	£50	[redacted]
Colonoscopy	£1,624	£0	£1,624	£1,624	[redacted]
PS	£1,052,713	£1,437,416	-£384,703	£384,703	[redacted]
ITx	£62,177	£51,700	£10,477	£10,477	[redacted]
IFALD	£9,781	£14,687	-£4,906	£4,906	[redacted]
CKD	£43,467	£64,778	-£21,311	£21,311	[redacted]
Adverse events	£48,661	£74,481	-£25,820	£25,820	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: CKD, chronic kidney disease; IFALD, intestinal failure-associated liver disease; ITx, intestinal transplantation; L, Litre; PS, parenteral support.

5.2.10 Sensitivity analyses

The company submission reported results for deterministic sensitivity analysis (one-way and scenario analyses) and probabilistic sensitivity analyses for the adult and paediatric models.

PSA adult model

The company submission base case results based on 10,000 probabilistic iterations are summarised in Figures 8 and 9. Teduglutide is associated with an expected incremental cost of [redacted] (95% CI: £[redacted]), similar to the base case estimate of [redacted]. The mean incremental QALY estimate of 2.25 (95% CI: 1.26 – 3.52) is somewhat lower than the 2.60 in the deterministic analysis. The company states that this is due to the Bayesian approach to modelling the uncertainty surrounding transition probabilities. Patients in the PSA have a higher probability of transitioning back up to higher levels of PS dependence over time than in the deterministic analysis based on point estimates of the observed transition probabilities. Consequently the probabilistic ICER comes to £222,971, which is higher than the £193,549 in the deterministic analysis.

Key: ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life years.
Note: The dashed red line represents the 95% confidence ellipse surrounding the probabilistic ICER, signified by a blue square; the red triangle represents the deterministic ICER estimate.

Figure 8 Adult model – incremental cost-effectiveness plane (10,000 PSA simulations) (Source company submission – Figure 26)

Figure 9 Adult model - cost-effectiveness acceptability curve (Source company submission – Figure 27)

Deterministic SA adult model

Using the upper and lower credible values for each parameter, the company also conducted one-way sensitivity analyses. Table 30 states the one-way sensitivity analyses conducted while Figure 10 shows a tornado diagrams which illustrate the parameters that have the biggest effect on model results. The tornado diagram shows, on the x-axis, the incremental net monetary benefit. Namely, the incremental QALYs valued at £30,000 minus the incremental cost. If positive (negative), it shows how much more (less) cost-beneficial teduglutide is compared with standard care.

The tornado diagram shows that,

[redacted].

Table 30 List of variables included in deterministic sensitivity analysis (Source – company submission Table 86)

Parameter group	Distribution	Rationale
Discount rate for costs and health benefits	No distribution, varied from 0 to 6%	As per NICE guidance
Transition probabilities	Dirichlet with cumulative gamma	Based upon available trial data
Survival for PS0 and PS1-7	Multivariate normal distribution: 95% CI, based on trial data	Based upon available trial data
Cycle probabilities of AEs	Beta distribution: 95% CI, based on trial data	Based upon available trial data
The utility value for each health state	Beta distribution: 95% CI, SE assumed 20% of the mean	Assumption
The utility decrements for AEs	Beta distribution: 95% CI, based on trial data	Assumption
The cost of resource use	Gamma distribution: 95% CI, SE assumed 20% of the mean	Assumption
The cost of PS	Gamma distribution: 95% CI, based on trial data	Assumption
The cost of AEs	Gamma distribution: 95% CI, SE assumed 20% of the mean	Assumption
Key: AEs, adverse events; CI, confidence interval; PS, parenteral support; SE, standard error.		

Key: PS, parenteral support.

Figure 10 Tornado diagram (adult model) (Source – company submission Figure 28)

Scenario analysis adult model

The company carried out several scenario analyses to investigate sensitivity to structural uncertainties and assumptions applied in the adult model. The scenarios considered by the company are listed in Table 31 below. The corresponding results are presented in Table 32. The scenario where the annual discount rate for health outcomes was reduced to 1.5% resulted in the lowest ICER (£151,479). Removal of carer utilites generated the highest ICER £322,059 followed by the scenario where patient utility weights were mapped from SBS-QoL responses from the STEPS trial data (ICER = £272,914).

Table 31 Scenario analyses for the adult model (Source – company submission Table 72)

Scenario	Description
Length of model time horizon	Four scenarios are presented for different time horizons of 10, 20, 30 and 50 years, to examine the sensitivity of results to the extrapolation of efficacy and costs
No discounting	Instead of applying a discount rate of 3.5% to costs and health outcomes, no discount rates are applied
1.5% discount rate for health outcomes	Instead of applying a discount rate of 3.5%, a discount rate of 1.5% is applied to health outcomes (costs are still discounted at 3.5%)
No stopping rule	All patients who start treatment with teduglutide continue treatment until they die
Stopping rule at 12 months	The stopping rule is applied at 12 months instead of 24 weeks
Stopping rule at 24 months	The stopping rule is applied at 24 months instead of 24 weeks
No IFALD	It is assumed that patients do not develop liver disease
Mortality rates IFALD based on Delphi	The mortality rates for IFALD estimated by the Delphi panel are used instead of making the assumption that mortality of patients with IFALD is equal to that of PS-dependent patients.
No CKD	It is assumed that patients do not develop kidney disease
ITx included	It is assumed that some patients require ITx
Extrapolation teduglutide: Last observed transitions carried forward	It is assumed that patients treated with teduglutide continue to transition between PS health states as they did between Months 27 and 30 for the entire model time horizon
Extrapolation standard care: PS-requirement maintained beyond 24 weeks	It is assumed that patients treated with standard care maintain the same PS requirement as they had in Week 24
Survival curve fit	Five scenarios are presented for different curve fits to the survival curves: exponential, gamma, Gompertz, log-logistic, Weibull
Patient utilities	HRQL from STEPS, mapped to EQ-5D utilities are used for patient HRQL
Carer utilities 1	Utilities excluded for carers
Carer utilities 2	Carer utilities based on Delphi panel only

Scenario	Description
Carer utilities 3	Carer utilities based on carer utility study only
Carer utilities 4	Base utility value of 0, only utility decrements applied
Carer utilities 5	Age-adjusted carer utility
PS costs	Complication costs excluded from PS costs
Key: CKD, chronic kidney disease; HRQL, health-related quality of life; IFALD, intestinal failure-associated liver disease; ITx, intestinal transplantation; NHS, National Health Service; PS, parenteral support.	

Table 32 Results of scenario analyses for the adult model (Source – company submission Table 87)

Base case setting	Scenario setting	Incremental		ICER
		Costs	QALYs	
Base case model	N/A	[redacted]	2.43	£193,549
Time horizon: 40 years	10 years	[redacted]	1.32	£245,363
	20 years	[redacted]	2.07	£208,850
	30 years	[redacted]	2.45	£197,313
	50 years	[redacted]	2.62	£192,975
Uniform discount rate: 3.5%	No discounting	[redacted]	4.10	£174,853
	Discount rate health outcomes: 1.5%	[redacted]	3.32	£151,479
Teduglutide stopping rule applied at 24 weeks	Teduglutide stopping rule not applied	[redacted]	3.38	£196,388
	Stopping rule applied at 12 months	[redacted]	3.30	£187,605
	Stopping rule applied at 24 months	[redacted]	3.37	£186,775
Liver disease development based on Delphi meeting rates, mortality equal to SBS-IF population	Liver disease: not included	[redacted]	2.59	£194,861
	Delphi panel mortality rates	[redacted]	2.60	£193,509
CKD: Included	CKD: excluded	[redacted]	2.59	£196,081
ITx: Excluded	ITx: Included	[redacted]	2.62	£191,026
PS requirement maintained for teduglutide patients beyond 30 months	Last observed teduglutide transitions carried forward	[redacted]	2.83	£182,536
Standard care patients revert to baseline PS requirement beyond 24 weeks	PS-requirement maintained for standard care patients beyond 24 weeks	[redacted]	2.29	£238,519
	Exponential	[redacted]	3.05	£166,003

Base case setting	Scenario setting	Incremental		ICER
		Costs	QALYs	
Survival curve: log-normal	Gompertz	[redacted]	1.98	£232,352
	Weibull	[redacted]	2.36	£195,666
	Log-logistic	[redacted]	2.49	£197,450
	Gamma	[redacted]	2.74	£193,719
Patient utilities from vignette study	Patient utilities from mapped STEPS trial data	[redacted]	1.84	£272,914
Utility decrements for carers, base utility of 1	No utilities considered for carers (Carer utilities 1)	[redacted]	1.56	£322,059
	Utility decrements with base of 0 for carers (Carer utilities 2)	[redacted]	2.05	£245,189
Carer utilities based on midpoint between Delphi panel and carer utility study	Carer utilities based on Delphi panel (Carer utilities 3)	[redacted]	2.76	£182,152
	Carer utilities based on carer utility study (Carer utilities 4)	[redacted]	2.44	£206,468
	Ade-adjusted carer utilities (Carer utilities 5)	[redacted]	2.39	£210,067
PS costs include complication costs	Complication costs excluded from PS costs	[redacted]	2.60	£216,467

Key: AEs, adverse events; CKD, chronic kidney disease; ITx, intestinal transplantation; LYs, life years; p.a., per annum; PS, parenteral support; QALYs, quality-adjusted life years.

PSA paediatric model

The company also conducted probabilistic sensitivity analysis based on 10,000 iterations for the paediatric model. Incremental mean costs were £[redacted] (95% CI: [redacted]), and incremental mean QALYs were 1.83 (95% CI: -0.186 – 5.342), resulting in a probabilistic ICER of £143,851. The mean PSA ICER is higher than the deterministic base case ICER of £111,045. The rationale for the higher ICER for the PSA is similar to that exposed for the adult model: "is due to the allowance of non-observed transitions within the Dirichlet distribution used to sample the uncertainty around the model transition matrices". Figure 11 below reproduces the company's scatter plot of the probabilistic incremental cost-effectiveness results in the paediatric population.

Key: ICER, incremental cost-effectiveness analysis; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year.
Note: The 95% confidence ellipse is signified with a red dashed line.

Figure 11 Paediatric model - incremental cost-effectiveness plane (10,000 PSA simulations) (Source – company submission Figure 30)

Deterministic analysis Paediatric model

The same parameters varied in the adult model (Table 30 above) were also varied in one-way sensitivity analysis in the paediatric model. As the company submission notes, the annual costs of high dependence PS and annual cost and effect discount rates are the parameters which exert the greatest impact on the net monetary benefit at a willingness to pay threshold of £30,000. The company's tornado diagram is reproduced as Figure 12 below.

Key: PS, parenteral support

Figure 12 Tornado diagram (paediatric model)

Scenario analysis paediatric model

Again, similar scenario analyses were applied in the paediatric model as were applied in the adult model. The results of these are reproduced in Table 33 below. Of the scenarios assessed by the company, removal of the teduglutide stopping rule was found to generate the highest ICER (ICER = £407,215), followed by the omission of intestinal transplant as an event in the model (ICER £198,472), and then using patient utilities derived from SBS-QoL responses in STEPS (ICER £188,734). Applying the last observed teduglutide transition matrix carried forward over the entire model time horizon resulted in the lowest ICER to £67,700.

Table 33 Results of scenario analyses (Source – company submission Table 88)

Base case setting	Scenario setting	Incremental		ICER
		Costs	QALYs	
Base case model	N/A	[redacted]	2.61	£109,230
Time horizon: 96 years	30 years	[redacted]	1.98	£134,963
	50 years	[redacted]	2.36	£117,488
	70 years	[redacted]	2.55	£110,828
Uniform discount rate: 3.5%	No discounting	[redacted]	6.65	£70,348
	Discount rate health outcomes: 1.5%	[redacted]	4.13	£69,030
Teduglutide stopping rule applied at 12 weeks	Teduglutide stopping rule not applied	[redacted]	1.30	£407,215
	Stopping rule applied at 24 weeks	[redacted]	2.49	£134,410
Liver disease included	Liver disease: not included	[redacted]	2.53	£112,312
CKD: Included	CKD: excluded	[redacted]	2.60	£117,802
ITx: Included	ITx: Excluded	[redacted]	3.25	£198,472
	ITx + ITx waiting list included	[redacted]	4.10	£125,689
PS requirement maintained for teduglutide patients beyond 12 weeks	Last observed teduglutide transitions carried forward for entire model time horizon	[redacted]	3.21	£67,700
	Last observed teduglutide transitions carried forward until 30 months	[redacted]	3.10	£73,315
Standard care patients revert to baseline PS requirement beyond 24 weeks	PS-requirement maintained for standard care patients beyond 24 weeks	[redacted]	2.50	£132,360
Survival curve: log-normal	Exponential	[redacted]	3.24	£105,838
	Gompertz	[redacted]	0.98	£174,888
	Weibull	[redacted]	2.22	£122,793
	Log-logistic	[redacted]	2.42	£112,351
	Gamma	[redacted]	2.85	£103,150
Patient utilities from Vignettes study	Patient utilities from mapped STEPS trial data	[redacted]	1.51	£188,734

Utility decrements for carers, base utility of 1	No utilities considered for carers (Carer utilities 1)	[redacted]	1.81	£157,476
	Utility decrements with base of 0 for carers (Carer utilities 2)	[redacted]	2.65	£107,380
Carer utilities based on midpoint between Delphi panel and carer utility study	Carer utilities based on Delphi panel (Carer utilities 3)	[redacted]	2.85	£100,068
	Carer utilities based on carer utility study (Carer utilities 4)	[redacted]	2.37	£120,239

5.2.11 Model validation and face validity check

The company reported on several steps undertaken to assess internal validity and generalisability of the model findings. On the point of generalisability, the company note the tailoring of parameter inputs to reflect a UK perspective where data are available. They also describe the consultation of a Delphi panel through two rounds of questionnaires and a face-to-face meeting, to help validate the values and assumptions applied in the model, and to estimate some values not available from other sources. The company also note that a UK advisory board was assembled to discuss the applicability of the values used in the model. The company submission notes that the experts consulted acknowledge the "*lack of power of the utility data from the pivotal trials, and thought that using values from the vignette study instead would be valid*". The ERG acknowledges that the trials of teduglutide were insufficiently powered to detect between group differences in HRQoL, but are not convinced that the trial data are insufficient for informing the relationship between level of PS dependence and HRQoL. These data do appear to show a trend towards lower patient utility with increasing levels of PS days, but as noted in section 5.2.7 (Figure 7) the relationship is much flatter based on the observed trial data than it is with the vignette data. It is possible that the vignette study generates an isolated focus on the positive impact of reduced PS days as a driver of HRQoL, without considering other important drivers that may be unrelated or even negatively correlated with PS days. For example, it is possible that some patients who manage to reduce dependence face a trade-off with increasing fatigued over the interval between PS days. The vignette data do not allow for such possibilities.

With respect to the internal validity of the models, the company compared the modelled average number of PS days with the actual observed average number of PS days in the trial data informing the transition matrices. These comparisons are presented in Table 75 of the

company submission for the adult model and Table 81 of the paediatric model. They generally show good consistency across the observed time horizon of STEPS and TED-C13-003. The average number of days on PS is higher in the model at 30 months than it was in STEPS 2, because the stopping rule and assumptions applied in the model were not applied in STEPS and STEPS2. Of course, the duration of observed follow-up is short, particularly for the standard care arm in the adult population and both arms in the paediatric population. The vast majority of the modelled QALY gains (>99%) accrue in the extrapolation period beyond 24 weeks in the adult model, and beyond 12 weeks in the paediatric model. There is significant uncertainty surrounding long-term extrapolations based on such short-term data, and it is not possible to assess the external validity of this output.

Further checks of internal consistency were carried out by the ERG. This included: cell checking to ensure formulae were specified in line with the described approach and assumptions, and black box testing to ensure changes to modifiable input parameters produced expected outputs. Examples of the latter included: 1) setting utilities to 1 and disutility's to zero, and ensuring patient QALYs were equal life-years under this specification; 2) setting the transition matrices and adverse event probabilities to be equal in both arms and checking that this generated zero difference in QALYs. Other than the minor input errors and the adverse event rate bug identified in the previous section, the ERG found the model to be structurally sound and transparent.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

The ERG implemented several further exploratory analysis. First of all, the ERG corrected the apparent bug in the "Adverse events" sheet of the model, where cells C16:C47 (teduglutide) appear to reference adverse rates for the placebo arm of STEPS, and cells E16:E47 (standard care) appear to reference the adverse event rates observed in the teduglutide arm of STEPS. Following this change, the ERG re-ran the company's scenario analyses for both the adult and paediatric models. The revised results are presented in Table 34 for the adult population and Table 35 for the paediatric population.

In the adult model, this correction shifts the base case ICER from £193,549 to £206,690. Similar increases are seen the other scenarios assessed by the company (Table 34). A similar pattern is observed in the paediatric model, with the company's base case ICER increasing from £111,045 to £120,766, and the ICERs for the other scenarios similarly increasing.

Table 34 Results of scenarios analysis in the adult model with ERG corrected adverse event rates

Base case setting	Scenario setting	Incremental		ICER
		Costs	QALYs	
Base case model	ERG corrected adverse event rates (new reference for further scenarios)	[redacted]	2.51	£206,690
Time horizon: 40 years	Time horizon: 10 years	[redacted]	1.25	£265,766
	Time horizon: 20 years	[redacted]	1.99	£223,992
	Time horizon: 30 years	[redacted]	2.36	£210,927
	Time horizon: 50 years	[redacted]	2.53	£206,048
Uniform discount rate: 3.5%	No discounting applied	[redacted]	3.97	£185,744
	Discount rate health outcomes: 1.5%	[redacted]	3.21	£161,344
Teduglutide stopping rule applied at 24 weeks	Teduglutide stopping rule not applied	[redacted]	3.26	£209,530
	Stopping rule applied at 12 months	[redacted]	3.19	£199,995
	Stopping rule applied at 24 months	[redacted]	3.25	£199,178
Liver disease development based on Delphi meeting rates, mortality equal to SBS-IF population	Liver disease: not included	[redacted]	2.50	£208,092
	Liver disease: Delphi mortalities	[redacted]	2.51	£206,642
CKD: Included	CKD: excluded	[redacted]	2.50	£209,364
ITx: Excluded	ITx: Included	[redacted]	2.53	£203,705
PS requirement maintained for	LOCF for teduglutide transitions (horizon)	[redacted]	2.73	£194,210

Base case setting	Scenario setting	Incremental		ICER
		Costs	QALYs	
teduglutide patients beyond 30 months				
Standard care patients revert to baseline PS requirement beyond 24 weeks	PS maintained for SoC patients post-24 weeks	[redacted]	2.20	£255,460
Survival curve: log-normal	Survival: Exponential	[redacted]	2.96	£175,279
	Survival: Gompertz	[redacted]	1.89	£251,659
	Survival: Weibull	[redacted]	2.27	£208,960
	Survival: Log-logistic	[redacted]	2.40	£211,149
	Survival: Gamma	[redacted]	2.64	£206,987
Patient utilities from Vignettes study	Patient utilities from mapped STEPS trial data	[redacted]	1.75	£295,940
Utility decrements for carers, base utility of 1	No utilities considered for carers	[redacted]	1.47	£352,600
	Utility decrements with base of 0 for carers	[redacted]	1.96	£264,450
Carer utilities based on midpoint between Delphi panel and carer utility study	Carer utilities based on Delphi panel	[redacted]	2.67	£194,095
	Carer utilities based on carer utility study	[redacted]	2.34	£221,032
PS costs include complication costs	Complication costs excluded from PS costs	[redacted]	2.51	£230,457

Key: AEs, adverse events; CKD, chronic kidney disease; ITx, intestinal transplantation, LYs, life years; p.a., per annum; PS, parenteral support; QALYs, quality-adjusted life years; TED, teduglutide.

Table 35 Results of scenarios analysis with ERG corrected adverse event rates

Base case setting	Scenario setting	Incremental		ICER
		Costs	QALYs	
Base case model	ERG corrected adverse event rates (new reference for further scenarios)	[redacted]	2.48	£120,766
Time horizon: 96 years	30 years	[redacted]	1.86	£150,214
	50 years	[redacted]	2.24	£130,401
	70 years	[redacted]	2.42	£122,665
Uniform discount rate: 3.5%	No discounting	[redacted]	6.42	£76,850
	Discount rate health outcomes: 1.5%	[redacted]	3.95	£75,684
Teduglutide stopping rule applied at 12 weeks	Teduglutide stopping rule not applied	[redacted]	1.03	£538,451
	Stopping rule applied at 24 weeks	[redacted]	2.34	£149,664
Liver disease included	Liver disease: not included	[redacted]	2.39	£124,615
CKD: Included	CKD: excluded	[redacted]	2.47	£129,835
ITx: Included	ITx: Excluded	[redacted]	3.08	£214,634
	ITx + ITx waiting list included	[redacted]	4.01	£131,147
PS requirement maintained for teduglutide patients beyond 12 weeks	Last observed teduglutide transitions carried forward for entire model time horizon	[redacted]	3.08	£75,177
	Last observed teduglutide transitions carried forward until 30 months	[redacted]	2.97	£81,316
Standard care patients revert to baseline PS requirement beyond 24 weeks	PS-requirement maintained for standard care patients beyond 24 weeks	[redacted]	2.36	£145,741
Survival curve: log-normal	Exponential	[redacted]	3.13	£113,732
	Gompertz	[redacted]	0.84	£220,711
	Weibull	[redacted]	2.11	£135,749

	Log-logistic	[redacted]	2.28	£125,017
	Gamma	[redacted]	2.71	£114,027
Patient utilities from Vignettes study	Patient utilities from mapped STEPS trial data	[redacted]	1.38	£217,028
Utility decrements for carers, base utility of 1	No utilities considered for carers (Carer utilities 1)	[redacted]	1.68	£178,275
	Utility decrements with base of 0 for carers (Carer utilities 2)	[redacted]	2.52	£118,614
Carer utilities based on midpoint between Delphi panel and carer utility study	Carer utilities based on Delphi panel (Carer utilities 3)	[redacted]	2.72	£110,147
	Carer utilities based on carer utility study (Carer utilities 4)	[redacted]	2.24	£133,650
PS costs include complication costs	Complication costs excluded from PS costs	[redacted]	2.48	£193,737

Key: AEs, adverse events; CKD, chronic kidney disease; ITx, intestinal transplantation, LYs, life years; p.a., per annum; PS, parenteral support; QALYs, quality-adjusted life years; TED, teduglutide.

Further scenario analysis undertaken by the ERG

Over and above the scenarios assessed by the company, the ERG explored the impact of some further scenarios involving changes to other key parameters and assumptions, and further combinations of changes. These results are presented in Table 36 for the adult population and Table 37 for the paediatric population. The additional modelled scenarios are as follows:

1. Replacement of the health state costs with the ERGs reworked estimates (Appendix 1). These include the following assumptions:
    a. Nutrition bag costs are variable and are based on the number of PS days per week
    b. Delivery costs are fixed (by PS dependence) at two deliveries per month
    c. The percentage of patients who require nurse support is set at 40% (Parexel Access Consulting, 2017) and is independent of the number of PS days per

week required (ERG clinical advice). It is further assumed that 2 hours of nursing time is required per PN day in adults who need it (Parexel Access Consulting, 2017)

d. Taurolock use (yes/no) is independent of PS days, but number of uses per week follows the number of PN days per week (ERG clinical advice).
e. Use of additional medications is independent of the number of PS days.
f. Specialist follow-up visits per year are independent of PS days, and are fixed at three per year in adults and four per year in the paediatric cohort (Parexel Access Consulting, 2017).
g. The incidence rate for line sepsis is not correlated with number of PS days, and is fixed at a rate of 0.37 per 1000 catheter person days (= 0.135 per catheter person year) (Parexel Access Consulting, 2017).
h. Intensive care days (14) are required in 50% of patients hospitalised for line sepsis (Parexel Access Consulting, 2017).
i. The annual incidence of line fracture is fixed by number of PS days at once per year in adults (company submission). The PS fracture rate is once per year in low PS dependence children, and twice per year in mid PS to high PS dependence in children (company submission).

2. Replacement of the renal dialysis costs with the ERGs reworked estimates.
3. Extrapolations based on last observed health state carried forward in the standard care arm, in combination with the application of patient health state utility data from STEPS.
4. Extrapolations based on last observed health state carried forward in the standard care arm; application of health state utility data from STEPS; and age adjustment of carer utilites
5. Weibull distribution for survival; and last observed PS state maintained for SoC patients.
6. Weibull for survival; patient utilities from STEPS trial data; last observed PS state maintained for SoC patients; and base-level carer utility age-adjusted general population.
7. Patient utilities from STEPS trial data; last observed PS state maintained for SoC patients; base-level carer utility age-adjusted general population; and intestinal transplants included.

8. Patient utilities from STEPS trial data; last observed PS state maintained for SoC patients; base-level carer utility age-adjusted general population; and PS state costs as per ERG assumptions.
9. Last observed health state carried forward in the standard care arm; application of health state utility data from STEPS; and application of carer disutilities only.
10. Last observed health state carried forward in the standard care arm; application of health state utility data from STEPS; application of carer disutilities only; and application of ERG reworked health state costs.

Table 36 Further scenario analyses undertaken by the ERG (adult model)

ERG Scenarios	Scenario setting	Incremental		ICER
		Costs	QALYs	
Company base case corrected for adverse events	**ERG correction applied**	[redacted]	2.51	£206,690
1. Costs as given in company submission	PS state costs as for ERG assumptions	[redacted]	2.51	£269,174
2. CKD costs	Complications - ERG Costs of renal dialysis based on NHS Reference Costs	[redacted]	2.51	£207,628
3. Combination (a)	Patient utilities mapped from STEPS trial data and PS state maintained for SoC patients post-24 weeks	[redacted]	1.58	£356,862
4. Combination (b)	Patient utilities mapped from STEPS trial data, PS state maintained for SoC patients post-24 weeks, and base-level carer utility age-adjusted general population.	[redacted]	1.42	£396,839
5. Combination (c)	Weibull for mortality and PS state maintained for SoC patients post-24 weeks	[redacted]	2.00	£257,221

ERG Scenarios	Scenario setting	Incremental		ICER
		Costs	QALYs	
6. Combination (d)	Weibull for mortality, patient utilities from STEPS trial data, PS maintained for SoC patients post-24 weeks, and base-level carer utility age-adjusted general population.	[redacted]	1.30	£397,281
7. Combination (e) (adult)	Patient utilities from STEPS trial data, PS state maintained for SoC patients post-24 weeks, base-level carer utility age-adjusted general population, and intestinal transplants included.	[redacted]	1.44	£386,513
8. Combination (f)	Patient utilities from STEPS trial data, PS maintained for SoC patients post-24 weeks, base-level carer utility age-adjusted general population, and PS state costs as per ERG assumptions.	[redacted]	1.42	£492,898
9. Combination (g)	Last observed health state carried forward in the standard care arm; application of health state utility data from STEPS; and application of carer utility decrements only	[redacted]	0.98	£571,507
10. Combination (h)	Last observed health state carried forward in the standard care arm; application of health state utility data from STEPS;	[redacted]	0.98	£709,847

ERG Scenarios	Scenario setting	Incremental		ICER
		Costs	QALYs	
	application of carer utility decrments only; and application of ERG reworked health state costs			

Key: AEs, adverse events; CKD, chronic kidney disease; ITx, intestinal transplantation, LYs, life years; p.a., per annum; PS, parenteral support; QALYs, quality-adjusted life years; TED, teduglutide.

Table 37 Further scenario analyses undertaken by the ERG (paediatric model)

Base case setting	Scenario setting	Incremental		ICER
		Costs	QALYs	
Company base case corrected for adverse events	**Corrected by ERG**	[redacted]	2.48	£120,766
1. Costs as given in company submission	PS state costs reworked as per ERG assumptions	[redacted]	2.48	£185,922
2. CKD costs	Complications - ERG Costs of renal dialysis based on NHS Reference Costs	[redacted]	2.48	£123,894
3. Combination (a)	Patient utilities from STEPS trial data and PS maintained for SoC patients post-24 weeks	[redacted]	1.32	£261,487
4. Combination (b)	Patient utilities from STEPS trial data, PS maintained for SoC patients post-24 weeks, and base-level carer utility age-adjusted general population.	[redacted]	1.10	£314,316
5. Combination (c)	Weibull for mortality, and PS maintained for SoC patients post-24 weeks	[redacted]	2.00	£162,660
6. Combination (d)	Weibull for mortality, patient utilities from STEPS trial data, PS maintained for SoC patients post-24 weeks, and base-level carer utility age-adjusted general population.	[redacted]	0.94	£347,567
7. Combination (e) (paediatric)	Patient utilities from STEPS trial data, PS maintained for SoC patients post-24 weeks, base-level carer utility age-adjusted general population,	[redacted]	1.81	£399,016

Base case setting	Scenario setting	Incremental		ICER
		Costs	QALYs	
	and intestinal transplants excluded.			
8. Combination (f)	Patient utilities from STEPS trial data, PS maintained for SoC patients post-24 weeks, base-level carer utility age-adjusted general population, and PS state costs as per ERG assumptions.	[redacted]	1.10	£427,580
9. Combination (g)	Last observed health state carried forward in the standard care arm; application of health state utility data from STEPS; and application of carer utility decrements only	[redacted]	1.14	£303,011
10. Combination (h)	Last observed health state carried forward in the standard care arm; application of health state utility data from STEPS; application of carer utility decrements only; and application of ERG reworked health state costs	[redacted]	1.14	£412,201

Key: AEs, adverse events; CKD, chronic kidney disease; ITx, intestinal transplantation, LYs, life years; p.a., per annum; PS, parenteral support; QALYs, quality-adjusted life years; TED, teduglutide.

Further PSA undertaken by the ERG

To better characterise the uncertainty surrounding the ICERs for the scenario analyses presented in Tables 36 and 37, Table 38 presents the probabilistic results for selected scenarios in both the adult and paediatric cohorts. The selected scenarios include: the company base case with the adverse event rates corrected; ERG scenario 4 (patient utilities from STEPS, last observed health state carried forward in the standard care arm, and base-level carer utility age-adjusted general population); and ERG scenario 9 (patient health state utility data from STEPS, last observed health state carried forward in the standard care arm, and application of carer utility decrements only). It can be noted that for all of these scenarios, the probabilistic ICER is higher than the corresponding deterministic ICER. The probabilities of cost-effectiveness are shown in the final three columns.

Table 38 ERG adult and paediatric probabilistic results for selected scenarios

	Δ Costs	**Δ QALYs**	**ICER**	% at 50k	% at 100k	% at 250k	% at 500k
Adult – corrected company base case	[redacted]	2.15	£239,864	0.07%	1.24%	52.39%	97.23%
Adult – scenario 4	[redacted]	1.17	£477,809	0.04	0.18	6.89	1.41
Adult – scenario 9	[redacted]	0.85	£658,864	0.03	0.10	51.78	23.95
Paediatric – corrected company base case	[redacted]	1.72	£160,502	2.89	18.23	65.41	84.76
Paediatric – scenario 4	[redacted]	0.53	£610,499	0.24	1.51	1.76	36.97
Adult – scenario 9	[redacted]	0.87	£368,318	0.11	0.07	17.19	65.66

5.4 Conclusions of the cost effectiveness section

Adult model

The company base case deterministic analysis shows teduglutide to cost an additional £193,548 per QALY gained over standard practice. When the model is run probabilistically, the base case ICER increases to £222,971, due to the uncertainty surrounding the underlying

transition matrices. The incremental cost in the probabilistic analysis is £[redacted] (95% CI: [redacted] - [redacted]), for a corresponding QALY gain of 2.25 (95% CI: 1.26 – 3.52).

The key drivers of incremental cost are the teduglutide acquisition costs, the parenteral support health state costs, and the adverse event costs. The majority of the QALY gain associated with teduglutide accrues to patients in the No PS health state.

The company sensitivity and scenario analyses show the adult model results to be particularly sensitive to: the cycle costs for the high dependence (PS7) health state; the model time horizon; the choice of discount rates (particularly differential discounting); the extrapolation assumption for standard care (i.e. last state carried forward versus reversion to baseline beyond 24 weeks); the source of utility data for patients (STEPS versus vignette); and the method for incorporating carer utility (application of decrements versus health state utility values).

The ERG believes that the adverse event rates derived from STEPS were being inappropriately applied in the opposite arms of the model. Switching the event rates to mirror the observed data in STEPS, increased the company base case deterministic ICER to £206,690. The corrected model remained most sensitive to the same parameters and assumptions.

To more fully characterise the upward uncertainty in the ICER, the ERG explored several scenarios that combined some of the more conservative assumptions assessed in the company's scenario analysis. When, for example, patient utilities from STEPS are applied in combination with less pessimistic extrapolation assumptions for standard care (last observed state carried forward), and age adjusted carer health state utility values, the deterministic ICER for teduglutide rises to £396,839 (Table 36, scenario 4). When carer utility decrements are applied instead of age adjusted HSUVs in this combined scenario, the ICER increases to £571,507 (Table 36, scenario 9).

Over and above the switchable scenarios enabled in the company model, the ERG questions some of the assumptions informing the input values for health states costs by level of PS dependence. Based on a reworking of these costs, using alternative plausible assumptions, the ERG find the ICER increases even further. For example, adding the reworked costs on top of

the three changes described in the paragraph above, the ICER for teduglutide increases to £709,847 (Table 36, scenario 10).

Thus, overall, the ERG believe the company estimates of the ICER in the adult cohort reflect optimistic assumptions which have not been fully justified. Under alternative scenarios incorporating various combinations of modelling assumptions that the ERG believe to be more plausible (Table 36, scenarios 4, 9 and 10), the deterministic ICER varies from £396,839 per QALY gained to £709,847 per QALY gained

Paediatric model

The paediatric results follow a similar pattern to the adult model, although the company base case ICER is lower in this population; i.e. £111,045 per QALY gained. This reflects an incremental cost of [redacted] for an incremental QALY gain of 2.57. The company base case PSA results show a base case ICER of £143,851.

The company sensitivity analysis indicates that the results of the paediatric model are particularly sensitive to: the health state costs for high dependence PS; application of the teduglutide stopping rule; the discount rates applied; the inclusion/exclusion of ITx; and the source of utility data for patients.

With correction to the adverse event rate bug identified by the ERG, the deterministic ICER increases to £120,766. Applying more conservative assumptions in combination, the ICER increases significantly. For example, when patient utilities from STEPS are applied in combination with the assumption that patients in the standard care arm (or those discontinuing teduglutide) retain their last observed health state carried forward, and age adjusted HSUVs for carers, the ICER for teduglutide increases to £314,316 (Table 37, scenario 4). When carer utility decrements are applied in this combined scenario (rather than full carer health state values), the ICER for teduglutide comes to £303,011 (Table 37, scenario 9). When the ERG reworked health states costs are then applied in combination with the above three changes, the ICER increases further to £412,201 (Table 37, scenario 10).

Thus, overall, the ERG also believes that the company estimates of the paediatric ICER reflect optimistic assumptions which have not been fully justified. Combined plausible changes to these assumptions result in significant increases. The ERG preferred modelling

assumptions put the deterministic ICER somewhere between £303,011 and £412,201. Moreover, when accounting for joint uncertainty in the model input parameters using probabilistic analysis, all the ICERs increase further over their deterministic counterparts.

6 End of life

End of life criteria do not apply.

7 Overall conclusions

The company's submission considered teduglutide for treating people with SBS-IF. The comparator was established clinical management without teduglutide. In the UK, this equates to PS, antimotility and antisecretory agents, fluid restriction and dietary optimisation. Teduglutide has UK marketing authorisation for the treatment of patients aged 1 year and above with SBS.

Clinical effectiveness evidence

The company's systematic review identified three eligible RCTs and three non-randomised extension studies for the adult indication. The company focused its clinical evidence mainly on the STEPS trial, a phase III RCT, funded by NPS Pharmaceuticals. The other RCTs were largely reported in the Appendices, whereas in the main submission prominence was given to the results of three non-RCTs that were not eligible for inclusion in the review (Micic 2015, Joly 2017, Kochar 2017).

In both RCTs reporting the proportion of participants with a response (i.e. a 20-100% PS reduction from baseline at week 20 and week 24), there was a statistically significant difference between the teduglutide 0.05mg/kg/day group and the placebo group: STEPS, 27/43 (63%) versus 13/43 (30%) and CL0600-004, 16/35 (46%) versus 1/16 (6%). There was also evidence of a difference between the 0.05mg/kg/day dose and placebo for the ordinal definition of PS (graded response score). In the CL0600-004 study, there was no evidence for differences in PS outcomes between the 0.1mg/kg/day dose of teduglutide and placebo.

The company did not conduct meta-analysis, despite the fact that one of the remaining two trials (i.e. CL0600-004) also reported PS outcomes. The company's justification, that CL0600-004 had not met its primary endpoint, was not accepted by the ERG as a valid reason for the lack of a meta-analysis. The ERG conducted two meta-analyses for the binary definition of the primary outcome; first, comparing the 0.05mg/kg/day dose of teduglutide versus placebo, and, second, using data from all doses of teduglutide versus placebo. Including the CL0600-004 study in the meta-analyses did not change the overall interpretation and showed a statistically significant benefit of teduglutide compared to placebo. Adverse events were common in both teduglutide and placebo groups, with around

half being related to teduglutide treatment (in participants treated with teduglutide). Serious AEs were also common but were generally not related to treatment.

One non-randomised study was identified for the paediatric indication (TED-C13-003). This showed a reduction in PN volume in teduglutide groups but an increase in the standard of care group. Serious AEs were frequent but none were related to teduglutide treatment.

Cost-effectiveness evidence

The company's economic case considered the cost-effectiveness of teduglutide plus established clinical management versus established clinical management alone, for patients with SBS-IF on parenteral support who are stable following a period of adaptation following surgery.

The company submitted two economic models, one for the adult population and one for the paediatric population. The models were structured around a set of mutually exclusive health states defined by the level of PS dependence (i.e. number of days of PS required per week). The adult model used eight PS health states from PS seven days per week through to PS independence (zero days). The paediatric model utilised a smaller number of states, reflecting the more limited data available to populate the model; low-PS (1-3 days per week), mid-PS (4-5 days per week), high-PS (6-7 days per week). The data to inform transition probabilities between the PS health states were derived from the STEPS and STEPS2 studies for the adult population, and from TED-C13-003 for the paediatric cohort. Beyond the observed follow-up periods for the teduglutide and standard care arms of the studies, extrapolation assumptions were required. The models also included adverse event rates per cycle (derived from STEPS and STEPS2), SBS-IF associated complications (IFALD and stage 5 CKD), and intestinal transplant. The latter event was included in the base case model for the paediatric population, but was only included as a scenario analysis for the adult model.

Health state utility values (HSUVs) for patients and carers, by level of PS dependence (days per week), were available form a number of different sources. The base case models applied patient HSUVs derived from an ad-hoc study which utilised lead-time time trade-off methods to elicit UK general population values for health state vignettes describing different levels of PS dependence (zero through to seven days). Carer utilities, by level of PS dependence, were also included in the base case models. These were parametrised using the mid-point between

a set of EQ-5D utility values derived from a small survey of UK carers, and a set of values elicited from a panel of experts participating in a Delphi process. Rather than apply only the utility decrements associated with caring for patients on parenteral support, the company applied full health state utilities for carers up to the time of death of the patient.

The ERG are of the opinion that the company model is of adequate quality and that is has been clearly described in the company submission. In general, the modelling has been implemented as described. However, there are a number of key issues that generate significant upward uncertainty in the company base case ICERs:

- The ERG identified an error in the adverse event rates applied in the teduglutide and standard care arms of the model. This appears to result from the adverse event rates observed in respective arms of STEPS, being applied to the wrong arms in the model; i.e. the event rates being switched.
- An assumption is made that patients in the standard care arm of the model (and those modelled to stop teduglutide treatment) revert back to their baseline parenteral support state beyond the period informed by the observed trial data. Conversely, patients on-treatment in the teduglutide arm are assumed to maintain their last observed parenteral support state over the remaining time horizon of the model. This assumes that any observed PS reductions in the placebo arm of STEPS represent a temporary trial effect, while all of the observed PS reductions in the teduglutide arm represent real improvement. Given a lack of data to validate this assumption, the ERG believe that the same extrapolation assumptions should be applied to both arms.
- The utilities applied in the model are derived from an ad-hoc study commissioned by the company, in which TTO values were elicited for health state vignettes describing levels of dependence on parenteral support. These vignettes used some disease specific and potentially leading language, and may have created undue focus on the number of PS days as a driver of health related quality of life in SBS-IF patients. The elicited values show a steep negative relationship with increasing number of PS days. However, the actual observed utility data available from the trials shows a much flatter relationship with level of PS dependence. Use of the former (vignette) values results in substantially greater QALY gains for teduglutide compared to the application of values derived from the trial data.

- Carer health state utilities have been applied in the company models over the lifetime of SBS-IF patients. Rather than applying carer utility decrements for surviving SBS-IF patients, the company apply whole HSUVs for carers. This approach may exaggerate carer QALY gains associated with teduglutide, since it appears to attribute all of the carers QALYS to the SBS-IF patient while they are alive. Thus, in periods of extended survival with teduglutide, the carers entire QALYs are credited to teduglutide with no counterfactual applied in the standard care arm.
- Health state costs by level of PS dependence have been worked up using resource use scenarios that have not been well justified. In particular, the scenarios assume significant correlation between certain types of resource use by level of PS dependence, which do not appear well justified by the clinical advice the company received. For example, line sepsis, a high cost complication, is focussed exclusively in the highest PS dependence state, when the clinical advice received by the company suggests that such infections are not driven by number of days on PS, but on how well a patient looks after their line. The resource use assumptions serve to create a steep relationship between increasing levels of PS dependence (in days) and increasing health state costs. The ERG believe this relationship may be exaggerated, and it is a key driver of downstream cost savings for teduglutide in the model.

Overall, the issues identified above, result in a high degree of upward uncertainty in the company reported ICERs for both the adult and paediatric populations.

7.1 Implications for research

There is a relative lack of randomised evidence in this area. Only two small RCTs were identified examining the longer-term effects of teduglutide in the adult population. There are no RCTs in the paediatric population. Recruitment to new trials may be hampered by the rarity of this clinical condition.

8 References

1. O'Keefe SJ, Buchman AL, Fishbein TM, Jeejeebhoy KN, Jeppesen PB, Shaffer J. Short bowel syndrome and intestinal failure: consensus definitions and overview. *Clin Gastroenterol Hepatol* 2006;**4:**6-10.

2. Van Gossum A, Bakker H, Bozzetti F, Staun M, Leon-Sanz M, Hebuterne Z, et al. Home parenteral nutrition in adults: A European multicentre survey in 1997. *Clin Nutrit* 1999;**18:**135-40.

3. Goulet O, Ruemmele F. Causes and management of intestinal failure in children. *Gastroenterology* 2006;**130:**S16-S28.

4. Squires RH, Duggan C, Teitelbaum DH, Wales PW, Balint J, Venick R, et al. Natural history of pediatric intestinal failure: Initial report from the pediatric intestinal failure consortium. *J Ped* 2012;**161:**723-8.e2.

5. Jeppesen PB, Pertkiewicz M, Messing B, Iyer K, Seidner DL, O'Keefe S J, et al. Teduglutide reduces need for parenteral support among patients with short bowel syndrome with intestinal failure. *Gastroenterology* 2012;**143:**1473-81.e3.

6. Nightingale J, Woodward JM. Guidelines for management of patients with a short bowel. *Gut* 2006;**55:**iv1-iv12.

7. Weale AR, Edwards AG, Bailey M, Lear PA. Intestinal adaptation after massive intestinal resection. *Postgrad Med Jo* 2005;**81:**178-84.

8. Tappenden KA. Intestinal adaptation following resection. *Jpen* 2014;**38:**23S-31S.

9. Carroll RE, Benedetti E, Schowalter JP, Buchman AL. Management and Complications of Short Bowel Syndrome: an Updated Review. *Curr Gastroenterol Rep* 2016;**18 (7)**

10. Iyer K, Kunecki M, Boullata J, Fuhjioka K. Independence From Parenteral Nutrition and Intravenous Fluid Support During Treatment With Teduglutide Among Patients With Intestinal Failure Associated With Short Bowel Syndrome. *J Parent a Enterl Nutr* 2016 DOI: 10.1177/0148607116680791.

11. Huisman-de Waal G, Schoonhoven L, Jansen J, Wanten G, van Achterberg T. The impact of home parenteral nutrition on daily life-A review. *Clin Nutr* 2007;**26:**275-88.

12. Winkler MF, Hagan E, Wetle T, Smith C, O'Sullivan Maillet J, Touger-Decker R. An exploration of quality of life and the experience of living with home parenteral nutrition. *Jpen* 2010;**34:**395-407.

13. Winkler MF, Smith CE. Clinical, social, and economic impacts of home parenteral nutrition dependence in short bowel syndrome. *Jpen* 2014 **38:**32S-7S.

14. Seidner DL, Schwartz LK, Winkler MF, Jeejeebhoy K, Boullata JI, Tappenden KA. Increased intestinal absorption in the era of teduglutide and its impact on management strategies in patients with short bowel syndrome-associated intestinal failure. *Jpen* 2013;**37:**201-11.

15. Buchman AL. Etiology and initial management of short bowel syndrome. *Gastroenterology* 2006;**130:**S5-S15.

16. Kim ES, Keam SJ. Teduglutide: A Review in Short Bowel Syndrome. *Drugs* 2017;**77:**345-52.

17. McMellen ME, Wakeman D, Longshore SW, McDuffie LA, Warner BW. Growth factors: possible roles for clinical management of the short bowel syndrome. *Seminars in Pediatric Surgery* 2010;**19:**35-43.

18. McKeage K. Teduglutide: A Guide to Its Use in Short Bowel Syndrome. *Clin Drug Investig* 2015;**35:**335-40.

19. *Revistive: summary of product characteristics*: Electronic Medicines Compendium; 2017. http://www.medicines.org.uk/emc/medicine/29315 [Accessed September 2017]

20. *Single Technology Appriasal. Teduglutide for treating short bowel syndrome: final scope*. London: National Institute for Health and Care Excellence; 2017. https://www.nice.org.uk/guidance/indevelopment/gid-ta10048/documents [Accessed September 2017]

21. Carlsson E, Bosaeus I, Nordgren S. Quality of life and concerns in patients with short bowel syndrome. *Clin Nutr* 2003;**22:**445-52.

22. Higuera I, Garcia-Peris P, Camblor M, Breton I, Velasco C, Romero R, et al. Outcomes of a general hospital-based home parenteral nutrition (HPN) program; report of our experience from a 26-year period. *Nutr Hospital* 2014;**30:**359-65.

23. *BANS Report 2016: Artificial Nutrition Support in the UK 2005-2015 - Adult Home Parenteral Nutrition & Home Intravenous Fluids*: British Association for Parenteral and Enteral Nutrition; 2016. http://www.bapen.org.uk/images/pdfs/reports/bans-report-2016.pdf [Accessed September 2017]

24. Donohue C, Reynolds J. Short bowel syndrome. *Surgeon* 2010;**8:**270-9.

25. *NHS standard contract for intestinal failure (adult)*

NHS England; 2014. https://www.england.nhs.uk/wp-content/uploads/2013/06/a08-intestinal-failure-adult.pdf [Accessed September 2017]

26. Pironi L, Arends J, Bozzetti F, Cuerda C, Gillanders L, Jeppesen PB, et al. ESPEN guidelines on chronic intestinal failure in adults. *Clin Nutr* 2016;**35:**247-307.

27. *Nutrition support in adults Quality Standard QS24*. London: National Institute for Health and Clinical Excellence; 2012. https://www.nice.org.uk/guidance/qs24 [Accessed September 2017]

28. *Nutrition support for adults: oral nutrition support, enteral tube feeding and parenteral nutrition Clinical Guideline CG32*. London: Natioanl Institute for Health and Clinical Excellence; 2017. https://www.nice.org.uk/guidance/cg32 [Accessed September 2017]

29. *Intravenous fluid therapy in adults in hospital Clinical Guideline CG174*. London: National Institute for Health and Clinical Excellence; 2013. https://www.nice.org.uk/guidance/cg174 [Accessed September 2017]

30. Jeppesen PB, Sanguinetti EL, Buchman A, Howard L, Scolapio JS, Ziegler TR, et al. Teduglutide (ALX-0600), a dipeptidyl peptidase IV resistant qlucagon-like peptide 2 analogue, improves intestinal function in short bowel syndrome patients. *Gut* 2005;**54:**1224-31.

31. *Summary of opinion : revestive. EMA/CHMP/390445/2012*: European Medicines Agency; 2012. http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/002345/WC500129094.pdf [Accessed September 2017]

32. Cani PD, Possemiers S, Van De Wiele T, Guiot Y, Everard A, Rottier O, et al. Changes in gut microbiota control inflammation in obese mice through a mechanism involving GLP-2-driven improvement of gut permeability. *Gut* 2009;**58:**1091-103.

33. Drucker DJ, Ehrlich P, Asa SL, Brubaker PL. Induction of intestinal epithelial proliferation by glucagon-like peptide 2. *Proc Nat Acad Sci USA* 1996;**93:**7911-6.

34. Wojdemann M, Wettergren A, Hartmann B, Hilsted L, Holst JJ. Inhibition of sham feeding-stimulated human gastric acid secretion by glucagon-like peptide-2. *J Clin Endocrinol Metabol* 1999;**84:**2513-7.

35. Hartmann B, Harr MB, Jeppesen PB, Wojdemann M, Deacon CF, Mortensen PB, et al. In vivo and in vitro degradation of glucagon-like peptide-2 in humans. *J Clin Endocrinol Metabol* 2000;**85:**2884-8.

36. Carter BA, Cohran VC, Cole CR, Corkins MR, Dimmitt RA, Duggan C, et al. Outcomes from a 12-Week, Open-Label, Multicenter Clinical Trial of Teduglutide in Pediatric Short Bowel Syndrome. *J Ped* 2017;**181:**102-11.

37. Iturrino J, Camilleri M, Acosta A, O'Neill J, Burton D, Edakkanambeth Varayil J, et al. Acute Effects of a Glucagon-Like Peptide 2 Analogue, Teduglutide, on Gastrointestinal Motor Function and Permeability in Adult Patients With Short Bowel Syndrome on Home Parenteral Nutrition. *Jpen* 2016;**40:**1089-95.

38. Jeppesen PB, Gilroy R, Pertkiewicz M, Allard JP, Messing B, O'Keefe SJ. Randomised placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome. *Gut* 2011;**60:**902-14.

39. Schwartz LK, O'Keefe SJ, Fujioka K, Gabe SM, Lamprecht G, Pape UF, et al. Long-Term Teduglutide for the Treatment of Patients With Intestinal Failure Associated With Short Bowel Syndrome. *Clin Translat Gastroenterology* 2016;**7:**e142.

40. O'Keefe SJ, Jeppesen PB, Gilroy R, Pertkiewicz M, Allard JP, Messing B. Safety and efficacy of teduglutide after 52 weeks of treatment in patients with short bowel intestinal failure. *Clin Gastroenterol Hepatol* 2013;**11:**815-23.e1-3.

41. Joly F, Quilliot D, Beau P, Poullenot F, Armengol-Debeir L, Chambrier C, et al. First Study in Real Life on the Effect of Teduglutide at 3 Months in a Cohort of Adult Patients with Short Bowel Syndrome (SBS). *Transplantation* 2017;**101:**S9.

42. Kochar B, Long MD, Shelton E, Young L, Farraye FA, Yajnik V, et al. Safety and Efficacy of Teduglutide (Gattex) in Patients with Crohn's Disease and Need for Parenteral Support Due to Short Bowel Syndrome-associated Intestinal Failure. *J Clin Gastroenterol* 2017;**51:**508-11.

43. Micic D, Wall E, Rubin D, Semrad C. Teduglutide use for intestinal failure in inflammatory bowel disease. *Inflam Bowel Dis* 2016;**22:**S35.

44. *Single technology appraisal: User guide for company evidence submission template*. London: National Institute for Health and Care Excellence; 2017. https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/user-guide-company-evidence-submission-template-apr-17.docx [Accessed September 2017]

45. *Systematic reviews: CRD's guidance for undertaking systematic reviews in health care [document on the Internet]*. University of York 2009. URL: http://www.york.ac.uk/inst/crd/SysRev/!SSL!/WebHelp/SysRev3.htm [Accessed September 2017]

46. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Comm Health* 1998;**52:**377-84.

47. Roskott AM, Groen H, Rings EHHM, Haveman JW, Ploeg RJ, Serlie MJ, et al. Cost-effectiveness of intestinal transplantation for adult patients with intestinal failure: A simulation study. *Am J Clin Nutr* 2015;**101:**79-86.

48. Migliaccio-Walle K, Caro JJ, Moller J. Economic implications of growth hormone use in patients with short bowel syndrome. *Curr Med Res Opinion* 2006;**22:**2055-63.

49. *CADTH Canadian Drug Expert Committee final recommendation: Teduglutide for the tretament of adult patients with short bowel syndrome (SBS) who are dependent on parenteral support*: Candian Agency for Drugs and Technologies in Health; 2016. https://www.cadth.ca/sites/default/files/cdr/complete/SR0459_Revestive_complete_Jul-29_16.pdf [Accessed Setember 2017]

50. Lopushinsky SR, Fowler RA, Kulkarni GS, Fecteau AH, Grant DR, Wales PW. The optimal timing of intestinal transplantation for children with intestinal failure: A Markov analysis. *Ann Surg* 2007;**246:**1092-9.

51. Amiot A, Messing B, Corcos O, Panis Y, Joly F. Determinants of home parenteral nutrition dependence and survival of 268 patients with non-malignant short bowel syndrome. *Clin Nutr* 2013;**32:**368-74.

52. *Annual Report on Intestine Transplantation. Repost for 2015/2016*: NHS Blood and Transplant; 2016. https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/1315/organ_specific_report_intestine_2016.pdf [Accessed September 2017]

53. Berghofer P, GFragkos K, Baxter J. Development and validation of the disease-specific Short Bowel Syndrome-Quality of Life (SBS-QoL) scale. *Clin Nutr* 2013;**32:**789-96.

54. Lloyd A, Kerr C, Breheny K, Brazier J, Ortiz A, Borg E. Economic evaluation in short bowel syndrome (SBS): an algorithm to estimate utility scores for a patient-reported SBS-specific quality of life scale (SBS-QoLTM). *Quali Life Res* 2014;**23:**449-58.

55. Shaw JW, Johnson JA, Coons SJ. US valuation of the EQ-5D health states: development and testing of the D1 valuation model. *Med Care* 2005;**43:**203-20.

56. *Guide to the methods of technology appraisal*. London: National Institute for Health and Care Excellence; 2013. https://www.nice.org.uk/article/pmg9/resources/non-guidance-guide-to-the-methods-of-technology-appraisal-2013-pdf [Accessed September 2017]

57. Chambers A, Hennessy E, Powell-Tuck J. Longitudinal trends in quality of life after starting home parenteral nutrition: A randomised controlled study of telemedicine. *Clin Nutr* 2006;**25:**505-14.

58. Culkin A, Gabe SM, Madden AM. Improving clinical outcome in patients with intestinal failure using individualised nutritional advice. *J Human Nutr Dietet* 2009;**22:**290-8.

59. Lachaine J, Gouault Laliberte A, Miron A, Xenopoulos A. Time trade off study for parenteral support in short bowel syndrome in Canada. *Value Health* 2016;**19 (3):**A251.

60. *NICE DSU Technical Support Document 12: The use of health state utility values in decision models.*: NICE Decision Supprt Unit; 2011. http://scharr.dept.shef.ac.uk/nicedsu/wp-content/uploads/sites/7/2016/03/TSD12-Utilities-in-modelling-FINAL.pdf [Accessed September 2017]

61. Johnson JA, Luo N, Shaw JW, Kind P, Coons SJ. Valuations of EQ-5D health states: are the United States and United Kingdom different? *Med Care* 2005;**43:**221-8.

62. Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. Catalogue of EQ-5D scores for the United Kingdom. *Med Decis Mak* 2011;**31:**800-4.

63. *Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy. Technology Appraisal Guidance TA352*. London: Natioanl Institute for Health and Clinical excellence; 2015. https://www.nice.org.uk/guidance/ta352 [Accessed September 2017]

64. Bermingham SL, Ashe JF. Systematic review of the impact of urinary tract infections on health-related quality of life. *BJU Int* 2012;**110:**E830-E6.

65. Brown RE, Hutton J, Burrell A. Cost effectiveness of treatment options in advanced breast cancer in the UK. *PharmacoEconomics* 2001;**19:**1091-102.

66. Cooper A, Floyd TF, Ross IAJ. Morbidity and mortality of short-bowel syndrome acquired in infancy: An update. *J Ped Surg* 1984;**19:**711-8.

67. Olieman JF, Penning C, Poley MJ, Utens EMWJ, Hop WCJ, Tibboel D. Impact of infantile short bowel syndrome on long-term health-related quality of life: A cross-sectional study. *J Ped Surg* 2012;**47:**1309-16.

68. O'Neill JK, O'Neill PJ, Goth-Owens T, Horn B, Cobb LM. Care-giver evaluation of anti-gastroesophageal reflux procedures in neurologically impaired children: What is the real-life outcome? *J Ped Surg* 1996;**31:**375-80.

69. Crossan C, Tsochatzis EA, Longworth L, Gurusamy K, Davidson B, Rodriguez-Peralvarez M, et al. Cost-effectiveness of non-invasive methods for assessment and monitoring of liver fibrosis and cirrhosis in patients with chronic liver disease: Systematic review and economic evaluation. *Health Technol Assess* 2015;**19:**1-458.

70. Cavicchi M, Beau P, Crenn P, Degott C, Messing B. Prevalence of liver disease and contributing factors in patients receiving home parenteral nutrition for permanent intestinal failure. *Ann Intern Med* 2000;**132:**525-32.

9 Appendices

Appendix 1 Reworked ERG health state costing assumptions

The ERG explored the impact of changing some of the resource use assumptions, by level of parenteral support (PS), underpinning the PS health state costs applied in the company model. The company assumptions and cost estimates are reproduced in Tables 22 (adult cohort) and Table 23 (paediatric cohort) of the main ERG report. Tables 39 and 40 below illustrate the ERG reworked costins applied in the exploratory analysis. They use the same unit costs applied in the company model, and only change the resource use assumptions. Figure 13 presents a plot comparing the company and ERG reworked health state costs per cycle. They key ERG assumptions are as follows:

a. Nutrition bag costs are variable and are based on the number of PS days per week
b. Delivery costs are fixed (by level of PS dependence) at two deliveries per month.
c. The percentage of patients who require nurse support is set at 40% (Parexel company submission ref 45), and is independent of the number of PS days per week (ERG clinical advice). It is further assumed that 2 hours of nursing time is required per PN day in adults who need it (Parexel company submission ref 45).
d. Taurolock use (yes/no) is independent of PS days, but number of uses per week follows the number of PN days per week (ERG clinical advice).
e. Use of additional medications is independent of the number of PS days.
f. Specialist follow-up visits per year are independent of PS days, and are fixed at three per year in adults and four per year in the paediatric cohort (Parexel company submission ref 45).
g. The incidence rate for line sepsis is not correlated with number of PS days, and is fixed at a rate of 0.37 per 1000 catheter person days (= 0.135 per catheter person year) (Parexel company submission ref 45)
h. Intensive care days (14) are required in 50% of patients hospitalised for line sepsis (Parexel company submission ref 45)
i. The annual incidence of line fracture is fixed by number of PS days at once per year in adults (as per company submission). The PS fracture rate is once per year in low PS dependence children, and twice per year in mid PS to high PS dependence in children (as per company submission).

Table 39 Breakdown ERG reworked adult health state costs

			Resource use per time unit								Annual Costs (with interpolation)							
Cost item	**Units**	**Cost per unit**	**No PS**	**PS1**	**PS2**	**PS3**	**PS4**	**PS5**	**PS6**	**PS7**	**No PS**	**PS1**	**PS2**	**PS3**	**PS4**	**PS5**	**PS6**	**PS7**
PN bag (≥8 ingredients) band A	day/ week	£119.03	0	1	2	3	4	5	6	7	£0	£6,190	£12,379	£18,569	£24,758	£30,948	£37,137	£43,327
Delivery	delivery/ month	£77.50	0	2	2	2	2	2	2	2	£0	£1,860	£1,860	£1,860	£1,860	£1,860	£1,860	£1,860
Nurse time	hour/ week	£99.64	0	0.80	1.60	2.40	3.20	4.00	4.80	5.60	£0	£4,145	£8,290	£12,435	£16,580	£20,725	£24,870	£29,015
Taurolock	day/ week	£12.52	0	1	2	3	4	5	6	7	£0	£651	£1,302	£1,953	£2,604	£3,255	£3,906	£4,557
PPIs	day	£8.81	0	1	1	1	1	1	1	1	£0	£3,218	£3,218	£3,218	£3,218	£3,218	£3,218	£3,218
Antimotility agents	day	£10.85	0	1	1	1	1	1	1	1	£0	£3,963	£3,963	£3,963	£3,963	£3,963	£3,963	£3,963
Fragmin 5---- unit (0.2mL syringe)	day	£2.82	0	1	1	1	1	1	1	1	£0	£1,030	£1,030	£1,030	£1,030	£1,030	£1,030	£1,030
Ondansetron	day	£22.78	0	1	1	1	1	1	1	1	£0	£8,320	£8,320	£8,320	£8,320	£8,320	£8,320	£8,320
Specialist visits	Visit/ year	£189.79	0	3	3	3	3	3	3	3	£0	£569	£569	£569	£569	£569	£569	£569
Line sepsis	episode/ year	£5,668.10	0	0.135	0.135	0.135	0.135	0.135	0.135	0.135	£0	£765	£765	£765	£765	£765	£765	£765
Line sepsis requiring critical care	day/ year	£1,516.50	0	0.945	0.945	0.945	0.945	0.945	0.945	0.945	£0	£1,433	£1,433	£1,433	£1,433	£1,433	£1,433	£1,433
Line fracture occlusion	episode/ year	£354.00	0	1	1	1	1	1	1	1	£0	£354	£354	£354	£354	£354	£354	£354
						ERG estimated total annual costs (no complications)					**£0**	**£29,946**	**£40,932**	**£51,917**	**£62,903**	**£73,889**	**£84,874**	**£95,860**
						ERG estimated 28 day cycle costs (no complications)					**£0**	**£2,296**	**£3,138**	**£3,980**	**£4,822**	**£5,664**	**£6,506**	**£7,349**
						ERG estimated total annual costs					**£0**	**£32,498**	**£43,484**	**£54,470**	**£65,455**	**£76,441**	**£87,427**	**£98,412**
						ERG estimated 28 day cycle costs					**£0**	**£2,491**	**£3,333**	**£4,176**	**£5,018**	**£5,860**	**£6,702**	**£7,544**

Table 40 Breakdown of ERG reworked paediatric health state costs

			Resource use per time unit				Annual Costs			
Cost item	**Unit**	**Cost per unit**	**No PS**	**PS3**	**PS5**	**PS7**	**No PS**	**PS 1-3**	**PS 4-5**	**PS 6-7**
PN bag (≥8 ingredients) band A	day/week	£119.03		3	5	7	0	£18,569	£30,948	£43,327
Delivery	delivery/month	£77.50		2	2	2	0	£1,860	£1,860	£1,860
Taurolock	day/week	£12.52		3	5	7	0	£1,953	£3,255	£4,557
PPIs + H2 receptor blocker	day	£10.64		1	1	1	0	£3,886	£3,886	£3,886
Antimotility agents	day	£5.42		1	1	1	0	£1,980	£1,980	£1,980
Fragmin 5----unit (0.2mL syringe)	day	£2.82		1	1	1	0	£1,030	£1,030	£1,030
Ondansetron	day	£11.39		1	1	1	0	£4,160	£4,160	£4,160
Haematology tests	tests/year	£3.10		4	4	4	0	£12	£12	£12
Inflammatory markers	tests/year	£6.42		4	4	4	0	£26	£26	£26
Clinical biochemistry	tests/year	£1.18		4	4	4	0	£5	£5	£5
Specialist visits	Visit/year	£268.41		4	4	4	0	£1,074	£1,074	£1,074
Line sepsis	episode/year	£5,668.10		0.135	0.135	0.135	0	£765	£765	£765
Line sepsis requiring critical care	day/year	£3,306.50		0.945	0.945	0.945	0	£3,125	£3,125	£3,125
Suspicion of sepsis	episode/year	£2,343.50		1	1	0	0	£2,344	£2,344	£0
Line fracture occlusion	episode/year	£654.00		1	2	2	0	£654	£1,308	£1,308
			ERG estimated total annual costs				**0**	**£41,442**	**£55,777**	**£67,115**
			ERG estimated 28 day cycle				**0**	**£3,177**	**£4,276**	**£5,145**

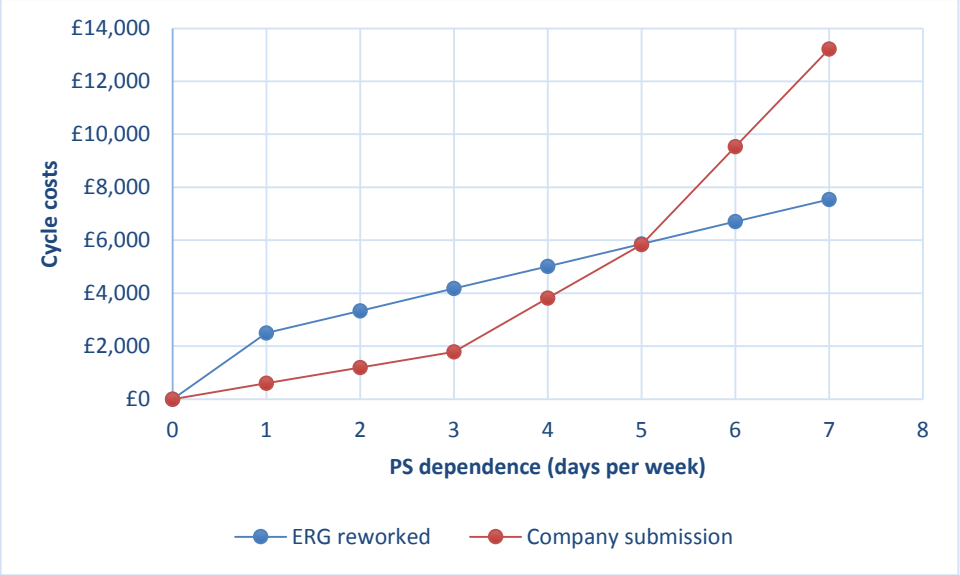


Figure 13 28 day cycle health state costs by level of PS dependence (days per week)