Teduglutide for treating short bowel syndrome [ID3937]

Produced by Aberdeen HTA Group

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Contribution of authors

Clare Robertson and Moira Cruickshank summarised and critiqued the company's definition of the decision problem and the clinical effectiveness evidence reported within the company submission. Dolapo Ayansina critiqued the statistical methods and analyses presented in the company submission and checked all the numerical results related to the review of the clinical effectiveness evidence. Charlotte Kennedy and Graham Scotland critiqued the cost-effectiveness evidence submitted by the company, checked their economic model, and conducted further sensitivity analyses. Paul Manson critiqued the methods used for identifying relevant studies and checked the search strategies presented in the company submission. Francesca Maroni provided clinical advice during the appraisal. Miriam Brazzelli acted as lead for the clinical effectiveness side of the appraisal. Graham Scotland coordinated all aspects of the appraisal and acted as lead for the cost-effectiveness side of the appraisal. All authors contributed to the writing of this report and approved its final version.

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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-2	Glucagon-like peptide-2
HD	Haemodialysis
HPN	Home parenteral nutrition
HRQoL	Health-related quality of life
HSUV	Health state utility values
IBDQ	Inflammatory bowel disease questionnaire
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
PSP	Patient support programme
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
SBS-QoL	Short bowel syndrome specific quality of life
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
TRAE	Treatment related adverse event

TSD	(NICE) technical support document
TTO	Time trade off

1 Executive summary

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.6 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main ERG report.

All issues identified represent the ERG's view and opinion, not that of NICE.

1.1 Overview of the ERG's key issues

The focus of the submission received from Takeda is teduglutide for treating short bowel syndrome. The clinical evidence for adults is provided mainly by data from two randomised controlled trials (STEPS and 004) and three open-label extension studies (STEPS-2, STEPS-3 and 005), eight non-interventional real-world studies and the Takeda Patient Support Programme (PSP) in Australia. Clinical effectiveness data for children are derived from two phase three trials (C13 and C14), their open-label extension studies (SHP633-303 and SHP633-304) and one non-interventional real-world study. Regarding the safety profile of teduglutide, the overall frequency and severity of adverse events in the two phase 3 RCTs, STEPS and 004, was broadly similar between participants treated with teduglutide and those treated with placebo, apart from upper respiratory tract infection in the pooled analysis of STEPS and 004 only, which was noticeably higher in the teduglutide group compared with the placebo group.

Table 1 Summary of key issues

Issue	Summary of issue	Report sections
1	Modelling of health state transitions (and the placebo response in STEPS)	3.2.2, 4.2.6
2	Health state utility by PS frequency	4.2.7
3	Modelling of overall survival	4.2.6
4	Modelling of complications (IFALD and CKD)	4.2.6
5	Modelling of adverse events	4.2.6
6	PS health state costs (specialist visits and line sepsis)	4.2.8

1.2 Overview of the key model outcomes

The company utilise a Markov state transition model, with health states representing the number of days of parenteral support a patient requires per week (PS0-7) and death. Transition probabilities for those on teduglutide treatment are derived from the teduglutide arm of STEPS, STEPS-2 (open label extension to STEPS) and the Australian PSP data – allowing patients to reduce their PS requirement or to remain stable. In line with the explanation outlined above for the placebo response in STEPS, the company retain the baseline health state distribution for the standard of care arm over the lifetime horizon of the model. Long term complications of intestinal failure associated liver disease (IFALD) and chronic kidney disease (CKD) are assumed to be related to the frequency of PS use, and are modelled as expected proportions by number of PS days. Other adverse events are modelled

based on rates observed in STEPS and STEPs-2. Survival is assumed to be unaffected by treatment or health state.

Overall, teduglutide is modelled to affect QALYs by:

- Reducing the number of days that people require PS per week – modelled to improves the health-related quality of life of patients and carers.
- Reducing the incidence of complicaitons associated with the frequency of PS use.
- Changing the incidence of other adverse events compared to standards care.

Overall, the technology is modelled to affect costs by:

- Increasing drug treatment acquisition and monitoring costs
- Reducing the costs associated with PS
- Reducing costs associated with complications associated with PS frequency
- Changing adverse events compared to standards of care.

The modelling assumptions that have the greatest effect on the ICER are:

- The assumption that patients on SoC receive no reduction in their PS requirement over time
- The application of lower adverse event rates for those on teduglutide compared to SoC beyond 6 months
- The extrapolation of overall survival.

1.3 The decision problem: summary of the ERG's key issues

In general, the company decision problem is in line with the NICE final scope and no major issues were identified by the ERG

1.4 Summary of the key issues in the clinical effectiveness evidence

Data from STEPS and 004 showed that a significantly higher proportion of patients on teduglutide achieved a ≥20% reduction in parenteral support volume at week 20, maintained to week 24 (the definition of clinical response and primary endpoint of

STEPS) than patients on placebo and also in STEPS a significantly higher proportion of patients on teduglutide reported achieving at least one day off PS per week that those in the placebo arm. However, the company argue that the placebo response rate was unrealistically high and could be explained by reliance of the conservative weaning algorithm used in these clinical trials in comparison with the more liberal weaning approaches used in clinical practice. The company, therefore, present data from eight non-interventional, observational, studies and from their Australian PSP to support the effectiveness of teduglutide.

The company performed two meta-analyses to formally compare the pooled estimates derived from observational real-world studies to the estimates obtained from the teduglutide arm of STEPS/STEPS-2 trials. There is no direct comparison of teduglutide versus placebo as the real-world studies are non-interventional studies without a comparator arm. The meta-analyses were not conducted to pool the results of the clinical effectiveness of teduglutide against a comparator (standard care) but, rather, to compare the effect estimates of teduglutide arm between different study designs.

1.5 The cost-effectiveness evidence: summary of the ERG's key issues

The ERG identifies the following key issues and uncertainties in the company's economic case:

Issue 1 Modelling of health state transitions.

Report section	Section 4.2.6
Description of issue and why the ERG has identified it as important	The company argue that the placebo response in STEPS is an artefact of the weaning algorithm applied in the trial, and that no such reductions would be expected for these patients in routine practice where weaning algorithms are not used. Conversely, they argue that the weaning algorithms applied in STEPS and STEPS-2 lead to underestimation of the reduction in PS frequency that patients can expect in the absence of weaning algorithms. This is backed up by the reductions observed in real-world cohort studies and the Australian PSP data used in the

	model. The company's explanation is plausible, but some uncertainty remains as we do not have any comparative evidence between SoC and teduglutide under routine practice.
What alternative approach has the ERG suggested?	The ERG accept the company base case as plausible, but provide a scenario that applies the placebo response from STEPS to the SoC arm, and holds the 6 months health state distribution constant for the remainder of the model horizon. The ERG acknowledge that this is likely overly conservative.
What is the expected effect on the cost-effectiveness estimates?	The scenario has a substantial upward impact on the ICER
What additional evidence or analyses might help to resolve this key issue?	Further comment from clinical experts on the company's assumptions would be beneficial. In particular, comment on the potential for patients that were included in STEPS or the PSP to experience any sustainable reduction in PS in the absence of teduglutide treatment.

Issue 2 Health state utility by PS frequency

Report section	Section 4.2.7
Description of issue and why the ERG has identified it as important	The company provide strong arguments, backed up by testimonies form patients and clinical experts, that a reduction in PS days is the most relevant outcome of teduglutide treatment in terms of impact on quality of life of patients and carers. However, quality of life data collected in STEPS fails to show a significant effect of treatment and indicates an inconsistent relationship between PS days and health state utility which lacks face validity. The company, therefore, rely on values obtained for health state vignettes. The ERG acknowledges the reasoning for this but have some concern that the approach may

	exaggerate the quality of life benefit of PS reductions, and note the lack of comparability of the modelled QALYs with other appraisals. Similarly, carer QALYs are assumed to be related to PS days in the model, but the empirical evidence to support a quantitative relationship between PS days and carer utility is weak. Therefore, the applied utility decrements rely heavily on clinical expert opinion. A further issue is that the utility decrements have been estimated relative to perfect health.
What alternative approach has the ERG suggested?	There is little that can be done with respect to selecting alternative sources for utility inputs, as these provide values that are inconsistent with the argument that reductions in PS improve health state utility. The ERG accepts the company's approach but has further explored the uncertainty by reducing the range in utility between the PS0 and PS7 health state by 10% and 20%.
What is the expected effect on the cost-effectiveness estimates?	This has a modest upward impact on the ICER.
What additional evidence or analyses might help to resolve this key issue?	Little can be done with respect to identifying further data. Some further insight from patients and carers who have experienced treatment and PS reductions with teduglutide may be useful.

Issue 3 Modelling of survival

Report section	Section 4.2.6
Description of issue and why the ERG has identified it as important	Survival in the model is based on extrapolation of published Kaplan-Meier data on patients with SBS-IF on long term PS. It is not influenced by health state or treatment. The extrapolation period is long given the time horizon of the model, and the company's base case curve

	selection in the adult model may lack face validity as the projected mortality rate drops below that of the general population whilst a substantial proportion of the cohort remains alive. Whilst this is overridden in the model by equalising mortality to the age/sex match general population mortality rate from this point onwards, other curve selections that mitigate this issue may be preferable. A further limitation relates to the fact that mortality is assumed to be unaffected by the incidence of long-term complications that are likely to increase the mortality risk (see issue 4).
What alternative approach has the ERG suggested?	The ERG suggest an alternative more conservative extrapolation of overall survival that does not project mortality rates below the general population mortality rate until later in the time horizon when a lower proportion of the modelled cohort are still alive.
What is the expected effect on the cost-effectiveness estimates?	This has a modest upwards impact on the ICER
What additional evidence or analyses might help to resolve this key issue?	Further comment from clinical experts on whether it is reasonable for a proportion of patients with SBS-IF on long-term parenteral nutrition to achieve mortality rates in line with the general population. Or would SBS-IF patients continue to have an excess mortality risk compared to age/sex matched general population controls.

Issue 4 Modelling of complications

Report section	Section 4.2.6
Description of issue and why the ERG has	IFALD (of different levels of severity) and CKD are modelled as expected cumulative proportions by PS health state, and the risk of developing these is assumed to

identified it as important	increase with higher PS frequency. Teduglutide reduces the incidence of these complications by reducing PS frequency and generates associated cost savings and QALY gains. The approach to calculating the cumulative proportions with IFALD and CKD is based on elicitation of expert opinion, and involves further structural assumptions which may generate biases. In particular, the lack of a structural link in the model between the proportions surviving with these complications and the risk of death may lead to their overestimation over time; in turn leading to overestimation of the associated costs and utility losses attributable to living with the conditions (biasing in favour of teduglutide). Conversely, it may result in failure to capture a small expected survival benefit for teduglutide (biasing against teduglutide). The magnitude and direction of bias is unclear.
What alternative approach has the ERG suggested?	The model structure and data limitations preclude the creation of link in the model between the proportion with IFALD and CKD and the risk of mortality. Given the uncertainties introduced by the approach to modelling these complications, the ERG believe it is important to assess the impact of excluding them s in scenario analysis. The company and the ERG have done this.
What is the expected effect on the cost-effectiveness estimates?	Excluding them has a modest upward impact on the ICER. This is likely to be conservative as it is plausible that teduglutide has some effect on reducing their incidence and associated costs and QALY losses.
What additional evidence or analyses might help to resolve this key issue?	Further clinical expert opinion on whether it is reasonable to assume teduglutide would reduce these complications. Attempts by the company to better account for fact that patients these complications, particularly with more

	advanced stages of liver disease, are at greater risk of mortality.

Issue 5 Modelling of adverse events

Report section	Section 4.2.6
Description of issue and why the ERG has identified it as important	The adverse event rates utilised in the economic model decrease substantially from 6 months in the teduglutide arm (based on data from STEP-2). This suggests a diminishing event rate with respect to time and that the safety profile of teduglutide improves over standard care. The ERG finds that the company has not clearly justified these findings and the calculation of the rates in a clear and transparent manner. The section of the company submission presenting the pooled safety data did not make a case for diminishing rates of adverse events (events/patient time at risk) over time. The calculation of AE rates in the model has not been transparently presented, and there are no comparative data to demonstrate a reduced rate of AEs compared to SoC.
What alternative approach has the ERG suggested?	The ERG explored the uncertainty by using only rates from the STEPS trial and applying the standard of care rates to the teduglutide arm from 6 months in the model.
What is the expected effect on the cost-effectiveness estimates?	The above changes have modest upward impact on the ICER, but the company may be able to better justify their assumptions and approach.
What additional evidence or analyses might help to resolve this key issue?	It would be beneficial if the company can clearly and transparently justify the case that teduglutide has more favorable safety profile compared to SoC in the longer term. Further clarity regarding the calculation of the applied rates from the trial data would also be of value.

Issue 6 PS health state costs

Report section	Section 4.2.8
Description of issue and why the ERG has identified it as important	The company apply health state costs that account for PS resources that are required to fulfill a patient PS needs. The costs increase with the number of days PS is required. The costs factor in 3 gastroenterology (multi-professional) specialist visits per year for everyone on PS (1 to 7 days), and assume no specialist visits for those who achieve PS independence. Based on clinical advice, the ERG believe that all patients with SBS-IF may require 3-4 specialist visits per year, including those who achieve PS independence. A further uncertainty relates to the inclusion of line sepsis in the PS health state costs, with the incidence of line sepsis assumed to increase with increasing frequency of PS. The evidence and clinical support for this appears to be mixed.
What alternative approach has the ERG suggested?	The ERG prefers to include an equal number of specialist visits for those who achieve independence, and also assesses the impact of assuming flat rate of line sepsis across the PS health states (1-7 days).
What is the expected effect on the cost-effectiveness estimates?	The changes have modest upward impact on the ICER.
What additional evidence or analyses might help to resolve this key issue?	Clinical expert opinion on whether: • Achieving PS independence would be expected to reduce the number of gastroenterology visits per year for patients with SBS-IF. • Whether it is reasonable to assume that line sepsis rates are correlated with the number of days of PS a patient required per week.

1.6 Summary of ERG's preferred assumptions and ICER

Given the uncertainties outline above, and other issues raised in the report, the ERG prefers to:

1) Correct a minor cell referencing issue for an adverse event disutility in the company model.

2) Assume an equal number of gastroenterology specialist visits per year for those remain on PS and those who achieve PS independence.

3) Recalculate the utility decrement applied for line sepsis relative the EQ-5D norm rather than 1.

4) Apply the more conservative exponential extrapolation of overall survival to the adult model

Further scenario analysis on the ERG base case explores the removal of IFALD and CKD complications, the removal of carer disutility, and alternative extrapolations of time on treatment (section 6.3).

Table 2 ICER resulting from ERG's preferred assumptions

Preferred assumption	Section in ERG report	Incremental costs (£)	Incremental QALYs	Cumulative ICER £/QALY
Company base case		[redacted]	[redacted]	£16,652
1) Correct disutility cell referencing error	5.3	[redacted]	[redacted]	£16,344
2) Equal gastroenterology visits for PS0	4.2.8	[redacted]	[redacted]	£16,947
3) Recalculation of utility decrement applied for line sepsis	4.2.7	[redacted]	[redacted]	£17,158
4) Exponential extrapolations of survival	4.2.6	[redacted]	[redacted]	£20,314

Note, separate analyses are provided for the paediatric population in chapter 6.

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

The relevant health condition for the submission received from Takeda UK Ltd is short bowel syndrome with type 3 intestinal failure (SBS-IF) in people aged at least 1 year of age. The company's description of this health condition in terms of prevalence, symptoms and complications appears generally accurate and in line with the decision problem. The relevant intervention for this submission is teduglutide (Revestive®)

2.2 Background

The company submission (CS) 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] Short bowel syndrome is when less than 200cm of the bowel remain, at which point intestinal failure can occur.[1-3] Common reasons for surgical resection of the intestine in adults are malignancy, Crohn's disease, vascular insufficiency or radiation.[4] In children, the main causes of SBS are prenatal (such as atresia or gastroschisis), neonatal (such as necrotising enterocolitis) or postnatal (such as midgut volvulus, arterial thrombosis or inflammatory bowel disease.[5, 6]

Some intestinal adaptation occurs following extensive resection of the small bowel, with the intestine experiencing structural changes which deliver an increase in the absorptive surface area.[7, 8] The extent of intestinal adaptation by the remnant bowel is a factor in the occurrence of permanent intestinal failure and the requirement for parenteral support (PS).[8] Parenteral support maintains fluid, electrolytes, trace elements, vitamins and nutrient balances and consist of parenteral nutrition and/or intravenous fluid.[1, 9] 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.[10] 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.[11-14]

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. In those patients who require PS, reduction of PS requirements can improve quality of life and minimise complications.[15]

Treatments for SBS have traditionally focused on optimising dietary interventions, and antisecretory and antidiarrhoea medication, with surgery a further option for some patients.[15, 16] 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, 15] 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.[9, 15] Teduglutide (Revestive®) 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.[17, 18] Teduglutide improves the structure and function of the remaining intestine, thus enhancing fluid and nutrient absorption.[17, 19] It has been reported that teduglutide reduces PS volume requirements which may be associated with a reduction in PS burden.[17]
Teduglutide was granted European marketing approval in August 2012 for adults with SBS. The license was extended in 2016 to include patients at least 1 year of age. 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 recommended dose is 0.05mg/kg body weight once daily.[20]

The proposed place of teduglutide in the treatment pathway is presented in Document B, Figure 4 of the CS and is reproduced below as Figure 1. The ERG agrees that the company's proposed pathway is representative of current clinical practice and the anticipated positioning of teduglutide is within its licensed indication.

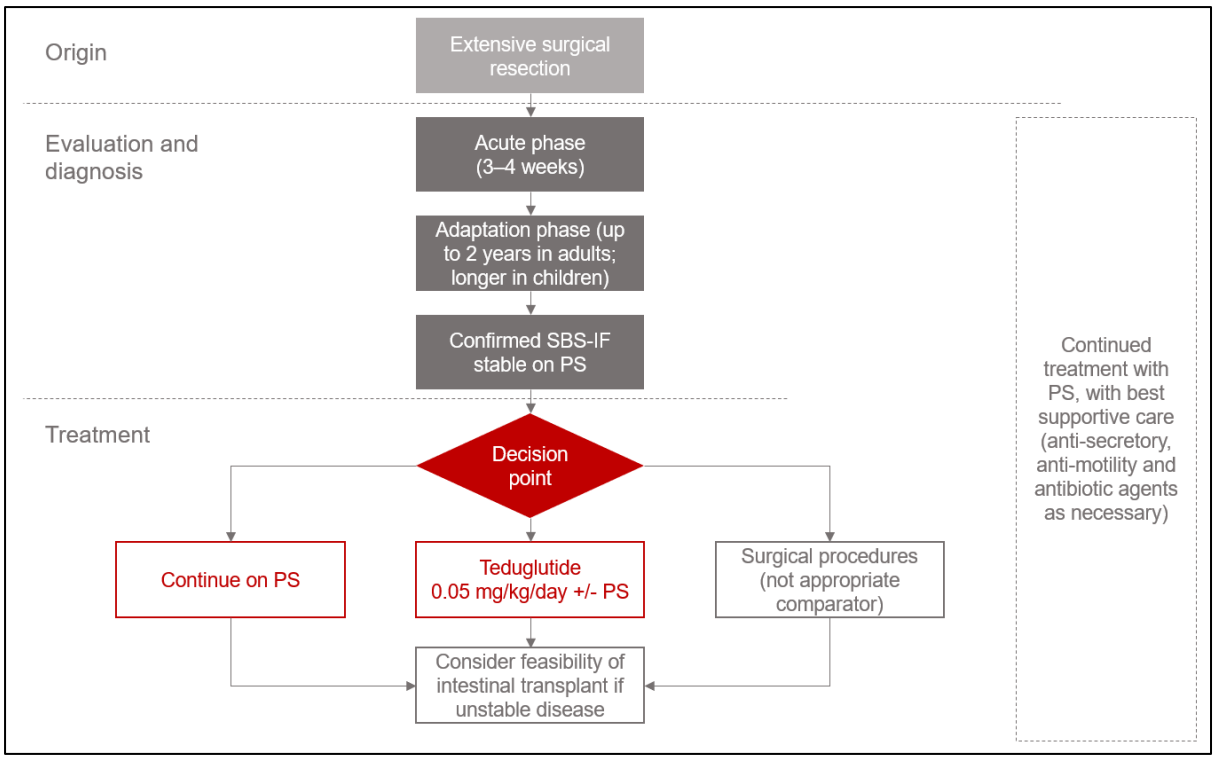


Figure 1 Company's proposed treatment pathway and positioning of teduglutide for adults and children with SBS-IF [reproduced from Document B, Figure 4 of the CS]

2.3 Critique of company's definition of decision problem

A summary of the company's decision problem in relation to the NICE final scope is presented in Table 3 below. A critique of adherence of the company's economic modelling to the NICE reference case is presented in Chapter 4.

Table 3 Summary of the company's decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Population	People with short bowel syndrome who are stable following a period of intestinal adaptation after surgery	People aged ≥1 year old with short bowel syndrome who are stable following a period of intestinal adaptation after surgery	Teduglutide is licensed in patients at least 1 year old	The ERG agrees that the population addressed in the CS is appropriate for this appraisal
Intervention	Teduglutide in addition to established clinical management	As per scope	NA	The intervention described in the CS matches that described in the NICE final scope. Teduglutide was granted European marketing approval in August 2012 for adults with SBS. The license was extended in 2016 to include patients of at least 1 year of age
Comparator(s)	Established clinical management without teduglutide (including parenteral support, antimotility and antisecretory agents, fluid restriction and dietary optimisation)	As per scope	NA	The comparator described in the CS matches the comparator described in the final scope
Outcomes	• reduction in parenteral support requirements (volume and frequency) • overall survival • adverse effects of treatment • health-related quality of life • impact on carers	As per scope	NA	The outcomes reported in the CS match the NICE final scope. The ERG clinical expert considers the outcomes to be appropriate for addressing the topic of this appraisal
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness	Most aspects of the economic analysis are per the reference case (all direct health effects considered, lifetime time horizon, systematic review for synthesis of evidence, use of QALYs, equity considerations, NHS and PSS perspective for costs and	The only patient-reported utilities available are derived from the STEPS trial. [redacted] Clinicians state that this is not realistic.	The ERG finds the economic analysis to be broadly in line with reference case. See chapter 4 for detailed comments.

	should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account	resource use, 3.5% discount rate). The only exception is the source of data for measurement of health-related quality of life: derived from Ballinger 2018, a vignette study using utilities provided by UK general population		
Subgroups	No subgroups were specified in the NICE final scope			
Special considerations including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator			The CS states that no equality considerations were identified by the company. The ERG is in agreement that there are no equity issues for this submission

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

Full details of the methods used to identify and select the clinical evidence relevant to this appraisal are reported in Appendix D of the CS. The ERG appraisal of the company's systematic review methods is summarised in Table 4.

Table 4 ERG's appraisal of the systematic review methods presented in the CS

Review process ERG	ERG response	Comments
Were appropriate searches (e.g., search terms, search dates) performed to identify all relevant clinical and safety studies?	Yes	The CS provides full details of the searches used to identify the studies for the clinical effectiveness review. The search strategies include relevant controlled vocabulary and text terms with appropriate use of Boolean operators and are fully reproducible. Details provided in Appendix D of the CS.
Were appropriate bibliographic databases/sources searched?	Yes	Sources included Embase, Medline, and CENTRAL for primary research, DARE and CDSR for evidence syntheses. Relevant conference proceedings were also searched. Full details are provided in Appendix D of the CS.
Were eligibility criteria consistent with the decision problem outlined in the NICE final scope?	Yes	The eligibility criteria were not used in the clinical effectiveness searches, ensuring the search returned any relevant results.
Was study selection conducted by two or more reviewers independently?	Yes	Appendix D, SLR report, page 20 states that for the SLR update "*Two independent reviewers screened citations by title/abstract, with any conflicts regarding eligibility resolved by discussion between the two reviewers. Where necessary, arbitration was provided by a third, more senior reviewer. Full-text publications were also evaluated by two independent reviewers, with any disputes regarding eligibility resolved by dialogue between the two reviewers. Again, arbitration was provided by a third, more senior reviewer if required"* Appendix D, SLR report page 61 states that for the original SLR "*Two reviewers independently reviewed each reference (title and abstract) identified by the literature search and applied basic study*

		selection criteria (population, intervention and study design). Where a consensus was not reached, any uncertainty about the inclusion of studies was checked and judged by a third senior researcher. For potentially relevant articles, the full article was obtained and independently reviewed against each eligibility criterion."
Was data extraction conducted by two or more reviewers independently?	Yes	Appendix D, SLR report, page 20 states that for the SLR update "*Data from the included publications were extracted by one reviewer into standardised, piloted data extraction tables (DETs) in Excel. To ensure that all data in the final DETs were accurate, all extracted data were checked and validated by a second independent reviewer*." Appendix D, SLR report, page 61 states that for the original SLR "*Data were extracted from the included full-text articles by one reviewer. All extracted data were then quality checked against the original source article by a second, independent reviewer*."
Were appropriate criteria used to assess the risk of bias of identified studies?	Yes	Critical appraisal of the STEPS and 004 RCTs appears to have been conducted using an adapted version of the University of York Centre for Reviews and Dissemination checklist. The non-randomised trials and observational studies were quality-assessed using the Downs and Black checklist.
Was risk of bias assessment conducted by two or more reviewers independently?	Yes	Quality assessments were performed by one reviewer and then checked and validated by a second independent reviewer
Was identified evidence synthesised using appropriate methods?	Yes	The meta-analyses were not conducted to pool the results of the clinical effectiveness of teduglutide against a comparator (standard care). Rather, they compared the effect estimates of teduglutide arm between different study types.

The ERG conducted a quality assessment of the methods used by the company for the systematic review of clinical evidence using the Centre for Review and Dissemination (CRD) criteria.[21] The results are presented in Table 5.

Table 5 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

3.2 Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

3.2.1 Included studies

Details of the key clinical effectiveness evidence are provided in Document B, Section B.2 of the CS. The company presents clinical effectiveness evidence from a number of clinical trials, open-label extensions, and real-world studies for adults and children. For adults, clinical effectiveness data are derived from two randomised controlled trials (STEPS and 004),[9, 22] three open-label extension studies (STEPS-2, STEPS-3 and 005),[23-25] a company-sponsored real-world patient support programme (PSP)[26] in Australia, and eight non-interventional real-world studies; for children, clinical effectiveness data are derived from two phase three trials (C13 and C14),[27, 28] their open-label extension studies (SHP633-303 and SHP633-304)[29, 30] and one non-interventional real-world study.

For their economic model, the company focused on data from STEPS, STEPS-2, and the Australian PSP. The company presents details of the studies excluded from the economic model, along with the rationale for exclusion in Tables 6 and 7 of the CS. The ERG critique of the company's economic model will be discussed in chapter 4.

While the company have not included studies listed in Table 6 of the CS in their economic model, they present clinical evidence from some of them in the clinical

effectiveness section of the CS. They present efficacy data from STEPS-3, 004, C13 and C14 and safety data from 004, 005, C13, C14, SHP633-303 and SHP633-304. It is unclear why they have not presented data from SHP633-302 and TED-C14-004, two open-label studies - one enrolling children (SHP633-302) and one adults (TED-C14-004). At clarification, the company explained that they decided to exclude these studies as they had been conducted in Japan and were of small sample size. While the ERG agrees with the company that addition of these studies would be of limited value, the reason for their exclusion is not entirely justified.

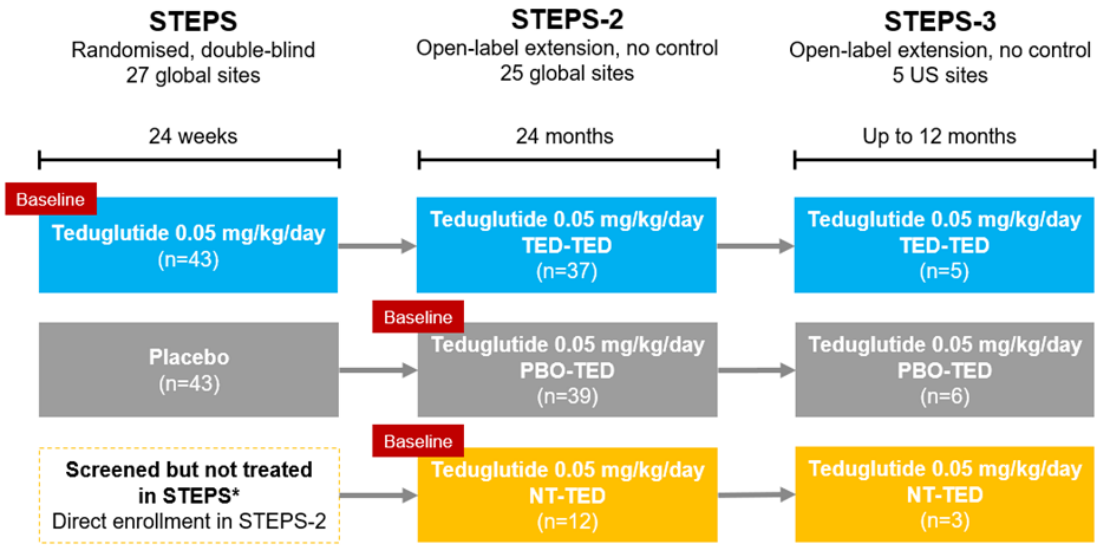
Details of the relevant clinical effectiveness evidence are presented in section B.2.2 of the CS. STEPS, 004, 005, SHP633-303, SHP633-304, C13, C14 and the PSP study received funding from Takeda, or by companies affiliated with Takeda.

Methodology of the RCTs included in the CS and their extension studies
The methodology of the two RCTs included in the CS are presented in Table 8. The methods used in **STEPS** and **004** were broadly similar with some differences. The baseline characteristics of the two trials are provided in Table 10 of the CS and the company provides a comparison of the STEPS population and a database study of the UK SBS-IF population in Appendix L. The ERG notes that the populations are comparable in terms of their demographic characteristics, and the ERG's clinical expert believes that the patient populations in both STEPS and 004 are representative of the patients currently seen in UK clinical practice.

The ERG generally agrees with the company's critical appraisal of the STEPS and 004 (presented in Appendix D, Tables 1 and 2 and assessed using adapted CRD guidance) and is satisfied that the trials are of good methodological quality.[21] The ERG considers the methodology of these two trials broadly similar, although there are variations in terms of their eligibility criteria, primary endpoints and some subgroups. The most important difference between the two trials is the more restrictive weaning algorithm adopted in 004. The company maintain that the weaning algorithms used in both trials are more conservative than the PS weaning used in clinical practice; in particular, the company claim that the algorithm used in 004 is unduly restrictive in that it allows only a maximum of 10% PS reduction and the trial, therefore, lacks external validity. The ERG accepts the company's argument that the weaning

algorithm used in STEPS is a closer match to clinical practice than the weaning algorithm used in 004.

STEPs-2 (24-month follow-up) and **STEPS-3** (12-month follow-up) were open label extension studies to the STEPS trial. An overview of the methodology of the extension studies is provided in section B.2.3.2 and Figure 6 of the CS, reproduced here as Figure 2 below. The extension studies followed the same weaning algorithm as STEPS but there were fewer opportunities for PS reduction. The baseline characteristics of the two extension studies are provided in Appendix L, Tables 22 and 23. The ERG notes the relatively small sample size of STEPS-3 (n=14), and that the number of patients providing outcome data for given timepoints in this trial is variable due to the rolling study start dates and fixed end date. STEPS-3 was also conducted exclusively in the USA, although the ERG has no concerns on this point.



Abbreviations: NT-TED, not treated in STEPS and treated with teduglutide in STEPS-2; PBO-TED, treated with placebo in STEPS and treated with teduglutide in STEPS-2; TED-TED, treated with teduglutide in STEPS and STEPS-2

Notes: *Patients who completed fluid optimisation and stabilisation but were not randomised in STEPS because of full study enrolment were eligible for direct enrolment into STEPS-2

Source: STEPS primary publication;[9] STEPS-2 primary publication;[23] STEPS-3 primary publication[31]

Figure 2 Overview of the STEPS clinical programme (reproduced from Document B, Figure 6 of the CS)

Methodology of the Australian PSP

The methodology of the **PSP** in Australia is outlined in section B.2.3.3 of the CS. The PSP included training and guidance for healthcare professionals and patients, as well as home nursing support. [redacted] Data are presented in the CS for [redacted] The company presents a comparison of the baseline characteristics of the PSP patients and the STEPS teduglutide patients in Table 16 of the CS. The ERG notes that the two populations are [redacted] The company notes that while there is variability across sources of data with respect to the proportion of patients with colon-in-continuity and end-stoma, the presence of colon-in-continuity and end-stoma within patients in STEPS was balanced between study arms and therefore did not contribute to any difference in treatment effect between the teduglutide and placebo arms. The presence of colon-in-continuity and end-stoma within patients in STEPS was also representative of patients treated with teduglutide in the real-world.

Methodology of the real-world studies

Details of the eight non-interventional, observational studies of teduglutide are presented in section B.2.6.4 of the CS and the baseline characteristics of these studies are presented in Table 15 alongside a comparison with the STEPS teduglutide population. The company assessed the methodological quality of the real-world using the Downs and Black checklist.[32] The ERG broadly agrees with the company's assessment but notes that the observational study design (and lack of a comparator treatment) are inherently at greater risk of bias than randomised controlled trials, which are regarded as the gold standard for evaluating healthcare interventions.

Methodology of the paediatric studies

The company present efficacy and safety data from studies that focused on a paediatric population to compare their results with those that focused on an adult

population. The company presents a summary of the methodology of the trials conducted in children in section B.2.3.4 and Table 9 of the CS. Both C13 and C14 were open-label, dose-finding studies conducted in paediatric patients with SBS-IF. Patients received treatment with teduglutide or standard care for 24 weeks in C14, and for 12 weeks in C13. While study patients in both studies were not randomised to receive teduglutide or standard care (C14 n=9, C13 n=5), patients who chose treatment with teduglutide in C14 were randomised to receive either teduglutide 0.025 mg/kg/day (n=24) or teduglutide 0.05 mg/kg/day (n=26). No randomisation was performed in C13 and patients were enrolled to receive one of three doses of teduglutide: 0.0125 mg/kg/day (n=8), 0.025 mg/kg/day (n=14), or 0.05 mg/kg/day (n=15). In C13 and C14, the investigators were provided with weaning guidance, but the decision to wean at study visits was ultimately at the investigator's and patient's discretion. In C13, guidance suggested that PS volume could be decreased if fluid intake exceeded output by >400 mL/m^2. In C14, guidance suggested that PS volume could be decreased by ≥10% if urine output was ≥25mL/kg/day, if urine specific gravity was <1,020, if the patient gained weight, and if patients had <10 stools per day (not in nappies), or stool/mixed output was <75 mL/kg/day (in nappies), or ostomy output <80 mL/kg/day.

The company also presents evidence of teduglutide 0.05 mg/kg/day in children from a real-world observational study of 17 patients conducted in eight sites in Spain.[33] The ERG notes that this is a small observational study with no comparator treatment. The baseline characteristics of the paediatric studies are reported in Appendix L, Tables 25, 26 and 35. The ERG's clinical expert is satisfied that the study populations are representative of the UK paediatric SBS-I population. The company provides their critical appraisal of C13 and C14 in Appendix D, Tables 3 and 4, and of Ramos Boulda in the SLR Appendix D, Table 29 using the Downs and Black checklist.[32] The ERG broadly agrees with the company's quality assessment of these studies.

A summary of the clinical evidence considered in the CS is presented in Table 6 below.

For the adult population, a comparison of the baseline characteristics of the STEPS and 004 trials, real-world studies, and the PSP data is presented in the Table 7 below.

The ERG noted some differences in the interpretation of the baseline data presented in the primary publications compared with data presented in the CS, although these differences are minor and unlikely to influence the results.

Table 6 Summary of the clinical evidence considered in the company submission

Name	Design	Location	Population	Intervention	Comparator	Relevant outcomes	Clinical efficacy data presented in the CS	Safety data presented in the CS	Used in the meta-analysis	Used in the economic model
STEPS	Phase 3, multi-national, randomised, double-blind, placebo-controlled, 24-week study **Weaning protocol**: PS volumes could be reduced if urine volumes during the preceding 48 hours were ≥10% above baseline from between 10–30% of baseline PS volume at each timepoint	27 sites in 10 countries: Canada, Denmark, France, Germany, Italy, Netherlands, Poland, Spain, UK, and USA	Adults (≥18 years old) with SBS-IF who were receiving PS for ≥3 days per week	Teduglutide 0.05 mg/kg/day (n=43)	Placebo (n=43)	Days per week of PS Volume of PS: percentage of patients who demonstrated a ≥ 20% reduction in PS volume at week 20, and maintained this to week 24 Safety	Yes	Yes	Yes	Yes

	(study visits on weeks 2, 4, 8, 12, 16, 20 and 24)									
004	Phase 3, multi-national, randomised, double-blind, placebo-controlled, 24-week study **Weaning protocol:** PS volumes could be reduced if urine volumes during the preceding 48 hours were ≥10% above baseline by up to 10% of baseline PS volume at each timepoint (Study visits on weeks 4, 8, 12, 16, 20 and 24, and reduced on no more than 5	32 sites in 9 countries: Belgium, Canada, Denmark, Germany, France, Netherlands, Poland, UK, and USA	Adults (≥18 years old) with SBS-IF who were receiving PS for ≥3 days per week	Teduglutide 0.05 mg/kg/day (n=35) Teduglutide 0.10 mg/kg/day (n=32)	Placebo (n=16)	Days per week of PS Volume of PS: graded response score, defined as a combination measure of magnitude of response and duration at weeks 16 to 24 (graded response score of ≥1 considered equivalent to the primary endpoint in STEPS) Safety	Yes	Yes	No	No

	of these 6 timepoints) If, in addition, urine volume was over 2.0 L/day, PS volume could be reduced by ≥10% of baseline PS volume (as clinically appropriate)									
STEPS-2	Two-year, open-label, multi-national, extension study for patients screened or treated in STEPS	25 sites in 9 countries: Poland, Denmark, Italy, Canada, Germany, France, Spain, UK, and USA	Adults (≥18 years old) with SBS-IF screened or treated in STEPS	Teduglutide 0.05 mg/kg/day (n=88)	None	Days per week of PS Volume of PS: binary response at a given visit was defined as the achievement of at least a 20% reduction from baseline in weekly PN/I.V. volume Safety	Yes	Yes	Yes	Yes
STEPS-3	One-year, open-label extension	5 sites in USA	Adults (≥18 years old)	Teduglutide 0.05	None	Days per week of PS	Yes	No	No	No

	study for patients in STEPS-2 at 5 US sites		with SBS-IF who completed STEPS-2	mg/kg/day (n=14)		Volume of PS				
005	28-week, open-label, multi-national, extension study for patients treated with teduglutide or placebo in 004	32 sites in 9 countries: Belgium, Canada, Denmark, Germany, France, Netherlands, Poland, UK, and USA and Belgium	Adults (≥18 years old) with SBS-IF treated in 004	Teduglutide 0.05 mg/kg/day (n=31) Teduglutide 0.10 mg/kg/day (n=34)	Adults (≥18 years old) with SBS-IF treated in 004	Days per week of PS Volume of PS: binary response defined as a 20% to 100% reduction from baseline in the weekly PN/I.V. volume Safety	No	Yes	No	No
Joly 2020	Real-world, non-interventional multi-centre study	15 site in France	54 patients with SBS-IF	Teduglutide 0.05 mg/kg/day (n=54)	None	Percentage of patients achieving a clinical response (≥20 reduction in PS volume from baseline) Percentage of patients achieving independence from PS (100% reduction in PS	Yes	No	Yes	No

						volume from baseline)				
Lam 2018	Real-world, non-interventional single-centre study	1 site in USA	18 adults with SBS-IF	Teduglutide 0.05 mg/kg/day (n=18)	None	Percentage of patients achieving a clinical response (≥20 reduction in PS volume from baseline) Percentage of patients achieving independence from PS (100% reduction in PS volume from baseline)	Yes	No	Yes	No
Martin 2021	Real-world, non-interventional single-centre study	1 site in France	31 patients with SBS-IF	Teduglutide 0.05 mg/kg/day (n=31)	None	Percentage of patients achieving a clinical response (≥20 reduction in PS volume from baseline) Percentage of patients achieving independence	Yes	No	Yes	No

						from PS (100% reduction in PS volume from baseline)				
Pevny 2019	Real-world, non-interventional single-centre study	1 site in Germany	19 patients with SBS-IF	Teduglutide 0.05 mg/kg/day (n=27)	None	Percentage of patients achieving a clinical response (≥20 reduction in PS volume from baseline) Percentage of patients achieving independence from PS (100% reduction in PS volume from baseline)	Yes	No	Yes	No
Puello 2020	Real-world, non-interventional single-centre study	1 site in USA	18 adults with SBS-IF	Teduglutide 0.05 mg/kg/day (n=18)	None	Percentage of patients achieving a clinical response (≥20 reduction in PS volume from baseline) Percentage of patients	Yes	No	Yes	No

						achieving independence from PS (100% reduction in PS volume from baseline)				
Schoeler 2018	Real-world, non-interventional single-centre study	1 site in Germany	14 adults with SBS-IF	Teduglutide 0.05 mg/kg/day (n=14)	None	Percentage of patients achieving a clinical response (≥20 reduction in PS volume from baseline) Percentage of patients achieving independence from PS (100% reduction in PS volume from baseline)	Yes	No	Yes	No
Tamara 2020	Real-world, non-interventional single-centre study	1 site in Spain	4 adults with SBS-IF	Teduglutide 0.05 mg/kg/day (n=4)	None	Percentage of patients achieving a clinical response (≥20 reduction in PS volume from baseline)	Yes	No	Yes	No

						Percentage of patients achieving independence from PS (100% reduction in PS volume from baseline)				
Ukleja 2018	Real-world, non-interventional single-centre study	1 site in USA	6 adults with SBS-IF	Teduglutide 0.05 mg/kg/day (n=6)	None	Percentage of patients achieving a clinical response (≥20 reduction in PS volume from baseline) Percentage of patients achieving independence from PS (100% reduction in PS volume from baseline)	Yes	No	Yes	No
PSP data	A non-interventional Patient Support Programme in Australia	Australia (number of sites NR)	Real-world patients receiving teduglutide in Australia	Teduglutide 0.05 mg/kg/day [redacted]	None	Days per week of PS Percentage of patients achieving a clinical	Yes	No	Yes	Yes

						response (≥20 reduction in PS volume from baseline) Percentage of patients achieving independence from PS (100% reduction in PS volume from baseline)				
TED-C13-003	Phase 3, open label, non-randomised, 12-week study in the UK and US	17 sites in 2 countries: UK and USA	Children (aged 1 to 17 years old) with ≥12 month history of SBS	Teduglutide 0.0125 mg/kg/day (n=8) Teduglutide 0.025 mg/kg/day (n=14) Teduglutide 0.05 mg/kg/day (n=15)	Standard care (PS; n=5)	Days per week of PS Volume of PS Safety	Yes	Yes	No	No
SHP633-303	Open-label, long-term extension study to C13	10 sites in the UK and USA	Patients with SBS who completed C13	Teduglutide 0.05 mg/kg/day (n=29)	None	Days per week of PS Volume of PS Safety	Yes	Yes	No	No

TED-C14-006	Phase 3, multi-national, open label, non-randomised, 24-week study	27 sites in 7 countries: Belgium, Canada, Finland, Germany, Italy, UK, and USA	Children (aged 1 to 17 years old) with ≥12 month history of SBS	Teduglutide 0.025 mg/kg/day (n=24) Teduglutide 0.05 mg/kg/day (n=26)	Standard care (PS; n=9)	Days per week of PS Volume of PS Safety	Yes	Yes	No	No
SHP633-304	Open-label, multi-national, long-term extension study to C14 and SHP633-301	23 sites 6 countries: Belgium, Canada, Finland, Italy, UK and USA	Patients with SBS who completed C14 or SHP633-301	Teduglutide 0.05 mg/kg/day (n=61)	None	Days per week of PS Volume of PS Safety	Yes	Yes	No	No
Ramos Boluda 2020	Prospective observational 24-week study	8 centres in Spain	Children (aged 1 to 18 years old) with dependent on PN, and with no surgical interventions or changes in PN in the last 3 months	Teduglutide 0.05 mg/kg/day	None	PS volume	Yes	No	No	No

Abbreviations: SBS-IF, short bowel syndrome with type 3 intestinal failure; PS, parenteral support; PSP, patient support programme

Table 7 Summary of the baseline characteristics of the STEPS and 004 trials, real-world studies, and the PSP data

	STEPS		004		PSP	Joly 2020	Lam 2018	Martin 2021	Pevny 2019	Puello 2020	Schoeler 2018	Tamara 2020	Ukleja 2018
	TED 0.05mg/kg/day (N=43)	Placebo (N=43)	TED 0.05mg/kg/day (N=35)	Placebo (N=16)	[redacted]	TED 0.05mg/kg/day (N=54)	TED 0.05mg/kg/day (N=18)	TED 0.05mg/kg/day (N=31)	TED 0.05mg/kg/day (N=27)	TED 0.05mg/kg/day (N=18)	TED 0.05mg/kg/day (N=14)	TED 0.05mg/kg/day (N=4)	TED 0.05mg/kg/day (N=6)
Age, years, mean (SD) [range]	50.9 (12.6) [22–78]	49.7 (15.6) [18–82]	47.1 (14.2) [20-68]	49.4 (15.1) [20-72]		52.3 (2.1)	47[a] (20–81)	51[a] (IQR 37–59)	51 (17)	54.4[a] (28–74)	49.1 (18.7)	53 (20–74)	46.3 (18.1)
BMI, kg/m^2, mean (SD) [range]	22.5 (3.2) [17.6–29.8]	22.3 (3.1) [17.5–28.6]	21.2 (3.0) [15.6-26.7]	22.0 (2.9) [17.4-28.4]		21.4 (0.6)	NR	21.7[a] (IQR 19.2–23.3)	21.3 (2.6)	21.5[a] (17.6-32.8)	NR	NR	66.5 (15.5)
Women, n (%)	22 (51.2)	24 (55.8)	18 (51.4)	9 (56.2)		19 (35.2)	11 (61.1)	11 (35.5)	14 (51.8)	10 (55.5)	9 (64.3)	2 (50.0)	4 (66.7)
Cause of major intestinal resection, n (%)													
Ischaemia/vascular disease	13 (30.2)	16 (37.2)	14 (40.0)	3 (18.8)		21 (38.9)	7 (38.9)[b]	10 (32.3)	12 (44.4)	3 (16.7)	5 (35.7)	2 (50.0)	2 (33.3)[c]
Crohn's disease/inflammation bowel disease	10 (23.3)	8 (18.6)	10 (28.6)	7 (43.8)		16 (29.6)	7 (38.9)	10 (32.3)	4 (14.8)	12 (66.7)	7 (50.0)	0	2 (33.3)
Volvulus	3 (6.9)	6 (13.9)	5 (14.3)	2 (12.5)		7 (12.9)	1 (5.5)[d]	4 (12.9)	0	0	1 (7.1)[e]	0	0
Injury	4 (9.3)	4 (9.3)	3 (8.6)	1 (6.3)		0	NR	3 (9.7)	3 (11.1)	0	0	0	0
Cancer	1 (2.3)	2 (4.7)	NR	NR		NR	NR	NR	NR	NR	NR	NR	NR
Small bowel atresia	0	NR	NR	NR		NR	NR	NR	NR	NR	NR	NR	NR
Radiation enteritis	0	NR	NR	NR		3 (5.6)	NR	1 (3.2)	0	0	7%[f]	0	0

	STEPS		004		PSP	Joly 2020	Lam 2018	Martin 2021	Pevny 2019	Puello 2020	Schoeler 2018	Tamara 2020	Ukleja 2018
	TED 0.05mg/ kg/day (N=43)	Placebo (N=43)	TED 0.05mg/ kg/day (N=35)	Placebo (N=16)	[redacted]	TED 0.05mg /kg/day (N=54)	TED 0.05mg /kg/day (N=18)	TED 0.05mg /kg/day (N=31)	TED 0.05mg /kg/day (N=27)	TED 0.05mg /kg/day (N=18)	TED 0.05mg/ kg/day (N=14)	TED 0.05mg/ kg/day (N=4)	TED 0.05mg/kg/day (N=6)
Gastroschisis	0	NR	NR	NR	[redacted]	NR	NR	NR	NR	1 (5.5)	NR	NR	NR
Gastric cancer	1 (2.3)	NR	NR	NR	[redacted]	NR	NR	NR	NR	NR	NR	NR	NR
Other	12 (27.9)	7 (16.3)	3 (8.6)	3 (18.8)	[redacted]	7 (12.9)	NR	3 (9.7%)	8 (29.6)	5 (27.8)	1 (7.1)	2 (50.0)	2 (33.3)
Intestinal anatomy or remnant small bowel length unknown, n (%)	3 (6.9)	3 (6.9)	1 (2.9)	0	[redacted]	NR	NR	NR	2 (7.4)	3 (16.7)	NR	NR	NR
Patients with stoma, n (%)	21 (48.8)	17 (39.5)	NR	NR	[redacted]	NR	NR	15 (48.4)	6 (22.2)	10 (55.5)	NR	3 (75.0)	3 (50.0)
Types of stoma, n (% of patients with stoma)													
Jejunostomy	11 (52.3)	5 (29.4)	6 (UC)[g]	4 (UC)[g]	[redacted]	19 (UC)[g]	NR	13 (86.7)	1 (16.7)	3 (30.0)	NR	NR	2 (66.7)
Ileostomy	6 (28.6)	9 (52.9)	2 (UC)[g]	1 (UC)[g]	[redacted]	NR	NR		3 (50.0)	6 (60.0)	NR	NR	0
Colostomy	4 (19.0)	1 (5.9)	NR	NR	[redacted]	2 (UC)[g]	NR	2 (13.3)	0	1 (10.0)	NR	NR	1 (33.3)
Descendostomy	0	0	NR	NR	[redacted]	NR	NR	0	1 (16.7)	0	NR	NR	0
Other (duodenostomy; jejunostomy + ileostomy)	0 (0)	2 (11.8)	NR	NR	[redacted]	NR	NR	0	1 (16.7)	0	NR	NR	0
End stoma, n (%)	21/42 (50.0)	NR	NR	NR	[redacted]	NR	3 (16.7)	NR	NR	NR	NR	NR	NR

	STEPS		004		PSP	Joly 2020	Lam 2018	Martin 2021	Pevny 2019	Puello 2020	Schoeler 2018	Tamara 2020	Ukleja 2018
	TED 0.05mg/ kg/day (N=43)	Placebo (N=43)	TED 0.05mg/ kg/day (N=35)	Placebo (N=16)	[redacted]	TED 0.05mg /kg/day (N=54)	TED 0.05mg /kg/day (N=18)	TED 0.05mg /kg/day (N=31)	TED 0.05mg /kg/day (N=27)	TED 0.05mg /kg/day (N=18)	TED 0.05mg/ kg/day (N=14)	TED 0.05mg/ kg/day (N=4)	TED 0.05mg/kg/day (N=6)
Colon in continuity, n (%)	26 (60.5)	23 (53.5)	26 (74.3)	11 (68.8)	[redacted]	35 (64.8)	15 (83.3)	16 (51.6)	21 (77.8)	9 (50.0)	9 (64.3)	1 (25.0)	3 (50.0)
Overall remnant small bowel length, cm													
n	40	40	31	15	[redacted]	54	18	31	27	18	14	4	6
Mean (SD)	84.4 (64.6)	68.7 (63.9)	58 (44)	77 (53)	[redacted]	61.8 (5.9)	55[a] (6–180)	74[a] (IQR 34–100)	NR	100[a] (40–240)	64.5 (20–150)	70 (60–80)	75 (32)
Average percent of colon remaining													
n	24	NR	NR	NR	[redacted]	NR	NR	NR	NR	NR	NR	NR	NR
Average % (SD)	55.6 (20.8)	NR	NR	NR	[redacted]	NR	NR	NR	NR	NR	NR	NR	NR
Mean time receiving PS, years (SD)	6.8 (6.3)	5.9 (5.7)	6.6 (6.5)	7.9 (7.5)	[redacted]	9.8 (1.2)	3.0[a] (0.3–8)	4.8[a] (IQR 2.3–8.3)	4.3 (5.8)	NR	NR	3.5 (NR)	4.6 (4.8)
Mean parenteral volume, mL/day (SD)	1,844 (1,057)	1,929 (1,026)	1,374 (639)[ǂ]	1,531 (874)	[redacted]	2,295 (344)	NR	NR	NR	NR	NR	NR	NR
Weekly PS volume at baseline, L (SD)	12.6 (7.4)	NR	NR	NR	[redacted]	11.2 (1.1)	9.9[a] (2.7–30)	7.5[a] (IQR 3.5–15)	13.7 (7.9)	9.9 (95% CI 6.7–13.2)	12.2 (SEM 2.3)	10.8 (1.3)	7.7 (4.3)
Time receiving PS at baseline, n (%)													

	STEPS		004		PSP	Joly 2020	Lam 2018	Martin 2021	Pevny 2019	Puello 2020	Schoeler 2018	Tamara 2020	Ukleja 2018
	TED 0.05mg/ kg/day (N=43)	Placebo (N=43)	TED 0.05mg/ kg/day (N=35)	Placebo (N=16)	[redacted]	TED 0.05mg /kg/day (N=54)	TED 0.05mg /kg/day (N=18)	TED 0.05mg /kg/day (N=31)	TED 0.05mg /kg/day (N=27)	TED 0.05mg /kg/day (N=18)	TED 0.05mg/ kg/day (N=14)	TED 0.05mg/ kg/day (N=4)	TED 0.05mg/kg/day (N=6)
<1 year, n (%)	0 (0)	NR	NR	NR	[redacted]	NR	NR	NR	NR	NR	NR	NR	NR
≥1 year to <2 years, n (%)	11 (25.6)	NR	NR	NR	[redacted]	NR	NR	NR	NR	NR	NR	NR	NR
≥2 years, n (%)	32 (74.4)	NR	NR	NR	[redacted]	NR	NR	NR	NR	NR	NR	NR	NR
Mean days per week of PS (SD)	5.6 (1.7)	5.9 (1.5)	5.1 (1.6)[‡]	5.3 (1.7)	[redacted]	4.4 (0.2)	NR	4[a] (IQR 3–5)	5 (2)	6.1 (95% CI 5.2–6.9)	5.6 (NR)	5 (0)	4.8 (2)
Days per week of PS at baseline (SD)	5.6 (1.7)	NR	NR	NR	[redacted]	4.4 (0.2)	4[a] (IQR 3–5)	5 (2)	6.1 (95% CI 5.2–6.9)	5.6 (NR)	5 (0)	4.8 (2)	4[a] (IQR 3–5)
Concomitant medication													
Antidiarrhoeals, n (%)	22 (51.2)	16 (37.2)	22 (62.8)	8 (50.0)	[redacted]	NR	NR	NR	NR	NR	NR	NR	NR
Antisecretory agents, n (%)	25 (58.1)	22 (51.2)	19 (54.3)	7 (43.8)	[redacted]	NR	NR	NR	NR	NR	NR	NR	NR

Abbreviations: 95%C, 95% confidence interval; BMI, body–mass index; PS, parenteral support; med, median; NR, not reported; R, range; SD, standard deviation; SEM, standard error of the mean; UC, unable to calculate

Notes:

a represents median (min – max)

b The Lam 2018 publication reports n=7 for mesenteric ischemia[34]

	STEPS		004		PSP	Joly 2020	Lam 2018	Martin 2021	Pevny 2019	Puello 2020	Schoeler 2018	Tamara 2020	Ukleja 2018
	TED 0.05mg/ kg/day (N=43)	Placebo (N=43)	TED 0.05mg/ kg/day (N=35)	Placebo (N=16)	[redacted]	TED 0.05mg /kg/day (N=54)	TED 0.05mg /kg/day (N=18)	TED 0.05mg /kg/day (N=31)	TED 0.05mg /kg/day (N=27)	TED 0.05mg /kg/day (N=18)	TED 0.05mg/ kg/day (N=14)	TED 0.05mg/ kg/day (N=4)	TED 0.05mg/kg/day (N=6)

c The company reports n=0 for vascular disease in Table 15 of the CS. Table 1 in the Ukleja 2018 publication reports n=3 for vascular disease[35]

d The company reports n=0 for volvulus in Table 15 of the CS. Table 2 of the Lam 2018 publication reports n=1 for volvulus[34]

e The company reports n=0 for volvulus in Table 15 of the CS. Table 2 of the Schoeler 2018 publication reports n=1 for small intestine volvulus[36]

f The ERG were unable to verify the company's reporting of the percentage of people with radiation enteritis in Table 15 of the CS

g Unable to calculate the percentage as the number of patients with stoma was not reported

ǂ n=34 as baseline PS data were not provided for one patient

Source: STEPS primary publication; STEPS CSR; STEPS-2 primary publication; STEPS-2 CSR; 004 primary publication; 004 CSR; [redacted], real-world study publications[9, 22, 23, 26, 34-44]

3.2.2 Primary and secondary efficacy endpoints

The outcomes presented in the CS match those specified in the NICE final scope: reduction in parenteral support requirements, overall survival, adverse effects of treatment, health-related quality of life, and impact on carers.

Reduction in parenteral support

The company presents a naïve comparison of responder rates in 004 and STEPS in Table 14 of the CS, and this is reproduced by the ERG as Table 8. In STEPS, teduglutide patients had significantly greater reduction in PS volume at eight weeks, and were more likely to achieve at least one day off PS per week after 24 weeks of treatment weeks compared with the placebo patients (53.8% vs 23.1%, p=0.005). Data for STEPS-2 and STEPS-3 are provided in section B.2.6.2.1, and B.2.6.2.2 respectively, and in Appendix L of the CS. The data for STEPS-2 and STEPS-3 support sustained reductions in days per week of PS and PS volume with longer-term treatment.

[redacted]

[redacted] Long-term data are presented in Appendix L, Figure 13. By week 52, results from the open label extension study 005 demonstrated that 68% of teduglutide patients achieved ≥1 day off PS by week 52.

Table 8 Naïve comparison of responder rates in 004 and STEPS

		STEPS	004
% of patients who achieved a ≥20% reduction in PS volume at week 20 sustained to week 24 (primary endpoint in STEPS)	Teduglutide 0.05 mg/kg/day	63% (n=27/43)	46% (n=16/35)
	Placebo	30% (n=13/43)	6% (n=1/16)
% PS volume reduction at week 24 (from baseline)	Teduglutide 0.05 mg/kg/day	[redacted]	[redacted]
	Placebo	[redacted]	[redacted]

Abbreviations: PS, parenteral support

Source: STEPS primary publication;[9] STEPS CSR;[38] 004 primary publication;[22] 004 CSR[39]

The company state that the results from STEPS and 004 are limited by the conservative PS weaning algorithms, especially in 004, compared with more liberal clinical practice. The company also states that the high placebo response seen in STEPS is an artefact of the PS weaning algorithm, [redacted].[45] The company presents the rationale for this in section B.2.6.1.4 of the CS. The ERG's clinical expert notes the company's position but also suggests that the trial participants might show increased adherence to other aspects of their day-to-day management due to their active participation in a clinical trial (e.g., hypertonic solutions). If this were the case, the placebo response could be due to participants experiencing reduced fluid losses and improved hydration, rather than improved bowel absorption. Moreover, after reviewing the published data from the STEPS trial it appears that urine output in the placebo group may have raised as a consequence of increased oral intake, although the ERG notes the trial authors' argument that this could be due to daily fluctuation in urine volume.[9] However, the ERG accepts that in the teduglutide group the increase in urine output, which occurred without a raise in oral intake, was a result of the increased absorption effect of the drug.

The company presents a comparison of the PS reduction data from STEPS and STEPS-2 with the real-world studies and the Australian PSP in section B.2.6.4 and the ERG presents a summary of the data in Table 9 below. The ERG notes that the definition of patients achieving a clinical response in this comparison (≥20% reduction in PS volume from

baseline) differs from that used in STEPS (≥20% reduction at week 20 maintained to week 24), although the ERG believes that this is unlikely to have any impact on the study results. Greater responses were shown in the real-world studies for the percentage of patients achieving a clinical response over time and gaining independence from PS compared with STEPS/STEPS-2. In the PSP study, following [redacted]

Table 9 Percentage of patients achieving clinical response, ≥1 day off PS, and gaining independence from PS in the real-world studies, Australian PSP, and STEPS/STEPS-2 TED-TED cohort

	Timepoint	Real-world studies	PSP	STEPS/STEPS-2
Clinical response ≥20% reduction in PS volume	**Month 6**		[redacted]	69% (27/39)
	Month 12	55% to 100%	[redacted]	92% (33/36)
≥1 day off PS	**Month 6**		[redacted]	53.8% (21/39)
	Month 12		[redacted]	52.8% (19/36)
PS independence 100% reduction in PS volume	**Month 6**		[redacted]	0% (0/39)
	Month 12	17% to 40%	[redacted]	6% (2/36)
	Abbreviations: PS, parenteral support; **Notes:** Month 6 data for the STEPS programme taken from the TED arm of the STEPS study, month 12 data are taken from the TED-TED cohort of STEPS-2 **Source:** STEPS primary publication;[9] STEPS CSR;[38] STEPS-2 primary publication;[23] STEPS-2 CSR;[40] Revestive atHOME PSP reduction report ;[26]real-world study publications[34-37, 41-44]			

PS reduction data for the studies conducted in children are provided in section B.2.6.5. Results are supportive of the effect of teduglutide seen in the adult studies. Comparable numbers of adult and child teduglutide patients achieved a ≥20% PS volume reduction at week 24 in C14 and STEPS (69% for both), and 12% of children receiving teduglutide achieved PS independence by week 24 in C14, while none of the teduglutide adult patients had achieved independence at this timepoint. In the real-world study, 87% (13/15) of patients

achieved a ≥20% reduction, and 44% (n=7/16) gained PS independence at 24 weeks. In C13, [redacted].

Overall survival

The company state that the 42-month follow-up time period provided by STEPS is insufficient to evaluate life time survival or allow any consideration of a potential treatment effect on mortality. Instead, the company reports an estimation of survival using pseudo individual patient data in section B.3.3.4. The ERG agrees that the company's argument is reasonable. Overall survival will be discussed further in Chapter 4.

Three deaths were reported in the STEPS2 teduglutide group, one of which was treatment related (a case of metastatic adenocarcinoma which may have been secondary to Hodgkin's lymphoma treated with chemotherapy and radiotherapy). One death occurred in the screening period of 004, but no deaths occurred in the active phase of the trial. The company reports that one patient died in the pooled data from C13, SHP633-303, C14, and SHP633-304 (Table 21 of the CS); however, the SHP633-304 CSR (page 99) reports two deaths: one 16-year old patient and one 1-year old patient. Both deaths were considered unrelated to treatment.

3.2.4 Health-related quality of life

No statistically significant differences were observed for any of the quality of life measures used in 004 (SF-36, EQ-5D, and IBDQ) and STEPS (SBS-QoL). The company do not make any specific comment on the quality of life results of 004, other than noting that no disease-specific quality of life measures were available at the time the trial was conducted, and that the small number of patients and heterogeneity in symptoms make quality of life in SBS difficult to measure. The company focuses discussion on the SBS-QoL, noting that, while the tool was developed to measure quality of life in SBS patients, the tool was not designed to measure quality of life driven by PS. The company also argue that, in addition to the issue of heterogeneity, randomisation in STEPS was not intended to balance the 17 SBS-QoL items between treatment groups, which may have resulted in baseline imbalances in quality of life, that STEPS was not powered to detect statistically significant changes in the SBS-QoL score, and that the tool may not be sensitive enough to detect differences between the two treatment arms. The company further argues that [redacted]

[redacted]. Whilst recognising the company's argument, the ERG's clinical expert notes that increasing days of PS could improve quality of life in some patients if this leads to better hydration, and nutritional and calorie intake.

3.2.5 Adverse reactions

The company presents pooled safety data in adults from STEPS, STEPS-2, 004 and 005, and pooled safety data in children from C13 and C14 in section B.2.10, and in Tables 20 and 21 of the CS. The ERG agrees that pooling of the safety data from these trials is appropriate for patients treated with teduglutide.

In adults, the most reported adverse events were gastrointestinal stoma complication, abdominal pain, upper respiratory tract infection, and nausea. Numerically, more teduglutide patients experienced adverse events leading to treatment discontinuation compared to placebo arm patients in the STEPS/004 RCTs: 9.2% (=10/109) of participants treated with teduglutide for up to 24 weeks (77 receiving 0.05 mg/kg/day and 32 receiving 0.10 mg/kg/day) compared with 6.8% (=4/59) receiving placebo (no statistical testing conducted). In the teduglutide group of the STEPS/STEPS-2/004/005 studies, 19.7% of participants (n=173, 134 received 0.05 mg/kg/day and 39 received 0.10 mg/kg/day) treated for up to 30 months were reported to experience adverse events leading to discontinuation. The frequency and severity of adverse events were broadly similar between the teduglutide and placebo patients. Adverse events that tended to be reported more frequently in the STEPS/004 teduglutide group versus the STEPS/004 placebo group were abdominal pain (38.5% versus 27.1%), gastrointestinal stoma complications (37.8% versus 13.6% in patients with stoma [n=45 and n=22, respectively]), upper respiratory tract infection (27.5% versus 13.6%) and abdominal distension (16.5% versus 1.7%). The company states that the observed adverse events were believed to be mainly related to either the pro-absorptive and intestinotrophic effects of teduglutide, insufficient PS weaning, or due to the underlying nature of SBS-IF. The ERG clinical expert agrees that adverse events are mainly related to the effects of treatment or the underlying health condition. The ERG recognizes that respiratory tract infections are reported as a very common adverse reaction in the SmPC, and part of the known safety profile of teduglutide.[20] However, the ERG are unclear why the number of patients with reported upper

respiratory tract infection in the STEPS/004 teduglutide group is so much higher (approximately double) than the number reported in the STEPS/004 placebo group. As discussed earlier, three deaths occurred in the adult teduglutide population. One death was considered treatment related (a case of metastatic adenocarcinoma which may have been secondary to Hodgkin's lymphoma treated with chemotherapy and radiotherapy). The other two deaths were related to lung cancer and catheter-related sepsis with urinary tract infection. The ERG agrees that the overall frequency and severity of adverse events is broadly similar between the teduglutide and placebo groups, and in keeping with the safety profile of teduglutide.

Safety results for the paediatric population are presented in Table 21 of the CS. In children, 77.5% experienced a serious adverse event, 39.3% experienced a treatment-related adverse event (TRAE), and 3.4% experienced a serious TRAE. The most commonly reported adverse events were vomiting (51.7%), pyrexia (43.8%), upper respiratory tract infection (41.6%), cough (33.7%), and device-related (central venous catheter) infection (29.2%). Two patients (2.2%) discontinued teduglutide treatment, however, the company states that neither event was considered treatment-related. The most common adverse events considered related to treatment were vomiting and abdominal pain. Compared with the adult studies, upper respiratory adverse events, pyrexia, vomiting, and catheter complications (device breakage, occlusion, and dislocation) were reported to be more common in the paediatric studies. The company states that this might be expected in a younger population.[47] As discussed earlier, the company reports that one patient died in the pooled data from C13, SHP633-303, C14, and SHP633-304 (Table 21 of the CS); however, the SHP633-304 CSR (page 99) reports two deaths: one 16-year old patient and one 1-year old patient. Both deaths were considered unrelated to treatment. The ERG agrees that the safety profile is similar to that observed in the adult population

3.2.6 Subgroup analyses

No subgroup analyses were specified in the NICE final scope. The company did not present any subgroup analysis data in the CS but state that post-hoc analysis of STEPS found that higher baseline PS volumes was a predictor of improved response to teduglutide.[46] A second post-hoc analysis including the two extension studies indicated that patients with lower baseline PS needs were more likely to wean off PS, although the company state that a pooled

analysis of data from STEPS, STEPS-2, STEPS-3, 004 and 005 found no predictive characteristics for PS weaning.[11, 31]

3.2.7 Meta-analyses

The company presents details of their meta-analyses in section B.2.8. The company performed two meta-analyses to formally compare the pooled estimates derived from observational real-world studies to the estimates obtained from the teduglutide arm of STEPS/STEPS-2 trials and the Australian PSP data. There is no direct comparison of teduglutide versus placebo as the real-world studies are non-interventional studies without a comparator arm.

[redacted]

The ERG notes that while the pooled estimates from real-world data do suggest that a higher proportion of patients receiving teduglutide gain independence from PS than in STEPS/STEP-2, it is worth noting that the real-world studies are observational with no comparator treatment and, therefore, more prone to methodological bias. Any comparison of effects between observational studies and randomised trials should be interpreted with caution.

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

No indirect or multiple treatment comparisons were performed by the company was as the only relevant comparator to teduglutide was standard care and the two RCTs considered in the CS directly compare teduglutide with standard care.

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

N/A

3.5 Additional work on clinical effectiveness undertaken by the ERG

No additional work on clinical effectiveness was carried out.

3.6 Conclusions of the clinical effectiveness section

The company presented evidence from the STEPS trial that showed that a significantly higher proportion of patients on teduglutide achieved the primary endpoint of a clinical response (defined as ≥20% reduction in parenteral support volume at week 20, maintained to week 24) than patients on placebo and also that a significantly higher proportion of patients on teduglutide reported achieving at least one day off PS per week that those in the placebo arm. The company argue that the placebo response rate was unrealistically high and could be explained by reliance of the weaning algorithm on urine output with a relative increase in oral fluid intake in the placebo arm not accompanied by a commensurate increase in urine volume. The ERG notes that this a plausible argument and that the changes in PS intake in clinical practice does not rely on urine output alone.

The company also presented evidence from pooled estimates of 'real-world' studies showing higher estimates for response to teduglutide than in the STEPS trial. However, this was only the case for the outcome of 100% reduction in PS volume at 12 months and the effects compared did not include a comparator group. The ERG notes that formal comparison of effects from observational studies with those from randomised trials could be liable to the biases inherent in observational studies and, therefore, results should be interpreted with caution.

While the ERG agrees that there is evidence from the STEPS and 004 trials that teduglutide has superior efficacy than placebo, the weaning algorithms used in the trials is restrictive and

may not reflect usual clinical practice. However, since the algorithms were applied to both arms of the trials, the internal validity of the results could be considered robust, but the absolute effects may not be externally valid.

4 COST EFFECTIVENESS

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

The company conducted two literature searches in 2021 to update those conducted in the previous NICE submission in late 2016. Given that the company has included the results of the previous SLR, the time limit consists of publications from 2005 to May 2021. The search objectives were to capture economic evaluations relating to teduglutide and/or parenteral nutrition and HCRU studies in patients with SBS-IF type III. The literature searches did not contain any age-specific search terms, therefore results included both the paediatric and adult SBS-IF type III population. Relevant publications were sourced through searches in Embase, MEDLINE, the Centre for Reviews and Dissemination (CRD), National Health Service Economic Evaluation Database (NHS EED), the CRD Health Technology Assessment Database (HTAD), and Econlit. Further searches of relevant conference abstracts were also conducted where those published before 2019 were excluded.

The updated literature search identified 28 additional publications, two of which were economic evaluations (added to the three previously identified to give 5 in total). The company did not identify any studies where the population and costs used in the economic models were in line with the NICE reference case. Therefore, a de novo economic model was developed for this submission. Full information of the company's search strategy can be found in appendix G of the company submission, and a brief description can be found on page 89 of the main company submission, document B.

The ERG is satisfied that the updated SLRs conducted in 2021 are appropriate for the objectives the company sought to address. The search strategies and eligibility criteria are comprehensive, and an appropriate selection of databases was included. The company chose to extend the previous SLR conducted in 2016 rather than overwrite previous work. The previous SLR was criticised by the ERG for methodological reasons related to the MeSH and EMTREE terms for Embase and MEDLINE. The cost-effectiveness studies identified in the SLR are broadly similar to the methodology undertaken by the company. Of the 5 studies identified, 3 utilised a similar Markov model structure. These models are relevant to this submission; however, each are from an alternate payer perspective. Of the remaining studies identified, these did not report differences in quality of life or support the granularity required for modelling the benefit of a reduction in days of PS per week. Therefore, the ERG

agrees that these cost-effectiveness studies are not appropriate for assessing the cost-effectiveness of teduglutide in this submission.

4.2 Summary and critique of the company's submitted economic evaluation by the ERG

4.2.1 NICE reference case checklist

Table 10 NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Aligns with the NICE reference case. However, the ERG questions the strengths of evidence for a direct health effect on carers of a reduction in a patient's PS days (Section 4.2.7).
Perspective on costs	NHS and PSS	Aligns with the NICE reference case.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Aligns with the NICE reference case.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	Aligns with the NICE reference case.
Synthesis of evidence on health effects	Based on systematic review	Aligns with the NICE reference case.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	The analysis utilises a vignette study for health state utilities. This is not aligned with the reference case as the measure is not validated or standardised. The company has provided some evidence to show that the EQ-5D and the SBS-QoL, captured in STEPS, mapped to health state utilities lack face validity or responsiveness in this patient population. Carer utilities were obtained from two sources. One source measured utilities using the EQ-5D-5L instrument which was mapped EQ-5D-3L values.[48, 49]. The other source used direct elicitation from a Delphi panel of 9 clinical experts.

Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	The vignette study used for the company base case sourced utility values from 100 members of the general population. However, SBS-IF patients were interviewed in the development of the health state vignettes.[50] Carer utilities are sourced from a study of 47 UK caregivers of SBS-IF patients[48] and a Delphi panel of 9 clinical experts.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	The participants of the vignette study included proportionally more females (67% versus 50.1%), and were younger (median age: 32 versus 40) and educated to a higher level (any higher education 65% versus 27%) compared to the general population.[50]
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Aligns with the NICE reference case.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Aligns with the NICE reference case. However, further information should be provided regarding the Takeda home service to provide reassurance that no further monitoring burden would fall on the NHS or PSS upon a positive recommendation of teduglutide.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Aligns with the NICE reference case.
PSS, personal social services; QALYs, quality-adjusted life years; EQ-5D, standardised instrument for use as a measure of health outcome.		

4.2.2 Model structure

The company developed a Markov model consisting of 9 health states reflecting the number of days per week of PS (PS0-7) and death. This model structure was chosen to capture what the company argue to be most relevant outcome associated with teduglutide treatment, a reduction in the number of days per week PS is required. The distribution of the health states at the beginning of the model is equal between arms and is determined by the baseline days of PS required by patients enrolled in the studies informing the model efficacy inputs: STEPS and the Australian PSP. The company base case assumes that the PS needs of patients

receiving standard of care would not change over time since there is no *"…biological reason why patients who are stable on PS should experience a change in their PS needs"* (Company submission, section B.3.3.1).

Transition matrices of 28-day transition probabilities, used to inform patient movements between PS health states, are applied to the teduglutide treatment arm only. These are calculated using STEPS and PSP data over a series of six-month intervals (0-6, 6-12, 12-18, 18-24 and 24-30). It is assumed that whilst on teduglutide treatment, patients can either reduce their PS requirement by a maximum of 1 day per 28-day cycle, or remain stable. No further transitions between PS states are assumed to occur after cycle 30 unless a patient discontinues treatment, in which case they are assumed to revert immediately to their baseline requirement.

Treatment discontinuation is modelled using a parametric survival curve fitted to observed time on treatment data from STEPS, STEPS-2 and the PSP. Furthermore, based on information from the SmPC, clinical advisory board and a British Intestinal Failure Alliance (BIFA) position statement, a stopping rule is applied for patients who do not achieve a reduction in PS of at least 1 day per week compared to baseline at 12-months.[20, 51, 52] Adjustment for treatment discontinuation in the teduglutide arm is modelled using off-treatment health states (PS0-7 days), with those who discontinue reverting to (or remaining at) the number of PS days required at baseline for the duration of the model time horizon. Further discussion of the treatment discontinuation approach is provided in section 4.2.6 below.

PS treatment is associated with an increased risk of intestinal failure associated liver disease (IFALD) and chronic kidney disease (CKD). Therefore, expected cumulative proportions with these long-term complications are modelled by four categories of PS requirement; none (PS0), low (PS1-3 days), medium (PS4-5 days) and high (PS6-7 days). Costs and utility decrements are applied in each model cycle to the calculated proportion experiencing these complications based on the cohort distribution across the PS health states. No additional mortality risk is applied to these patients over the disease specific mortality in the company base case.

All patients are at equal risk of death regardless of health state. The company base case utilises parametric extrapolations of KM curves from studies of SBS-IF to inform the proportion of patients who transition to the death state in each cycle. Further discussion regarding transition matrices, overall survival and treatment discontinuation is found in section 4.2.6.

Overall, the ERG is satisfied with the companies chosen model structure. The assumption that patients can only improve or remain stable may be a simplifying assumption from a clinical standpoint, but the ERG finds the model structure agreeable due to the complexities of modelling such a heterogenous disease.

There is some confusion in the model and company submission between what is defined as a cycle and a month. For example, some transition matrices are described to apply for 6 months in the company submission but are applied for 6 28-day cycles in the model. Similarly, adverse event rates which are described as rates per month in the CS are applied per 28-day cycle in the model. It is unclear whether this is a typo in the submission or an error in the coding of the model. However, the ERG believes that any slight inconsistency between the model cycle length and the time period over which transition probabilities and adverse event rates are calculated is unlikely to have a material impact on the ICER.

One further structural limitation relates to the fact that the long-term complications of IFALD and CKD are not explicitly accounted for in the Markov states of the model. As a result, the model cannot accurately account for an increased risk of mortality in patients that develop these complications, potentially leading to bias in the estimated proportion of the surviving cohort affected by them.

4.2.3 Population

The population considered in the company submission is in line with teduglutide's marketing authorisation, SBS-IF patients aged 1 year and above who are stable following a period of intestinal adaption after surgery. The company presents its results in two populations, paediatric (aged 1-17 years) and adult (≥18 years). The decision to conduct the analysis separately for these populations is due to the differing aetiology of the disease and pathology between the patient groups. Table 11 details the key input differences and similarities

between the company base case for each population considered with the company rationale for each input.

Table 11 Summary of key model input differences and similarities between the paediatric and adult base cases

	Paediatric	Adult
Starting age	6 years. Average age of the C14 trial population.	50 years. Average age of the STEPS trial population.
Time horizon	94 years	50 years
Survival	Parametric survival curves fitted to 5-year pooled survival data of children who are candidates and non-candidates for intestinal transplant. Sourced from European HPN centres between 2004 and 2008 sourced from Pironi 2011.	Parametric survival curves fitted to Canadian HPN registry data sourced from Salazar 2021.[53]
Hospital costs for visits and line sepsis	Paediatric HRG codes for gastroenterology specialist visits and critical care	Adult HRG codes for gastroenterology specialist visits and critical care
Effectiveness of teduglutide treatment	STEPS, STEPS-2 and PSP data. It is assumed that the effectiveness of teduglutide is the same in children as adults. The company presents evidence that suggests teduglutide may offer greater reductions in PS for children however, given a limited evidence base, adult data has been used.	
Rate of PS-related complications	Same rates of complications in children as in adults. The company presents limited evidence that catheter related infections and liver disease are less common in children.	
Dosage of teduglutide	All patients are modelled to receive the larger 5mg vial of teduglutide. Given that those who weigh less than 20kg can receive the 1.25mg vial, the paediatric base case overestimates treatment costs.	

The baseline number of days of PS and percentage female were sourced from STEPS (TED-TED) and the PSP. The company made a comparison with the distribution of patient days of PS in a UK database study (Table 12). [redacted]

Table 12 Baseline days of PS used in the paediatric and adult base case compared with UK SBS-IF population (adapted from table 21 Appendix L of company submission)[54]

Days of PS per week	STEPS(TED-TED) & PSP	UK database study
0 (independent)	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]
6	[redacted]	[redacted]
7	[redacted]	[redacted]

The ERG clinical expert advises that patients are considered severe if the remnant bowel length is less than one metre. The mean remnant bowel length of all patients in the STEPS and PSP is less than one metre. The ERG clinical expert agrees that the population analysed for the economic model is generalisable to the UK context as is it those SBS-IF patients who are most severe that would receive long-term home parenteral nutrition.

The ERG agrees that the paediatric and adult populations should ideally be considered separately. However, given the limited differences between the adult and paediatric models, this critique focusses primarily on the adult model. The paediatric model may be considered less well informed due to data limitations.

4.2.4 Interventions and comparators

Teduglutide is licensed in patients one year and above with SBS-IF who are stable following a period of intestinal adaption.[20] Teduglutide is intended to be given alongside the standard of care with the intention of increasing the absorptive capacity of the intestine. The standard of

care for SBS-IF patients is a combination of PS, antimotility and antisecretory agents, fluid restriction and dietary optimisation in order to manage a patient's symptoms.

Teduglutide is administered by subcutaneous injection of 0.05mg/kg once daily at alternating sites between the four quadrants of the abdomen. Two vial sizes are available, where a 5mg vial is appropriate for patients who weigh 20-100kg and 1.25mg for patients who weigh less than 20kg. Treatment should be initiated under the supervision of a medical professional. The company state a company-sponsored homecare service would be provided should teduglutide be approved.

The comparator for teduglutide is the clinical management of symptoms, without which a patient would die of dehydration or malnutrition. The treatment consists of factors which provide patients with sufficient nutrients and fluids (PS), reduce gastric acid secretion (e.g. H2 receptor antagonists, proton pump inhibitors) and relieve symptoms of motility, diarrhoea (e.g. loperamide, diphenoxylate) and bacterial overgrowth (e.g. antibiotics, probiotics). The standard of care is an appropriate comparator to teduglutide as there are no other treatments available to SBS-IF patients with the intention of reducing the dependency on PS.

The ERG is satisfied that the intervention and comparator are in line with the marketing authorisation and standard practice for SBS-IF in the UK NHS.

4.2.5 Perspective, time horizon and discounting

The submission conducts the analysis from the NHS perspective. The costs of treatment are based upon costs to the health service. These include treatment acquisition costs, PS-related costs and adverse event costs. The paediatric and adult base cases are very similar in terms of health service inputs; however, the company has utilised paediatric specific HRG unit costs where appropriate.

Health effects are measured for health states as a composite of the utility decrement for the patient and carer which increase as the patient's PS need increases. The health effects associated with adverse events and complications are also included. This perspective is in line with the NICE reference case.

The economic model adopts a lifetime time horizon of 94 years for paediatric patients and 50 years for adult patients based on the baseline ages of 6 and 50 in the C14 and STEPS trials respectively. At the end of the modelled time horizon, 1% of patients remain alive in all populations.

Costs and health effects are discounted at 3.5% per annum which is in line with the NICE reference case. The company has also provided a scenario where a discount rate of 1.5% is applied to both costs and QALYs.

The ERG is satisfied that the submission aligns with the NICE reference case in terms of the perspective, time horizon and discounting.

4.2.6 Treatment effectiveness and extrapolation

Estimation of transition probabilities

As indicated in 4.2.2 above, the model is structured around the number of PS days required by patients per week. Thus, the key efficacy inputs in the model are matrices of 4-weekly transition probabilities that govern the flow of the cohort through the model's PS requirement states. Since the label for teduglutide is for patients who are stable on PS following a period of intestinal adaptation, the company maintain the baseline PS requirement of standard care patients over their lifetime. As discussed in Chapter 3.2.2 (above), they argue that there is no biological reason why the PS requirements of such patients should change over time, and that the PS reductions observed in the placebo arm of the STEPS trial are an artefact of the weaning algorithm used; i.e. reflect inappropriate reductions that lead to risks of dehydration and weight loss (see CS, document B, section B.3.3.1).

Conversely, the company argue that reductions in PS support observed for patients in the teduglutide arm of STEPS are likely to underestimate the reductions that can be expected when teduglutide is used in a real-world setting. They justify this based on the reductions in PS days that have been observed in several real-world observational cohort studies and in the company's patient support programme (PSP) in Australia, where weaning algorithms are not applied. Therefore, the company estimated transition probabilities for teduglutide using pooled individual patient data from STEPS, STEPS-2 (using data from those who received teduglutide in STEPS and continued to receive to teduglutide in STEPS-2 (TED-TED cohort)) and the Australian PSP. The STEPS trial provides data out to 24 weeks and STEPS 2

provides data from 24 weeks to 30 months. The company note that the PSP data was only used to inform transition probabilities out to 12 months because [redacted]. Between 12 and 30 months, data from STEPS2 alone are used to inform transition probabilities. The company reject the use of data from the 004 trial and its extension (005) on grounds that it had a stricter and even less generalisable weaning algorithm than STEPS.

For the paediatric model, rather than relying on the small amount of data available from the trials in children (C13 and C14), the company use the transition probabilities derived for the adult population. They justify this on grounds it is likely to be conservative, as a naïve comparison of C14 and STEPS suggests a greater proportion of children are able achieve complete independence from PS (see Table 19 of the CS, document B).

The 4-week (28 day) transition probabilities were estimated separately for a series of 6-month intervals (0-6, 6-12, 12-18, 18-24, and 24-30 months), under the constraint that patients could either remain stable or reduce their PS requirement by a maximum of one day in any 4 week cycle. Beyond 30 months, the last health state is carried forward unless discontinuation occurs (see below), in which case patients are assumed to immediately revert back to their baseline PS requirement. These assumptions may be considered conservative because data for a small number of patients recruited to STEPS3 indicate that some teduglutide treated patients may continue to achieve further reductions in PS days after 30 months, and the time it takes patients to return to their baseline PS requirement following discontinuation is uncertain. The transitions probabilities were fitted using the *Optim* package in R, to minimise "*the sum of the squared difference between the predicted outcome vector (proportion of patients in each health state after applying the transition matrix) and the observed outcome vector (proportion of patients across each health state actually observed)*" (CS, document B, section B.3.3.2). The company note that the transitions are only applied to those remaining on teduglutide treatment in the model, and therefore the initial patient vector for each 6-month interval reflects the number of patients in each health state still on treatment at that timepoint. It is not clear to the ERG if patients meeting the 12 month stopping rule criteria have been removed from the calculation of transition probabilities beyond 12 months to align with the modelling assumptions. However, there appears to be only one less patient used to inform the transition probabilities from 12 months ([redacted]) than the total number recruited to the TED-TED cohort of STEPS-2 ([redacted]) – suggesting this may not be the case.

ERG commentary

In general, the ERG agrees with the company's selection of data sources to inform transition probabilities in the economic model. Based on the ERGs clinical expert advice, it appears justified not to include data from 004 as it will be less generalisable than STEPs, and it appears reasonable to expect greater reductions in PS days in routine practice compared to STEPS due to the absence of strict weaning algorithms. The inclusion of PSP IPD appears justified given the comparability of outcomes in this cohort compared to those observed in the other real-world observational studies reviewed by the company (see section B.2.8 of the CS, document B). With respect to the paediatric model, the ERG agrees that the percentage of children achieving complete independence by 6 months was higher in the paediatric trial (C14) than in STEPS, suggesting a greater potential for children to benefit. However, C14 had no strict weaning algorithm, and comparison with the PSP data (also no weaning algorithm) shows a lower proportion achieving complete independence by 6 months (12% versus 44%) (see Table 19 of the CS). Therefore, some uncertainty remains regarding the claim that children may benefit more from treatment. That said, the comparisons are based on small numbers, and in another real-world study in children, 69% (11 of 16) were reported to have achieved independence by 12 months.[33] *Given the limited data available in children, it appears reasonable to utilise the adult transition probabilities in the paediatric model Whether this is conservative or not remains to be proven.*

Regarding the decision to include data from the PSP in the calculation of transition probabilities for teduglutide, the ERG accepts the company's reasoning. The ERGs clinical expert agreed that it is plausible to expect greater reductions in PS days outside the trial setting in the absence of weaning algorithms. However, there is some remaining concern that there is no control group for the PSP patients. Therefore, we have to accept that the PSP patients are comparable to those recruited to STEPS and that none of the patients in the PSP would otherwise have reduced their PS requirement without teduglutide treatment. The company show that the PSP patients are generally comparable on a range of observed baseline characteristics to those recruited to the teduglutide arm of STEPS. They also provided further reassurance in response to the clarification letter that patients in STEPS and the PSP are comparable (question A9) and unlikely to be undergoing any ongoing adaptation that could explain reductions in PS requirements (A8).

There is still some uncertainty regarding the company's explanation for the reduction in PS observed in the placebo arm of STEPs, but the ERG agrees that random fluctuations in urine output in combination with the weaning algorithm offers a plausible explanation. Alternatively, the ERGs clinical expert advised that some of the reductions in PS in both arms of STEPS could have been due to improved adherence to other interventions to reduce losses from the bowel, resulting in increased urine losses and subsequent reductions in PS. Such a trial effect might imply that it would be appropriate to remove the placebo arm response from the teduglutide arm response of STEPS, while keeping the SOC arm stable at baseline. The company noted, however, in their response to the clarification letter, that standard of care (which includes use of concomitant medications) was optimised prior to entry into steps, and therefore they believe it is implausible that this impacted PS reductions during the trial (see company response to the clarification letter, questions A5 and A6). The company also note in their submission, and in response to the clarification letter (B4), that such a trial effect would result in smaller reductions in PS in the teduglutide arm that are more inconsistent with the larger reductions observed for teduglutide in the real-world evidence identified. Therefore, the ERG accept that the company's approach offers a reasonable base case. However, given the observed reduction in PS in the placebo arm of STEPS, and the lack of control group in the real-world PSP data, we cannot be certain that patients treated with teduglutide, in STEPS or the PSP programme, would not otherwise have experienced any reduction in PS requirement over time, e.g. due to improved management or some ongoing adaptation. Therefore, the ERG requested a scenario that included health state transitions for SoC as observed in the placebo arm of STEPS.

The ERG has some further minor concerns regarding assumptions in the calculation of transition probabilities.

- *The decision to include data from the PSP only to 12 months did not appear well justified in the original submission, and the ERG sought clarity on this in the clarification letter to the company. The company clarified that based on the method of carrying forward the last observed PS state, the censoring of follow-up in the PSP beyond 12 months would have inappropriately diluted the observed treatment effect observed in STEPS-2 where patients were systematically followed-up to 30 months. The ERG understands the logic of this but has some remaining uncertainty as to why the number remaining in follow-up at the start of each 6-month interval could not be retained, and censored patients dropped for the purpose of calculating transitions*

probabilities. However, the company did provide scenarios that used the PSP data beyond 12 months, and it wasn't until the last state of censored patients was carried through to 30 months that it had a significant upward impact on the ICER. The ERG agrees that this is likely to bias against teduglutide and accepts the company's approach.

- *It was not clear if the calculation of the transition matrices beyond 12 months accounted for the stopping rule applied in the model. The ERG suspects not, but the direction of any associated bias is unclear. Further clarity on this would be beneficial.*
- *Whilst the company provided some internal validation of their model output in terms of the percentage of the cohort achieving PS independence in their submission, they did not provide a full comparison with observed state occupancy. This was requested at the clarification stage, and the company provided this in the response (see Clarification letter, Question B5). For comparability, this required the same assumptions about reverting back to baseline PS requirements for patients stopping treatment in the observed data and carrying forward the last observed state for those with short follow-up in the PSP. The model appears to align reasonably well with the observed data, with no obvious bias.*

Time on treatment

A combination of observed treatment discontinuation from the STEPS trial and the PSP and a proposed treatment stopping rule were applied in the company model to reflect expected usage of teduglutide in clinical practice.

Standard parametric survival curves were fitted to the time on treatment data from STEPS, STEPS-2 and the PSP combined (see Figure 22 and Figure 23 of the CS, document b). The company selected the Weibull curve based on it having the best statistical fit, good visual fit, and offering a plausible extrapolation (hazard of discontinuation reducing with longer time on treatment). The log-normal and log-logistic were tested in scenario analysis as the next best fitting curves, with these both tracking above the preferred Weibull extrapolation (See Figure 23 of the CS).

In addition to the time on treatment curves, the company implemented a stopping rule in the model, noting the fact that some patients in the clinical trials remained on treatment for many months despite receiving no benefit. They argue that this is an artefact of the trial environment and would not be expected in clinical practice. The SmPC suggests that the treatment effect should be assessed at 6 and 12 months, and *"if no overall improvement is achieved after 12 months, the need for continued treatment should be reconsidered*". To align with this and advice from clinical experts at an advisory board meeting, the company applied a treatment stopping rule to anyone who has not achieved a reduction of at least one day of PS support per week at 12 months. The company implement this by determining the proportion of patients who experienced no reduction in PS days per week, relative to the observed number of patients remaining on treatment in each health state at this timepoint (see Table 25 of the CS). They move these proportions to the corresponding off-treatment PS health states, where there is no further probability of PS requirements changing.

The ERG accepts the logic for applying a stopping rule to teduglutide treatment. However, there is some uncertainty regarding wider clinical support for the specific criteria applied. For example, the company's criteria is not entirely consistent with the British Intestinal Failure Alliance (BIFA) 2018 position statement on the use of peptide growth factors for adult patients with intestinal failure, which states that the aim of treatment is: "a) To have a reduction in stomal output of more than 1.5 L/24 hrs; b) To stop or achieve more than 2 night off/week of parenteral support; c) To have an improved quality of life (QOL)." The position statement further notes that treatment should be stopped "if the treatment goals of reducing PS are not achieved after 24 weeks". [55]

For those modelled to discontinue treatment based to the chosen extrapolation of time on treatment, the company determine the proportional distribution of PS health states from which observed discontinuations occurred, and the baseline PS health state distribution of these patients. These distributions are calculated separately before and after 12 months when the stopping rule is implemented (see Tables 26 and 27 of the CS). After 12 months, the company note that the proportional distributions are calculated using data only for those patients who discontinued after 12 months who would not have stopped treatment based on the treatment stopping rule ([redacted]). It is not clear if this number is different to the total number of discontinuations occurring after 12 months in the observed data. However, inspection of

the Kaplan-Meier curve suggests there may only have been [redacted] in total.

With respect to the discontinuation curves, the ERG acknowledges the company's base case curve selection, but note that the log-normal and log-logistic curves may also provide plausible extrapolations since it is only the responders who are assumed to remain on treatment beyond 12 months.

With the stopping rule and time on treatment curves combined, there could be potential to overestimate discontinuation probabilities after 12 months if some of the discontinuation events in the KM curve occurred in patients captured by the 12 month stopping rule. However, the company's explanation and presented data suggests that all the discontinuation events occurring after 12 months in the KM curve may have been in patients that had achieved a reduction in PS days at 12 months. This suggests that the discontinuation probabilities among those remaining on treatment beyond 12 months in the model (i.e. in those who achieved a reduction in PS days at 12 months) may in fact be underestimated - because patients who would be captured in the stopping rule may still be counted in the number at risk beyond 12 months in the KM curve. Nevertheless, the number of discontinuation events occurring beyond 12 months remains very low ([redacted]) for informing the health state discontinuation distributions. The company have therefore included as scenario to assess the impact assuming no further discontinuation beyond 12 months. An alternative scenario could have been to assume an equal proportional discontinuation distribution across the model PS states, but this would then require a further assumption regarding the appropriate baseline health state distribution of these patients.

Survival

Given a lack of direct evidence for an effect of teduglutide on survival, or robust evidence examining the relationship between PS requirements and mortality, the company assume equivalent survival across treatment arms and health states. This appears to have been backed up by clinical expert opinion, suggesting that mortality rates for people on PS are more likely to be related to the underlying SBS-IF rather than their PS.

The ERG acknowledges the company's reasoning for assuming no mortality effects in the model. However, the assumption does create some anomalies with respect to certain

complications related to the level of PS requirement; intestinal failure associated liver disease (IFALD) and chronic kidney disease (CKD). People with higher PS needs in the model are assumed to be at higher risk of IFALD and CKD, and these complications would be expected to increase the mortality risk. By assuming no structural link between the proportions with these complications and mortality, the model potentially ignores a small survival benefit for teduglutide, but also potentially overestimates ongoing costs associated with these complications. This criticism depends on whether it is appropriate to include a causal effect for teduglutide induced PS reductions on these complications in the first place (discussed further below). It should be further noted that the company provide a scenario analysis in which an IFALD specific mortality rate is applied to the expected proportion of patients with this complication. The model does not, however, have the functionality to reduce the modelled proportion of the cohort with IFALD accordingly.

With respect to the mortality rates applied in the model, the company used published survival data. For adults, they used data on 218 patients with SBS-IF on PS (from a Canadian PS registry) who were followed up for up to 15 years (from 2003 to 2018).[53] The company digitised the published Kaplan-Meier plots and generated pseudo individual patient data (IPD) using the algorithm published by Guyot et al (see Figure 24 of the CS, document B).[56] They then fitted the standard parametric survival curves to the generated IPD (see Figure 25 of the CS, document B) and selected the log-normal for their base case based on a combination of statistical fit (AIC and BIC) and consistency with the observed hazard function in the data reported by Salazar et al, which increased initially but then diminished over time (see Figure 26 of the CS, document B).[53]

The ERG identifies several potential limitations of the company's approach to extrapolating mortality in adults:

1. *The numbers of patients are low, particularly beyond 10 years of follow-up (only 10 remaining at risk at 10 years), making the shape of the longer-term hazard function highly uncertain.*
2. *Whilst the length of follow-up is substantial, the data is relatively immature (66% still alive at 10 years) compared to the life-time horizon of the model, resulting in a long and uncertain extrapolation period.*
3. *The company's selected log-normal curve may lack plausibility for the long-term extrapolation of all-cause mortality, as it results in the hazard dropping below that of*

age/sex matched general population mortality by year 24 in the model. To overcome this, the company apply general population mortality from this time point onwards. This seems uncertain given the complex underlying health conditions of the population with SBS-IF.

Given the above issues, the ERG believes that extrapolation of survival may be overly optimistic in the company's base case. The ERG further notes that there is little to choose between the curves in terms of the measures of statistical fit. However, on the grounds that the exponential has lowest AIC and BIC, and that it retains a mortality hazard that is higher than that of the general population mortality for longer (to 31 years), the ERG suggests this more conservative extrapolation curve may be appropriate.

For paediatric survival, the company adopt a similar approach, but use published survival data on 88 children on home parenteral nutrition, followed up for up to 5 years. Again, pseudo IPD were generated by digitising the published Kaplan-Meier curve, and parametric survival models were fitted (see Figures 27 and 28 of the CS, document B). Based on consideration of the AIC and BIC, the company selected the exponential distribution as offering the best statistical fit.

There is even greater uncertainty associated with the extrapolation of survival in the paediatric population, owing to the immaturity of the survival data (91% survival at the maximum 5-year follow-up) relative to the lifetime horizon of the model (up 94 years). Given the limited survival data on which to base the very long extrapolations, the ERG agrees with the company's base case exponential extrapolation, but believes the scenarios with alternative curves are also relevant for consideration.

Complications

In addition to adverse events which are included in the model (see Adverse events below), the company have included two serious long-term complications associated with PS that are not captured in the trial data: IFALD and CKD. Due to apparent lack of data on their incidence by level of PS requirement, the company conducted a Delphi panel to inform expected incidence. The exercise involved nine clinical experts.

It is reported in the company submission that the experts concluded that teduglutide would reduce the incidence of IFALD by reducing PS requirements, and that they expected its prevalence to be 0-1% after one year on PS, 0-3% after two years, and 0-3% after 10 years. However, the Delphi panel report states that these were the agreed prevalence estimates at 2, 6 and 10 years respectively. This is also how the estimates are applied in the company model, so the ERG assumes that the timepoints reported in the company submission document are typos. The company describe how they assumed that reduced PS would reduce the incidence of IFALD, and so they split the cohort into four groups based on number of PS days (no PS, PS1-3, PS4-5, and PS6-7) and interpolated expected prevalence by group based on the ranges provided by the experts (Table 13). Incidence (development) probabilities were then calculated to yield these expected prevalence rates and extrapolated onwards beyond 10 years.

Table 13. IFALD prevalence estimates from Delphi meeting and calculated development rates per 28 days (Source: Table 30 of the company submission, document B)

	No PS	**PS1–3**	**PS4–5**	**PS6–7**
Prevalence at 2 year on PS*	0.00%	0.33%	0.67%	1.00%
Prevalence at 6 years on PS*	0.00%	0.67%	1.33%	2.00%
Prevalence at 10 years on PS	0.00%	1.00%	2.00%	3.00%
Development rate years 0-2*	0.000%	0.013%	0.026%	0.039%
Development rate years 2-6*	0.000%	0.006%	0.013%	0.019%
Development rate years 6+*	0.000%	0.006%	0.013%	0.020%
Abbreviations: IFALD, intestinal failure-associated liver disease; PS, parenteral support **Source:** Delphi panel report[57]				

*Time periods corrected by the ERG to align with the Delphi panel report and the model

In the model, the company use the development probabilities to determine the expected proportion of patients with IFALD in each PS group over time in the model. These proportions are then taken forward into the model cost and QALY calculations. With respect to the cost calculations, the company rely on another calculation to estimate the proportion of time that people with IFALD can expect to spend in different stages of liver disease (liver disease, extensive fibrosis, and cirrhosis). For this the company use data from a study by Cavicchi et al on the development of liver disease in a cohort of patients (n=90) receiving home parenteral nutrition for permanent intestinal failure.[58] However, no description is provided by the company on how these data were used. In the model, it appears that

incidence rates for liver complications have been taken from Cavicchi et al., and then cycle specific probabilities of developing extensive fibrosis (conditional on having liver complications) and cirrhosis (conditional on having extensive fibroisis) have been calculated by manual calibration to data on their incidence as reported by Cavicchi. However, the specific calibration targets and approach are not described.

The ERGs clinical expert was generally supportive of applying a relationship between the level of PS required and the incidence of IFALD in the model, and that teduglutide can be expected to reduce the incidence of this complication. However, the ERG has several concerns regarding the company's approach to modelling IFALD.

1. *The proportion of the surviving cohort with IFALD, calculated based on the Delphi panel derived development probabilities, fails to account for the fact that those with IFALD are more likely to die compared to those without IFALD. This may lead to overestimation of the surviving proportion with IFALD over time. Furthermore, extrapolation of the development rate over time is uncertain.*
2. *Clinical experts consulted in the Delphi panel* [redacted] *[57] While the company have not used this to estimate the overall proportion with IFALD, they still use it to calculate the expected distribution of patients across IFALD severity levels. This could introduce bias to the estimated cost of IFALD.*
3. *Calculation of the proportional distribution of IFALD severity does not account for mortality or the relationship between increasing severity and increasing risk of mortality, and so may overestimate the expected time that surviving patients with IFALD can expect to spend in the more advanced stages that incur higher costs.*
4. *Patients who reduce their PS days with teduglutide attract a lower proportional weighting for IFALD, which may infer that IFALD is reversable in some cases (or only those without IFALD can improve their PS requirements). This could potentially overestimate the IFALD cost savings associated with reduced PS requirements. However, this bias is likely to be small as the IFALD proportions are low across the states in the early stages when patients are reducing their PS requirements under teduglutide treatment.*

The company apply a similar approach to estimate the expected proportion of the cohort with stage V CKD by level of PS requirement (no PS, PS1-3, PS4-5, and PS6-7). Again, the company rely on the Delphi panel meeting to estimate expected prevalence at 1, 2 and 10 years by the PS frequency groupings, and then use these to estimate development probabilities and build up expected proportions with the CKD over time.

The ERGs clinical expert was also generally supportive of assuming a link between PS requirement and CKD, but again the ERG notes that issues 1 and 4 identified above in the calculation of IFALD proportions also applies to the calculation of CKD proportions. The approach taken may overestimate the proportion of the surviving cohort that have CKD over time, resulting in overestimation of CKD costs in the model, and failure to capture a small potential survival benefit associated with its reduced incidence in the teduglutide arm. Ideally, if IFALD and CKD are to be included in the model, they should be incorporated using additional health states to reflect the history of these complications and their associated mortality risk. However, the ERG recognise that this would increase the number of model states substantially, and there may be limited data available to inform the expected mortality risks for SBS-IF patients with and without these complications. It is therefore useful that the company have provided a scenario analysis that excludes them, which shows a modest impact on the ICER. This is likely to be a conservative scenario given the plausible link between teduglutide use and a reduction in these serious complications.

Adverse events

Adverse event rates per model cycle are presented in table 33, page 119 document b of the company submission. The company has included adverse events which occurred in at least 5% of patients in either arm of the STEPS trial. The company reported 35 such events, and 32 were selected for consideration in the economic model. The decision to exclude three adverse events (device dislocation, epistaxis and nasopharyngitis) was made based on clinical expert advice to the company that these have minimal impact on cost and patient burden and would therefore have a negligible impact upon the cost-effectiveness results.

The company presents three different adverse event rates for use in the model which are informed by alternate patient-level data sets;

1. Up to 6 months for teduglutide. Informed by the teduglutide arm of STEPS.
2. Post 6 months for teduglutide. Informed by the three arms of the STEPS-2 trial.

3. Standard of care. Informed by the placebo arm of STEPS.

The standard of care adverse event rates are not time variable in the absence of data post 6-months from the STEPS trials.

The company did not stratify adverse event rates by the days of PS as it cannot be established whether the events are related to the patients underlying disease or their PS requirements.

The ERG is concerned that the adverse event rates utilised in the model have not been transparently reported and the case for a long-term reduction compared to standard care has not been fully justified. In the clinical trials, it was found that teduglutide had "a broadly similar adverse event profile compared to patients treated with placebo".[59] The section of the company submission presenting the pooled safety data did not make a clear case for diminishing rates of adverse events (events/patient time at risk) over time. It only presented total numbers and percentages of patients experiencing each type of event. However, the adverse event rates per cycle applied in the model decrease substantially after 6 months for teduglutide, which infer that the safety profile of teduglutide improves compared to standard of care. This is based on data from STEPS-2 for which no comparative SoC data exist. The calculation of the rates, and the case for diminishing rates in the teduglutide arm versus SoC, is lacking transparency and would benefit from further clarity. Given the uncertainty and lack of transparency around the calculations, the ERG suggests testing the use of non-time variable adverse event rates for both arms of the model.

Table 14 Adverse events rates included in the economic model (table 33, page 119 document b of the CS)

Adverse event	**Adverse event rate per cycle**		
	Teduglutide months 0-6	**Teduglutide after month 6**	**Standard Care**
Abdominal distension	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]
Bacteraemia	[redacted]	[redacted]	[redacted]
Catheter related infection	[redacted]	[redacted]	[redacted]
Central line infection	[redacted]	[redacted]	[redacted]

Constipation	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]
Dehydration	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]
Flatulence	[redacted]	[redacted]	[redacted]
Gastrointestinal stoma complication	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]
Injection site haematoma	[redacted]	[redacted]	[redacted]
Injection site pain	[redacted]	[redacted]	[redacted]
Muscle spasms	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]
Peripheral oedema	[redacted]	[redacted]	[redacted]
Bacterial overgrowth	[redacted]	[redacted]	[redacted]
Pain	[redacted]	[redacted]	[redacted]
Procedural site reactions	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]
Renal colic	[redacted]	[redacted]	[redacted]
Small intestinal stenosis	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]
Decreased weight	[redacted]	[redacted]	[redacted]
Increased weight	[redacted]	[redacted]	[redacted]

4.2.7 Health related quality of life

Teduglutide treatment aims to reduce a patient's reliance on PS by improving their intestinal absorption. As described in section 4.2.2, the company argue that the most relevant outcome associated with teduglutide treatment is a reduction in the days per week of PS a patient requires. The company explains that PS treatment is incredibly disruptive for patients, where

achieving at least one night off per week symbolises a great benefit to both patients and carers. Patient testimonials presented in section B.1.3.2 of the company submission report the tremendous burden that PS treatment has on their lives where one patient reports: *"I hate it [PS], absolutely hate it because I'm on three and a half litres, 12 hours, every single day, just don't have a life."* .[60] Clinicians at the company advisory board also described how reducing the number of days of PS each week is important to patients. Furthermore, a quality-of-life study in adults dependent on parenteral nutrition using the PNIQ instrument, which is designed to capture the impact PS has on a patient's everyday life, found that a reduction in days per week of PS was statistically significantly correlated with improvements in quality of life of patients with type 3 intestinal failure.[61, 62]

The ERG is satisfied that a reduction in days of PS per week is a meaningful outcome to capture in the economic model for SBS-IF, and that it is correlated with improvements in patients' health related quality of life – assuming it reflects an appropriate reduction.

Health state utility values

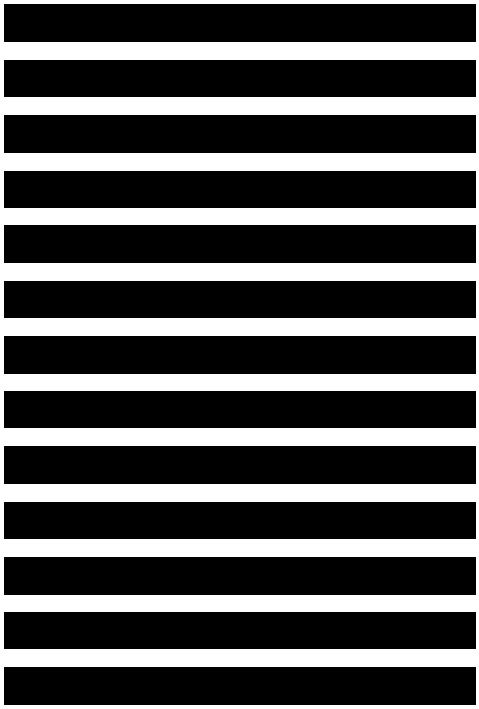
Clinical trials data

The company refers to quality of life data collected in the 004 and STEPS trials. Neither study found statistically significant differences in quality of life when comparing against the baseline or between trial arms at 24 weeks, nor was either study powered to detect such differences. This data is not used in the economic model due to a variety of limitations presented by the company.

The 004 trial collected quality of life data using the SF-36, EQ-5D and IBDQ instruments (data not presented in the company submission). The EMA acknowledged in the EPAR that none of these instruments had been developed for assessment in patients with SBS-IF stating "*low numbers of patients included in each treatment group in addition to the heterogeneity in symptoms between SBS patients, it is conceded that these tools may not have been appropriately sensitive to catch any potential difference."*[63] The ERG requested the company provide an analysis of the EQ-5D data at the clarification stage. The company declined on the basis that the data is not reported in the CSR for the 004 trial nor has any analysis been performed on the data.[39] The company believes that the data is "unnecessary and unhelpful" on grounds that the instrument lacks sensitivity for capturing the nuances of SBS-IF and its treatment.

The STEPS trial collected quality of life data using the SBS-QoL which is a disease specific instrument.[64] The SBS-QoL is not a preference-based measure, therefore utility values are derived using a scoring algorithm that was subsequently developed using a lead time time-trade-off technique.[65] Lloyd et al developed the algorithm whereby six-dimension health states were constructed using 8 of the SBS-QoL items. These items were selected based on an item performance analysis of a European SBS-QoL dataset and consultation with 3 SBS clinical experts. The health states were valued by a UK general population sample (N=250). Figure 3 below shows the utilities mapped using the Lloyd algorithm from the SBS-QoL data in STEPS by the number of days per week of PS.

Figure 3 Utilities mapped from the SBS-QoL data in STEPS (Figure 29, page 116 document B of the CS)



The company criticises the quality-of-life data from STEPS for several reasons:

1. The data lacks face validity.

[redacted]

2. The heterogeneity of the SBS-IF population makes differences in quality of life difficult to detect.[63] Patients with a chronic disease who require PS as a result may see it in a positive manner as it provides control over their underlying disease.[66]
3. STEPS was not powered to detect statistically significant differences in the SBS-QoL score.[9]
4. Lack of sensitivity of the SBS-QoL instrument.[63]

The ERG also requested that the company provide a further baseline adjusted analysis of the STEPS utility data mapped from the SBS-QoL instrument, to better explore the relationship between reductions in PS days and health state utility. The company declined, and offered further arguments as to why they believe re-analysis of the SBS-QoL data would be of no value (Company response to the clarification letter, question B9). This focuses on limitations of the SBS-QoL instrument, and refers to testimonies from clinicians, patients, and experts on patient reported outcome measures which: a) back-up their claims that the instrument lacks sensitivity for capturing meaningful improvements in HRQoL that patients experience with reductions in PS days, and b) identifies several flaws in the development of the instrument which undermines its validity.

Health-related quality of life studies

The company undertook a systematic literature review in May 2021 in addition to another in 2017 to identify relevant health-related quality of life or health state utility value studies for use in the economic model (appendix G of the CS). Of the 6 studies identified, a vignette study by Ballinger et al was selected for the company base case as the population providing the health state values was a sample of the UK general population.

The Ballinger et al study utilised a time trade-off preference elicitation technique, with a sample of the UK public (N=100) provided ratings and utility scores for 8 health state vignettes describing the impact of 0 days of PS up to 7 days of PS per week.[50] The health states included eight attributes, 3 of which were associated with SBS-IF and home PS and a further 5 focussed on the 5 EQ-5D domains. None of the health states referenced stoma use specifically.

The company also noted two other studies reporting utilities for health state vignettes based on the number of days of PS per week: Lachaine 2016 and Raghu 2020.[67, 68] However, as the Raghu study is simply the age adjusted values of the Ballinger study it was disregarded. The Lachaine study was deemed less appropriate as it used a sample of SBS patients and the Canadian general population to value the health state vignettes. The company provides sensitivity analysis where utilities for the Lachaine 2016 study are used.[67]

Based on the company's response to the clarification letter, the ERG is satisfied that re-analysis of the SBS-QoL data from STEPS, or EQ-5D data from 004, is unlikely to be helpful for informing utility values for the PS health states in the company model. However, whilst acknowledging the statements provided by patients and experts, which support the company's assertion that the SBS-QoL and EQ-5D lack sensitivity and face validity with respect to capturing changes in HRQoL associated with reductions in the number of PS days per week, the company has not provided much in the way of empirical evidence to show that the instruments lack content validity or perform "poorly on tests of construct validity and responsiveness" as suggested in the NICE methods guide.[69]

Accepting that the Ballinger et al. vignette study offers a relevant set of utility values to inform the company's economic model, the ERG has some concerns regarding potential for bias. Whilst it shows that more days on PS are perceived by a sample of the general population to have a strong negative impact on HRQoL, the health state vignettes are not based on actual differences in health status reported by teduglutide treated patients. There are a number of the health state dimension descriptions which could be considered leading. For example, the anxiety/depression dimension states the following in reference to 0 days of PS: "You are glad that you do not need to receive nutrients through a tube in your chest". The descriptions for 6-7 days of PS states "...you would value having 1 day per week without having treatment".[50] Other statements may exaggerate the impact of the condition. For example, it appears to have been stated for states PS1-PS7 that "...due to having a tube, you are unable to do physical exercise." It is not clear from the published paper if all respondents understood this to mean only when connected to PS. Furthermore, the health state descriptions do not consider the potential impact of the distribution of underlying conditions and common complications such as use of a stoma which could potentially limit the improvements in functioning ascribed to the vignettes for lower PS requirement states. Whilst the states were developed with input from semi-structured interviews with patients,

they do not appear to have been subsequently validated by patients. Finally, while the study sample for valuing the states 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, which could limit the generalisability of the elicited values. The NICE DSU TSD 12 provides guidance on the use of vignettes, stating those which "…have not been based on HRQL data do not meet the NICE methods guidance for alternatives to the EQ-5D. However, vignettes may have a limited role where there are no data available using validated HRQL measures".[70]

Overall, the ERG [redacted] *The ERG further acknowledges the low patient numbers and heterogeneity in the available sample and accepts that the inferred lack of change in HRQoL from baseline in the teduglutide arm of 004 lacks face validity. This limits the value of the EQ-5D data for the current appraisal. Whilst the company have not provided the EQ-5D data, their application would likely infer no substantive quality of life benefit to reducing the number of PS days, which is at odds with the testimonies of patients and clinical experts. However, use of the Ballinger study utilities is not well aligned with the NICE reference case and has the potential to exaggerate the quality of life benefit of reducing the number of days of PS per week for reasons identified above. Reflecting on the evidence, the ERG accepts the company's use of the vignette utilities but provide some further sensitivity analysis to assess the impact of reducing the range in utility between the PS0 and PS7 states, whilst maintaining the ratios between the elicited values for the states.*

Carer quality of life

The company explains that SBS-IF patients commonly require an informal caregiver to help with day-to-day tasks and emotional support.[71] It is assumed that each adult patient has on average one caregiver on the basis of a patient and carer survey of 181 adult patients and 121 carers from the US, UK, France and Germany.[72] Paediatric patients are assumed to require 2 caregivers on the assumption that they would have 2 parents who would provide care.

The company sought estimates from clinical experts participating in their Delphi panel, for the utility of carers with low (1-2 days), medium (3-5 days) and high (6-7 days) PS

requirements. These results were combined with directly reported EQ-5D results from a caregiver specific survey of 47 UK based carers for SBS-IF patients.[48] The calculation of utility decrements used in the model is the average of the Delphi panel estimates and the results from the patient and caregiver survey weighted by the distribution of respondents to this survey. The utility values and decrements have been provided in table 15 below. For example, the utility decrement for a carer of someone with a PS requirement of 4 days per week is calculated as follows:

$$-\frac{(1-0.77)+\left(1-\left(\frac{(0.77*5)+(0.95*9)}{5+9}\right)\right)}{2}=-0.17$$

Table 15 Carer quality of life decrements used in the economic model (reproduced from tables 34, 35 & 36 document b of CS)

Days per week of PS	Delphi panel	EQ-5D utilities from carer quality of life study (n)	Utility decrements used in economic model
0	NR	NR	0
1	0.89	NR	-0.10
2		1.00 (2)	-0.10
3		0.89 (10)	-0.10
4	0.77	0.77 (5)	-0.17
5		0.97 (9)	-0.17
6	0.67	0.89 (11)	-0.22
7		0.89 (10)	-0.22

The utilities are implemented into the model through the multiplication of the decrement by the undiscounted life years of the corresponding state for each cycle of the model. For paediatrics, utilities are applied in a similar manner however the decrements are multiplied by two to account for the two caregivers per patient.

The ERG notes that the Delphi panel estimates are not in line with the NICE reference case in for three reasons:

1. *The Delphi panel consisted of 9 clinical experts whereas health related quality of life should be reported directly by patients and/or carers.*

2. *The Delphi method is a not a choice-based method, it is used to reach a consensus between those involved in the panel.*
3. *Health state utility values should be based on a valuation of public preferences from a representative sample of the UK population.*

The ERG is note that the carer EQ-5D utilities derived from the UK caregiver survey [redacted] *. However, the survey is based on a very small sample of (N=47).*[48] *Conversely, the* [redacted] *Furthermore, the data in table 15 above suggests that carers would prefer 7 days over 4 days in terms of the EQ-5D- values (0.88(SD=0.12) versus 0.77(SD=0.26)) which appears unintuitive.*

In order to validate the results of the Delphi panel and UK caregiver survey, the company cites a global survey of N=121 carers from the UK, Germany, France and the US.[48, 57, 72] *This survey reported an average EQ-5D-5L value of* [redacted].[72] *It is worth acknowledging that the global caregiver survey EQ-5D-5L value is based on a distribution where* [redacted] *of the carers care for patients with 7 days per week PS requirements which is* [redacted] *than the baseline distribution used in the economic model (*[redacted]*). Of note, the global survey found* [redacted]

It should further be noted, that the application of utility decrements in the model assumes that any deviation from perfect health of carers is as a result of the patient's SBS-IF which is inherently flawed as the evidence from the UK caregiver survey does not suggest that carers have different utility values from the general population.[48]

The ERG finds that the company has not provided sufficient evidence to validate the assumption that carer health-related quality of life would increase as a result of patient's reducing their PS requirement. Further, the decrements that have been calculated are flawed, and may exaggerate the impact of any changes. Nevertheless, it is clear that SBS-IF and PS can impart a major burden on caregivers, but measuring and quantifying the impact accurately in terms of HRQoL represents a challenge. Given the limitations in the company

approach, the ERG suggest it is important to assess the impact on the ICER of both including and excluding the estimated carer disutilities. Further engagement with relevant patient and carer groups would be beneficial to understand the impact a reduction in PS days per week would have on carers HRQoL.

Complications (Intestinal Failure-Associated Liver Disease (IFALD) and Chronic Kidney Disease (CKD))

An equal utility decrement is applied to all patients in the IFALD disease state of the model. The decrement is calculated as the difference between the weighted average utility value of for those in PS1 to PS7 without IFALD and the weighted average utility value of for those in PS1 to PS7 with IFALD. The utility value for IFALD is sourced from the EQ-5D catalogue for the UK, and is applied multiplicatively.[73] The weighted average utility decrement is then multiplied by cycle length in years and applied to the total proportion of cohort with IFALD in each cycle of the model. The utility value for stage V CKD represents the utility of those with CKD on dialysis, which is sourced from a systematic review and meta-analysis of utility bases quality of life in chronic kidney disease treatments.[74] The utility decrement for CKD is calculated and applied in the model following the same approach as for IFALD.

The ERG has no major concerns with the approach to applying utility decrements to the proportion with IFALD and CKD. However, the ERG does have some concern that the proportions of the surviving cohort with these complications may be overestimated in the company model, since there is no structural link between them and an increased risk of mortality (see section 4.2.6 above). Therefore, the QALY losses attributable to the health-related quality of life impact of living with these complications may be overestimated (favouring teduglutide). However, this bias could be offset by the model failing to account for a small survival benefit that could be expected (for teduglutide) by reducing their incidence. The net impact on the ICER is uncertain.

Adverse events

The rates of all adverse events (section 4.2.6) are multiplied by the relevant utility decrements, which are sourced from external literature, to generate a total utility decrement which is applied for the duration of each model cycle. Therefore, it was assumed that all events would reach resolution in 28 days. Several adverse events which attract costs in the

model do not attract a utility decrement. These include: Dizziness, dyspnoea, muscle spasms, nausea, pain, pyrexia and renal colic.

The utility weights of adverse events are sourced from the catalogue of EQ-5D scores for the United Kingdom, the company submission of TA352 (vedolizumab for treating moderate to severely active Crohn's disease after prior therapy) and a systematic review of the impact of urinary tract infections on health-related quality of life.[73, 75, 76] The UK-based EQ-5D catalogue utilised regression methods to estimate the marginal disutility of several conditions controlling for covariates. TA352 cites Brown et al. 2001 for the utility decrement (serious infection) which informs bacteraemia, catheter-related infection, central line infection, bacterial overgrowth, and upper respiratory infection adverse events in the company model.[77] The adverse event disutility for injection site haematoma, injection site pain, procedural site reactions was sourced from Beusterien et al. 2009 cited in TA352.[78]

The decrement of -0.52 informed by Brown et al. is sourced from a sample of 30 UK oncology nurses using a standard gamble method. The decrement is calculated as =1-0.48.The health state utility value of 0.48 is for infection without hospitalisation. The ERG finds that, not only is this not aligned with the NICE reference case, the decrement assumes perfect health prior to infection which is not realistic with respect to SBS-IF patients. The ERG suggest the decrement should be calculated relative to the mean age specific population norm.

The ERG is unclear why several events which incur costs to the health service are assumed to attribute no utility decrement as the rationale is not provided in section B.3.4.3 of the CS. Given that these events require health care resource use to reach resolution, ideally an estimate of their utility impact should be included in the model. However, the ERG does not expect their omission to have a material impact on cost-effectiveness.

The costs associated with line sepsis are included in the health state costs in the model (section 4.2.8) using rates derived from a survey of clinical experts designed to assess resource use associated with the PS day requirements. However, the disutility associated with line sepsis is applied using the adverse event rates from the STEPS and STEPS-2 trials. The rationale for applying different rates to determine the cost and health impact of sepsis is not discussed in the company submission. The ERG would prefer to apply the same rates for

both. The ERG also notes the advice from the NICE DSU TSD 12 which states that "Where the adverse events are known to affect HRQoL they should be treated in the same way as the associated costs…".[79] It is uncertain the impact this disconnect creates upon the economic model given the issues raised by the ERG regarding adverse event rates discussed in section 4.2.6. However, given the detrimental health effect of these adverse events and its association with a patient's PS needs the ERG highlights this as an issue that could be address in technical engagement.

4.2.8 Resources and costs

Cost of the intervention

Teduglutide is available in either the 5mg or 1.25mg vial. The list price is £521.98 and £260.99 respectively. The company has proposed a simple PAS discount of [redacted] for both vial sizes. The SmPC recommends a daily dose of 0.05 mg/kg of body weight. Therefore, the smaller vial is appropriate for patients who weigh up to 25kg and the larger vial for patients who weigh up to 100kg. The model assumes that all patients would receive the 5mg vial, therefore wastage is accounted for in all scenarios considered by the company. The treatment acquisition cost per year for the 5mg vial with the PAS is [redacted].

Treatment with teduglutide requires colonoscopies at treatment initiation, 1 year, 2 years and every 5 years thereafter. This is consistent with clinical practice, where the ERG clinical expert states that colonoscopies are not frequently used in standard care (unless in IBD cases). All patients, including paediatric patients require this regimen of colonoscopies. The company has utilised adult specific colonoscopy HRG cost for both populations. Further details of the unit cost of a colonoscopy can be found in table 37, page 126 of document B.

Teduglutide does not require any further monitoring costs over and above what the patient receives as part of their PS care aside from the additional colonoscopies described. The company has advised that a Takeda sponsored homecare service would be provided upon approval of teduglutide.

The ERG finds it reasonable to assume that no patients would require more than 5mg per day as the maximum patient weight in [redacted][38] *However, the company has made the following assumptions which may inflate the treatment acquisition cost of teduglutide:*

- *No vial sharing. The company argue that since the eligible population for teduglutide is small, the potential for vial sharing is limited.*
- *Paediatric patients would receive the full 5mg dose. The WHO growth charts suggest that 50th percentile of children would reach 26kg at age 8.*[80]
- *No dose reductions for patients with renal impairment. The SmPC for teduglutide states that a 50% dose reduction should be administered to patients with end stage renal disease.*

The company asserts that these assumptions present a conservative case for teduglutide. The ERG would find it beneficial to quantify the degree to which treatment acquisition costs are overestimated in the company's analysis and whether this has a material impact upon the ICER.

The ERG also prefers to use the paediatric specific HRG unit cost for colonoscopy. Furthermore, the SmPC specifies that children should undergo faecal occult blood testing at treatment initiation and annually thereafter which has not been accounted for in the company's analysis.

Finally, it is not explicit within the company submission what additional monitoring and support the Takeda home care service would provide. Therefore, the ERG cannot comment on whether any additional monitoring/administration burden would fall onto the NHS.

Health state costs

The health state costs per cycle consist of the resource use required to fulfil a patient's PS requirements per week. Patients who receive home parenteral nutrition require a substantial amount of resource use, most of which is determined by the number of days per week of PS. The frequency of resource use and the unit cost of the corresponding resource use is found in tables 39 and 40, page 127 document b of the CS. For each health state, the health state cost per cycle is calculated by multiplying the unit cost by the relevant amount of resource use required to fulfil the patients required nights of PS per week. Therefore, the cost increases as a greater number of days of PS is required. Patients diagnosed with either IFALD or CKD have different PS bag requirements such as reduced lipid content and increased electrolytes. The ERG is unclear whether this would have cost implications.

The company has utilised NHS reference costs and BNF costs where possible which is in line with the NICE reference case. The provision of PS bags, which includes the bags themselves, delivery, nurse time, and taurolocks is agreed through private contracts with trusts. Therefore, a confidential appendix will be provided with this report.

The frequency of resource use by the number of days of PS required by UK adults and children was informed by studies utilising telephone interviews with experts in the provision of PS. The adult study involved four consultant gastroenterologists, five nurses, one

pharmacist and a dietician from specialised intestinal failure centres in England.[81] The company utilised the study to construct the estimated resource use by the patient's required days of PS.

The inclusion of line sepsis complications associated with PS into the health state costs is uncertain as there is not a clear consensus whether the incidence of line sepsis increases as the number of PS days increases. The ERG clinical expert concurs with the company's position, patients who require a greater number of days of PS would have more episodes of line sepsis given the greater exposure to infection that they experience. The company cited the Parexel resource use studies to support their position in response to clarification queries. However, these studies state; "Infections are not correlated with… number of PN nights; they are related to the patient's thoroughness in taking care of the line". Given the uncertainty, the ERG explores scenarios where the rate is kept constant across PS states 1-7 days (and zero in PS 0).

Patients who are PS independent incur no health state cost in the model. However. this is not suggested within the Paraxel study where, it indicates that all SBS-IF patients would receive the same level of monitoring regardless of their PN requirements. At the clarification stage, the company asserted that since the health state costs are specifically for the cost of the patient's PS requirements, it is justified that they would not require any health care resource use since these patients have weaned off PS. The company also argued that since the cost of managing a patient's underlying SBS-IF are assumed equal between the treatment arms, these do not need to be accounted for within the model. The ERG disagrees with this logic, if this were the case, then this assumes that patients who receive any PS would require 3 additional specialist visits each year for their PS plus the 3-4 monitoring visits per year as outlined in the Parexel study. The ERG clinical expert has clarified that all SBS-IF patients typically receive 3-4 clinic visits per year regardless of their PS requirements. The company did run a scenario in response to clarification queries, where patients who require 0 days of PS would receive 2 specialist visits per year which led to a small increase in the ICER.

Overall, the ERG finds the company's methodology transparent and agreeable. However, it would be beneficial if further data or clinical expert opinion was sought to validate the assumption that the incidence of line sepsis would increase as a patient's PS need increases. Furthermore, the ERG would prefer the exclusion of specialist visits from the health state

costs, as these are required to manage the patients underlying SBS-IF and not neccessarily related to their PS needs.

Complications (Intestinal Failure-Associated Liver Disease (IFALD) and Chronic Kidney Disease (CKD))

As discussed in section 4.2.2 and 4.2.6, all patients are at increasing risk of developing IFALD dependent upon their PS need in each cycle. A weighted cost is calculated using the expected time in state for three stages of liver disease: non-progressed, fibrosis and cirrhosis. The cost of each state was sourced from an NIHR HTA study of the management of patients with chronic liver disease. The time spent in each state was determined using a study of the prevalence of liver disease (of different levels of severity) for patients who receive PS at home with permanent intestinal failure.[58] This results in a weighted cost per cycle of £2,775, further information can be sourced from table 42, page 130 document B of the CS.

Kidney disease is modelled in a similar way to IFALD, where patients who require more days of PS per week are at a higher risk of developing CKD. Only stage V kidney disease is considered in the analysis, where the company argues that only "*Stage V CKD…impacts resource use in a manner relevant to our economic model*". Therefore, the company has applied the weighted HRG cost of chronic dialysis (LA08G and LA08P) to all stage V CKD patients resulting in a cost per cycle of £2,384.

The ERG finds the company's unit costs for IFALD and CKD to be appropriate but has concerns regarding the approach to estimating the proportions with these complications and the more severe forms of liver disease severity (see section 4.2.6 above). The ERG believes the company's approach may overestimate these, which in turn will overestimate the associated costs.

Adverse events

The cost of all other adverse events was calculated using the rate per cycle, sourced from STEPS and STEPS-2 (section 4.2.6), multiplied by the relevant unit cost for managing each event. Where possible, the company has used the relevant NHS reference cost. Where this was not possible, alternative costs were used based on the expected resource use an event requires. Several adverse events were assumed to attribute zero cost. These include decreased appetite, dehydration, fatigue, flatulence, headache and weight increase/decrease. These were

determined by the Delphi panel to be “largely transient”, therefore would not require additional resource use over and above what the patient requires for the management of SBS-IF.

The ERG is satisfied with the method and the majority of unit costs applied for adverse events in the model. However, the ERG is notes that renal colic is under costed as the NHS reference cost used does not include intervention. Management of renal colic in the UK varies from watchful waiting, medical expulsive therapy, and surgery, all of which depends on a patient’s risk factors and size of the stones.[82]

5 COST EFFECTIVENESS RESULTS

5.1 Company's cost effectiveness results

The model inputs and assumptions for the company's preferred base case are laid out in Tables 44 and 45 of their submission document. The deterministic base case results are presented in Table 46 for the adult population (start age 50 years) and Table 47 for the paediatric population (start age 6 years). The ICER in the adult population is £16,652, based on incremental cost of [redacted] and incremental QALYs of [redacted]. The breakdown of the cost (by categories and health states) and QALYs are provided in the company model, reproduced in Tables 16 to 18 below. The incremental cost is driven primarily by the treatment acquisition cost for teduglutide, and there are savings in PS, complications and adverse event costs driven by the reduced time spent in higher PS requirement states. Correspondingly, the QALY gain for teduglutide is driven the increased time spent in the low "No PS" and low PS requirement states (PS 1 day and PS 2 days per week).

Table 16 Breakdown of discounted costs by cost categories (Source, Company model)

	Teduglutide	Standard Care
Teduglutide	[redacted]	[redacted]
Colonoscopy	[redacted]	[redacted]
PS	[redacted]	[redacted]
Liver Complications	[redacted]	[redacted]
CKD	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]
Total	[redacted]	[redacted]

Table 17 Breakdown of discounted costs by health state

	Teduglutide	Standard Care
No PS	[redacted]	[redacted]
PS 1 day per week	[redacted]	[redacted]
PS 2 days per week	[redacted]	[redacted]
PS 3 days per week	[redacted]	[redacted]
PS 4 days per week	[redacted]	[redacted]
PS 5 days per week	[redacted]	[redacted]
PS 6 days per week	[redacted]	[redacted]
PS 7 days per week	[redacted]	[redacted]
Total	[redacted]	[redacted]

Table 18 Breakdown of QALYs by health state

	Teduglutide	Standard Care
No PS	[redacted]	[redacted]
PS 1 day per week	[redacted]	[redacted]
PS 2 days per week	[redacted]	[redacted]
PS 3 days per week	[redacted]	[redacted]
PS 4 days per week	[redacted]	[redacted]
PS 5 days per week	[redacted]	[redacted]
PS 6 days per week	[redacted]	[redacted]
PS 7 days per week	[redacted]	[redacted]
Liver disease Utility decrement	[redacted]	[redacted]
CKD Utility decrement	[redacted]	[redacted]
Carer QALYs	[redacted]	[redacted]
Total	[redacted]	[redacted]

For the paediatric population, the company base case ICER is lower at £4,811 per QALy gained, due to a lower incremental cost [redacted]) and larger incremental QALY ([redacted]) compared to adult base case. This is due to the longer survival time and time horizon in the paediatric model, leading to larger QALY gains arising from longer times spent in lower PS requirement states, and larger cost savings accruing from the reduced PS requirements.

5.2 Company's sensitivity analyses

The company present their probabilistic sensitivity analysis results in Table 48 and 49 of their submission document, for the adult and paediatric population respectively. The mean ICERs are slightly higher than the deterministic point estimates.

Corresponding cost-effectiveness scatter-plots and acceptability curves can be found in Figure 30 and 31 of the company submission document. The probability of teduglutide being cost-effective at ceiling threshold of £30,000 per QALY, is approximately [redacted] in the adult model and approximately [redacted] in the paediatric model.

The company also present the results of one-way sensitivity analysis on the adult and paediatric base cases (see Figures 32 and 33 of the company submission, document B). The tornado diagram for the adult base model indicates that the ICER is most sensitive to varying the cycle cost for PS 7, PS4, PS6 and PS5 days per week. Similarly, the cost of PS for these numbers of days are also the most influential parameters in the paediatric model. This is because it is by reducing time in PS4 - PS7 compared to SoC that teduglutide generates PS cost savings.

The company present the results of scenarios analyses in Table 50 of their submission document. For the adults model, the results show the ICER to be upwardly sensitive to several parameter assumptions, particularly: removal of treatment discontinuation beyond 12 months, the choice of extrapolation curve for survival, the health state utility data source, the removal of complications (IFALD and CKD), application of carer quality of life decrements from only the Delphi survey. The ICER was reduced by application of a lower discount rate of 1.5% on costs and outcomes, and application of carer quality of life decrements from only the Delphi panel. A similar pattern of results was found in the paediatric model, with the removal of discontinuation beyond 12 months having the largest upward impact on the ICER.

In addition to the scenarios provided in the company submission, the ERG asked the company to consider a few further scenarios in response to the clarification letter. These were provided as follows in Table X: 1) using the PSP beyond 12 months in the calculation of transition probabilities for teduglutide; and 2) Including health state transitions for SoC as observed in the placebo arm of STEPS. As indicated in the critique in 4.2.6 above, following further clarification from the company, the ERG agrees that carrying forward the last observed PS state, rather than censoring, will lead to dilution of the actual observed effects among those in STEP-2 who were followed systematically out to 30 months. Therefore, the 30-month scenario in Table 19 is likely conservative. It should also be noted that the scenario applying transition

probabilities to the SoC arm based on the placebo arm of STEPS, returns the cohort to the baseline state distribution from cycle 7 onwards. Hence the minimal impact on the ICER. The ERG had indented for this scenario to carry the 6 month state distribution forwards.

Table 19 Additional scenario analyses provided by the company in response to the clarification letter.

Model component	Base case	Scenario	ICER (£/QALY)
Base case			£16,652
1) Use of PSP data in transition probability estimation	Base case (PSP data up to 12 months)	PSP data up to 18 months	£14,891
		PSP data up to 24 months	£14,129
		PSP data up to 30 months	£22,138
2) Change in PS requirement in the SoC arm	Remains constant and baseline	Include health state transitions fitted to the placebo arm of STEPS	£17,616

5.3 Model validation and face validity check

The company describe how the data sources and key assumptions were validated by three clinicians experience in treating SBS-IF, and that there was consensus that the data sources were appropriate and that the applied assumptions were clinically plausible. They also note that advice was obtained from expert health economists regarding the incorporation of evidence and justification for assumptions. They also note that the model was reviewed by a health economist not involved in its development, to ensure accuracy of inputs and reliable functionality -with all minor issues amended prior to submission.

The ERG has also undertaken a number of "black box" tests, as suggested by Tappenden and Chilcott (2014), to assess model reliability, and has checked through the model formulae underpinning the cohort traces and calculations of costs and QALYs.[83] The results of ERG checks are presented in Table XX. One minor issue was identified where the incorrect adverse event utility parameter was referenced for

upper respiratory tract infections for teduglutide after month 6 and in the standard of care arm.

In terms of internal validity, the company initially provided a comparison of the percentage of the modelled cohort achieving PS independence (22%) against the observed proportion in the STEPS, STEPS-2 and PSP study population combined ([redacted]) – indicating a slight underestimation. The ERG asked for further validation of the modelled cohort distribution at set time points (6, 12, 18, 24 and 30 months), which the company supplied at the clarification stage. This showed slight overestimation of the percentage in PS1, PS4 and PS5 at 30 months, and slight underestimation of the proportion in PS0, PS3, and PS7.

The ERG is broadly satisfied that the model output for the teduglutide arm is consistent with the input subject to the assumptions applied to those who discontinue treatment; If anything, the model may slightly overestimate the expected number of PS days compared to the mean observed for the cohort. Note, the internal validity in the SoC arm cannot be assessed in the same manner due a lack of observed data (beyond 6 months) and the assumptions applied regarding the placebo arm response in STEPS. The ERG has identified some further face validity issues with respect to the modelling of complications (CKD and IFALD) as discussed in section 4.2.6 above

Table 20 Summary of "black box" checks of the model carried out by the ERG

Model component	Model test	Unequivocal criterion for verification	Issues identified in company model
Clinical trajectory	Set relative treatment effect (odds ratios, relative risks or hazard ratios) parameter(s) to 1.0 (including adverse events)	All treatments produce equal estimates of total LYGs and total QALYs	Minor issue found in cells H80:I80 of 'Adverse events' sheet which refers to the incorrect adverse event utility for urinary tract infections. Otherwise, no issues found.
	Sum expected health state populations at any model timepoint (state transition models)	Total probability equals 1.0	No issues found.
QALY estimation	Set all health utility for living states parameters to 1.0	QALY gains equal LYGs	No issues found.
	Set QALY discount rate to 0	Discounted QALYs = undiscounted QALYs for all treatments	No issues found.
	Set QALY discount rate equal to very large number	QALY gain after time 0 tend towards zero	No issues found
Cost estimation	Set intervention costs to 0	ICER is reduced	No issues found. Incremental costs behave as expected.
	Increase intervention cost	ICER is increased	No issues found.
	Set cost discount rate to 0	Discounted costs = undiscounted costs for all treatments	No issues found.
	Set cost discount rate equal to very large number	Costs after time 0 tend towards zero	No issues found.

Model component	Model test	Unequivocal criterion for verification	Issues identified in company model
Input parameters	Produce n samples of model parameter m	Range of sampled parameter values does not violate characteristics of statistical distribution used to describe parameter.	Sample tested. No issues found.
General	Set all treatment-specific parameters equal for all treatment groups	Costs and QALYs equal for all treatments	No issues found. Given the standard care arm does not use transition probabilities, all transition probabilities for the teduglutide arm were set to 0. Furthermore, all adverse event rates were equalized, treatment costs set to 0 and treatment discontinuation was turned off.
	Amend value of each individual model parameter	ICER is changed	Sample tested. No issues found. There are over 300 model parameters. Key modelling parameters such as transition probabilities, acquisition costs, adverse event rates and treatment discontinuation distributions adjust ICER as expected.

Model component	Model test	Unequivocal criterion for verification	Issues identified in company model
	Switch all treatment-specific parameter values	QALYs and costs for each option should be switched	Not possible under model structure as the standard of care arm is not informed by transition probabilities. However, when all treatment specific parameters are equalized to the standard of care arm, treatment discontinuation is removed, transition probabilities set to 0 the QALYs and costs for the teduglutide arm equal the standard of care arm.

6 EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1 Exploratory and sensitivity analyses undertaken by the ERG

The ERG carried out further scenario analysis to explore the uncertainties identified within chapter 4 of this report. A description of these scenarios is given in table 21. Results are presented and discussed within section 6.2. Some of the scenarios described below are only relevant to either the adult (scenario 8) or paediatric (scenarios 6, 7 & 9) population. Therefore, not all scenarios are included in the results tables 22 and 23.

Table 21 Summary of scenario analysis explored by the ERG

#	Scenario description	Section within ERG report
1	Correction to upper respiratory tract infection utility decrement	5.3
2	Application state transitions for the standard of care arm using data from the placebo group of STEPS where the final occupancy of the states at 24 weeks is held for the rest of the modelled time horizon	4.2.6
3	Post 6-month adverse event rates of teduglutide equalised to standard of care for the teduglutide arm	4.2.6
4	Post 6-month adverse event rates equalised to pre-6-month rates for the teduglutide arm	4.2.6
5	Removal of carer utilities	4.2.7
6	Paediatric patients receive smaller 1.25mg vial until age 8	4.2.8
7	Cost of paediatric colonoscopy applied (FE37C Endoscopic or Intermediate, Lower Gastrointestinal Tract Procedures, between 5 and 18 years)[84]	4.2.8
8	Three specialist visits per year applied to PS0 health state costs (Adult)	4.2.8
9	Four specialist visits, haematology tests, tests of inflammatory markers, clinical biochemistry tests per year applied to PS0 health state costs (Paediatric)	4.2.8
10	Removal of daily ondansetron treatment from health state costs	4.2.8
11	Utility decrements for bacteraemia, catheter-related infection, central line infection, bacterial overgrowth and upper respiratory infection calculated relative to UK population norms for EQ-5D[85]	4.2.7
12	Equal risk of line sepsis per year (0.44) assumed for all PS1-7 health states	4.2.8
13	Reduction in the range of utility values between PS0 and PS7 states by 10%.	4.2.7
14	Reduction in the range of utility values between PS0 and PS7 states by 20%.	4.2.7

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

The application of the state transitions observed in the STEPS trial placebo arm to the standard of care arm in the model, where the state occupancies observed at 24 weeks are retained for the rest of the modelled time horizon (scenario 2) has the greatest impact upon the ICER. This results in ICERs of £87,898 and £63,505 for the adult and paediatric populations respectively. In the company base case, patients in the standard of care arm can only transition to the death state. Therefore, utilising the reduction of days per week of PS observed in the placebo arm of the STEPS trial leads to lower PS-health state costs, lower risk of IFALD & stage V CKD complications, higher health state utility values and higher carer utility values which explains the significant increase in the ICER over the company base-case.

The ERG explored the impact of using alternative adverse event rates for the teduglutide arm in scenarios 3 and 4. These resulted in moderate increases in the ICER in both populations. In particular, scenario 4, where the post-6-month adverse event rates were equalised to the pre-6 month adverse event rates for teduglutide. Of the three adverse event rates used in the model (table 14), [redacted]

The removal of carer utility decrements from consideration in the analysis leads to a moderate increase in the ICER. A greater reduction is observed in the paediatric population as it is assumed that patients have two carers. The ERG also explored the scenario where the utility decrement associated with several adverse events was calculated relative to the UK population norm EQ-5D value (=0.85-0.48) rather than from perfect health (=1-0.48) (scenario 11).[85] This resulted in a very small increase in the ICER for both populations as the [redacted] A percentage reduction in the difference between the utility values of PS0 and PS7 states realises a moderate increase in the ICER. The correction of a minor error found within the economic model, where the incorrect utility decrement associated with upper respiratory tract infection was used (scenario 1), resulted in a small decrease in the ICER for both populations.

Finally, the ERG explored several alternative assumptions with regard to costs. Scenarios 7, 8, 9 & 12 resulted in small increases in the ICER. Scenario 10, where the assumption that patients would receive odansetron daily was removed, resulted in a moderate increase in the ICER for both populations. This is due to the greater proportion of patients in the teduglutide arm of the model who have weaned off PS and no longer accrue the cost of odansetron. Therefore, the standard of care arm realises a greater proportional reduction in cost when this is removed. Scenario 6 has the greatest impact upon the ICER. The assumption that all patients under the age of 8 in the model would receive the smaller 1.25mg vial of teduglutide prompts a significant reduction in teduglutide acquisition costs, dramatically decreasing the incremental costs of teduglutide treatment. However, its unclear what percentage of the eligible paediatric patients this would apply to in practice.

The results of the scenario analyses and its impact on the ICER can be seen in tables 22 and 23 below.

Table 22 ERG scenario results for the adult population

Scenario	Incremental costs	Incremental QALYs	ICER
Company base case	[redacted]	[redacted]	**£16,652**
1	[redacted]	[redacted]	£16,344
2	[redacted]	[redacted]	£87,898
3	[redacted]	[redacted]	£21,142
4	[redacted]	[redacted]	£28,614
5	[redacted]	[redacted]	£23,227
8	[redacted]	[redacted]	£17,266
10	[redacted]	[redacted]	£26,659
11	[redacted]	[redacted]	£16,752
12	[redacted]	[redacted]	£17,609
13	[redacted]	[redacted]	£17,799
14	[redacted]	[redacted]	£19,116

Table 23 ERG scenario results for paediatric population

Scenario	Incremental costs	Incremental QALYs	ICER
Company base case	[redacted]	[redacted]	**£4,811**
1	[redacted]	[redacted]	£4,736
2	[redacted]	[redacted]	£63,505
3	[redacted]	[redacted]	£8,193
4	[redacted]	[redacted]	£14,040
5	[redacted]	[redacted]	£7,586
6	[redacted]	[redacted]	Dominates
7	[redacted]	[redacted]	£5,280
9	[redacted]	[redacted]	£5,357
10	[redacted]	[redacted]	£13,772
11	[redacted]	[redacted]	£4,837
12	[redacted]	[redacted]	£5,630
13	[redacted]	[redacted]	£5,097
14	[redacted]	[redacted]	£5,418

[redacted]

6.3 ERG's preferred assumptions

The ERG preferred modelling assumptions and the rationale are as follows:

- Scenario 1.

  As detailed in the blackbox verification checks (table 20), there was a minor error where the incorrect utility decrement for urinary tract infections was used in two places in the model. This has been corrected by the ERG.

- Scenario 7.

  The cost of a colonoscopy applied in the paediatric company base case is for patients aged 19 and over. Clinical advice to the ERG stated that paediatric patients undergo general anaesthetic for the procedure, therefore the resource use required may not be comparable between the populations. The ERG prefers the use of the paediatric specific HRG code.

- Scenario 8 & 9.

These scenarios refer to the assumption that patients who have weaned off PS do not require specialist visits in the model. At clarification stage, the company explained that as these are costs related to a patient's PS need no visits are assumed. Clinical expert advice to the ERG states that all SBS-IF patients receive 3-4 clinic visits per year which is invariable to a patient's PS requirements. Therefore, the ERG prefers to assume equal frequency of specialist visits (and tests which monitor growth of paediatrics) in the PS0 state of the model to other health states.

- Scenario 11.
  The utility decrement of several adverse events in the model are sourced from TA352, where the decrement is calculated relative to perfect health. This leads to an overestimation of the decrement associated with these events. The ERG prefers to calculate the decrement relative to the UK population norm EQ-5D value.
- Exponential extrapolation of the overall survival curve for adults. As described in section 4.2.6, the exponential retains a mortality hazard higher than that over general population mortality for longer and has the lowest AIC and BIC statistics of all proposed extrapolations.

The cumulative impact of these scenarios upon the company base case are shown in tables 24 and 25 below. The resultant deterministic ICER of the ERG preferred base case is £20,314 per QALY for the adult population (table 24), and £5,797 for the paediatric population (table 25). The ERG also presents further sensitivity analysis upon its preferred base case in table 26. The results show that the ICER is sensitive to the removal of carer utilities from the analysis. However, all scenarios demonstrate an ICER which is below £30,000 per QALY.

Table 24 ERG's preferred model assumptions for adult population

#	Preferred assumption	Section in ERG report	Incremental		Cumulative ICER
			Cost	QALY	
Company base-case			[redacted]	[redacted]	£16,652
1	Correction to upper respiratory tract infection utility decrement	5.3	[redacted]	[redacted]	£16,344

8	Three specialist visits per year applied to PS0 health state costs (Adult)	4.2.8	[redacted]	[redacted]	£16,947
11	Utility decrements for bacteraemia, catheter-related infection, central line infection, bacterial overgrowth and upper respiratory infection calculated relative to UK population norms for EQ-5D	4.2.7	[redacted]	[redacted]	£17,158
	Exponential extrapolation of overall survival curve	4.2.6	[redacted]	[redacted]	£20,314

Table 25 ERG's preferred model assumptions for paediatric population

#	Preferred assumption	Section in ERG report	Incremental		Cumulative ICER
			Cost	QALY	
Company base-case			[redacted]	[redacted]	£4,811
1	Correction to upper respiratory tract infection utility decrement	5.3	[redacted]	[redacted]	£4,736
7	Cost of paediatric colonoscopy applied (FE37C Endoscopic or Intermediate, Lower Gastrointestinal Tract Procedures, between 5 and 18 years)	4.2.8	[redacted]	[redacted]	£5,189
9	Four specialist visits, haematology tests, tests of inflammatory markers, clinical biochemistry tests per year applied to PS0 health state costs (Paediatric)	4.2.8	[redacted]	[redacted]	£5,735
11	Utility decrements for bacteraemia, catheter-related infection, central line infection, bacterial overgrowth and upper respiratory infection calculated relative to UK population norms for EQ-5D	4.2.7	[redacted]	[redacted]	£5,797

Table 26 Sensitivity analysis on the ERG preferred base-case

Preferred assumption	Section in ERG report	Incremental		ICER
		Cost	QALY	
Adult population				
ERG preferred base-case		[redacted]	[redacted]	£20,314
Removal of carer utilities	4.2.7	[redacted]	[redacted]	£28,270
Log-normal extrapolation of time on treatment curve	4.2.6	[redacted]	[redacted]	£22,421
Weibull extrapolation of overall survival curve	4.2.6	[redacted]	[redacted]	£21,591
Paediatric population				
ERG preferred base-case		[redacted]	[redacted]	£5,797
Removal of carer utilities	4.2.7	[redacted]	[redacted]	£9,114
Log-normal extrapolation of time on treatment curve	4.2.6	[redacted]	[redacted]	£7,364

6.4 Conclusions of the cost effectiveness section

The company have provided a comprehensive submission which attempts to capture all health effects and costs associated with teduglutide in the NHS care pathway for SBS-IF patients. All ICERs of the scenarios presented by the company and ERG fall below £30,000 per QALY gained aside from the removal of the treatment stopping rule (table 50 document B of CS) and the application of STEPS placebo response and treatment distributions to the standard of care arm (ERG scenario 2). The ERG does not believe that either of these reflect likely scenarios for teduglutide given the plausibility of the company's arguments, but they highlight the importance for the ICER of these uncertain modelling assumptions. The economic case hinges on an evidence base with many uncertainties which cannot easily be resolved given the rarity and heterogeneity of SBS-IF. Evidence which informs HRQoL is not in line with the NICE reference case, but [redacted]lack face validity. Therefore, judgements must be made whether the health benefits

associated with teduglutide and standard of care have been appropriately captured in this submission given the evidence available.

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