NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Teduglutide for treating short bowel syndrome [ID3937]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Teduglutide for treating short bowel syndrome [ID3937]

Contents:

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website.

1. **Company submission from Takeda UK.**

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submissions from:**
   a. Dr Simon Gabe, LNWH Trust
   b. PINNT (Patients on Intravenous and Nasogastric Nutrition Therapy)
   c. Short Bowel Survivor and Friends

4. **Evidence Review Group report prepared by Aberdeen HTA Group**

5. **Evidence Review Group report – factual accuracy check**

6. **Technical engagement response from company**

7. **Technical engagement responses and statements from experts:**
   a. Dr Susan Hill– clinical expert, nominated by Takeda UK Ltd
   b. Carolyn Wheatley – patient expert, nominated by PINNT (Patients on Intravenous and Nasogastric Nutrition Therapy)
   c. Mary Foss, patient expert, Short Bowel Survivors and Friends

8. **Evidence Review Group critique of company response to technical engagement prepared by Aberdeen HTA Group**

9. **Post-technical engagement statements from experts:**
   a. Dr Susan Hill- clinical expert, nominated by Takeda UK Ltd
   b. Dr Simon Gabe- clinical expert, nominated by LNWH Trust

10. **Addendum to the Evidence Review Group critique of company response to technical engagement**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Teduglutide for treating short bowel syndrome [ID3937]

Document B

Company evidence submission

Takeda UK Ltd confirm that all information in the submission summary is an accurate summary or replication of evidence in the main submission and accompanying appendices and that wherever possible a cross reference to the original source is provided.

File name	Version	Contains confidential information	Date
Teduglutide NICE submission_ID3937_Document B_[redacted]	1.0	Yes	17th August 2021

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Tables and figures

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication. Teduglutide is indicated for the treatment of patients aged 1 year and above with Short Bowel Syndrome (SBS); patients should be stable following a period of intestinal adaptation after surgery.

Table 1: Decision problem

	Final scope issued by NICE	**Decision problem addressed in the company submission**	**Rationale if different from the final NICE scope**
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
Intervention	Teduglutide in addition to established clinical management	As per scope	NA
Comparator(s)	Established clinical management without teduglutide (including parenteral support, antimotility and antisecretory agents, fluid restriction and dietary optimisation)	As per scope	NA
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
Abbreviations: NA, not applicable			

B.1.2 Description of the technology being appraised

Table 2: Technology being appraised

UK approved name and brand name	Approved name: Teduglutide Brand name: Revestive®
Mechanism of action	Teduglutide is a modified analogue of the naturally occurring human glucagon-like peptide 2 (GLP-2), a peptide produced by enteroendocrine L cells mainly in the ileum and colon. GLP-2 is a key mediator of intestinal adaptation, with a number of intestinotrophic effects that include increasing intestinal and portal blood flow, stimulating growth of the gastrointestinal epithelium, inhibiting gastric acid secretion, and decreasing intestinal motility. Compared to GLP-2, teduglutide has a single amino acid substitution; an alanine at the second position of the N-terminus in GLP-2 is replaced by glycine in teduglutide. This improves teduglutide's resistance to degradation (by the enzyme dipeptidyl peptidase-IV) and lengthens *in vivo* half-life from 7 minutes to approximately 2 hours[1].
Marketing authorisation/CE mark status	European and UK marketing authorisation was granted on 30th August 2012 (European Commission date) for adult patients with short bowel syndrome (SBS). On the 29th June 2016, the indication was extended to include the treatment of patients aged 1 year and above with short bowel syndrome who are stable following a period of intestinal adaptation[1]. Teduglutide has been commercially available in the UK for treating SBS since September 2014, and was approved by the Scottish Medicines Consortium (SMC) for use in Scotland in 2018 for paediatric patients[2] and in 2020 for adult patients[3].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Teduglutide is indicated for[1]: "The treatment of patients aged 1 year and above with short bowel syndrome (SBS). Patients should be stable following a period of intestinal adaptation after surgery." *The SmPC gives the following key restrictions on the use of teduglutide in adults and children:* Teduglutide is contraindicated in patients with: • Hypersensitivity to the active substance or any excipients or to trace residues of tetracycline • Active or suspected malignancy • A history of malignancies in the gastrointestinal tract, including the hepatobiliary system and pancreas within the last five years Teduglutide therapy must be discontinued in the case of any of the following: • Malignancy resulting from a colorectal polyp

	• Malignancy resulting from gastrointestinal neoplasia (including hepatobiliary tract) The need for continued teduglutide therapy should be reassessed in the case of any of the following: • Gallbladder or bile-duct related symptoms • Pancreatic adverse events • Significant deterioration of cardiovascular disease • Recurrent intestinal obstructions Additionally, due to the risk of dehydration and acute renal failure in patients with SBS whilst receiving teduglutide, parenteral support should be reduced carefully and should not be discontinued abruptly. Similarly, discontinuation of treatment with teduglutide should be managed carefully to avoid dehydration. Patients receiving oral concomitant medicinal products should be monitored closely due to potential increased absorption. Caution should be exercised when prescribing teduglutide in patients with severe, clinically unstable concomitant diseases or with malignancies within the last five years.
Method of administration and dosage	*Treatment initiation (adults and children)*[1]*:* Treatment should be initiated under the supervision of a medical professional with experience in the treatment of SBS. Treatment should not be initiated until it is reasonable to assume that a patient is stable following a period of intestinal adaptation. Optimisation and stabilisation of intravenous fluid and nutrition support should be performed before initiation of treatment. *Dosing (adults and children)*[1]: Recommended dose is 0.05 mg/kg body weight, once daily. Teduglutide is provided in 5 mg and 1.25 mg vials (for patients >20 kg and ≤20 kg respectively). In adults and children with moderate and severe renal impairment (creatinine clearance less than 50 ml/min), and end-stage renal disease, the daily dose should be reduced by 50%. *Administration (adults and children)*[1]: The reconstituted solution should be administered by subcutaneous injection once daily, alternating sites between 1 of the 4 quadrants of the abdomen. In case the injection into the abdomen is hampered by pain, scarring or hardening of the tissue, the thigh can also be used. Teduglutide should not be administered intravenously or intramuscularly.

	Treatment course (adults) per SmPC[1]*:* Treatment effect should be evaluated after 6 months. Limited data from clinical studies have shown that some patients may take longer to respond to treatment (i.e., those who still have presence of colon-in-continuity or distal/terminal ileum); if no overall improvement is achieved after 12 months, the need for continued treatment should be reconsidered. *Treatment course (children) per SmPC*[1]*:* A treatment period of 6 months is recommended after which treatment effect should be evaluated. In children below the age of two years, treatment should be evaluated after 12 weeks.
Additional tests or investigations	A colonoscopy with removal of polyps should be performed at the time of starting treatment with teduglutide. For the first 2 years of treatment, annual follow-up colonoscopies (or alternative imaging) are recommended, and a minimum of every 5 years after that. An individual assessment on whether increased surveillance is necessary should be performed based on the patient characteristics (e.g. age, underlying disease). If a polyp is found, adherence to current polyp follow-up guidelines is recommended. Prior to initiating treatment with teduglutide, faecal occult blood testing should be done for all children and adolescents. Colonoscopy/sigmoidoscopy is required if there is evidence of unexplained blood in the stool. Subsequent faecal occult blood testing should be done annually in children and adolescents while they are receiving teduglutide. Colonoscopy/sigmoidoscopy is recommended for all children and adolescents after one year of treatment, every 5 years thereafter while on continuous treatment with teduglutide, and if they have new or unexplained gastrointestinal bleeding [1].
List price and average cost of a course of treatment	The list price is £521.98 per vial containing 5 mg of teduglutide and £260.99 per vial containing 1.25 mg of teduglutide. Average cost of a course of treatment is not possible to define, as teduglutide is administered indefinitely, with treatment recommended to be reviewed as described above.
Patient access scheme (if applicable)	A simple patient access scheme (PAS) discount of [redacted] on the list price has been agreed with the Patient Access Schemes Liaison Unit (PASLU)
Abbreviations: GLP, glucagon-like peptide; SBS, short-bowel syndrome; SMC, Scottish Medicines Consortium; SmPC, summary of product characteristics; PAS, patient access scheme; PASLU, Patient Access Schemes Liaison Unit **Source**: Teduglutide SmPC[1]	

B.1.3 Health condition and position of the technology in the treatment pathway

Short bowel syndrome with type 3 intestinal failure (SBS-IF) is an ultra-rare, highly-debilitating, life-threatening disease with significant costs to patient health and wellbeing, to patients' carers and loved ones, and to the National Health Service (NHS). SBS-IF results from a loss of intestinal length (and therefore absorptive capacity), usually as a result of massive surgical resection, and is characterised by an inability to absorb sufficient nutrients, electrolytes and/or water from enteral nutrition[4, 5]. Patients will die without life-sustaining, parenteral support (PS); a complex, sophisticated treatment that involves intravenous delivery of nutrients and fluids administered for an average of 10–14 hours overnight for 2–7 nights a week[6, 7]. Due to being 'hooked up' to an IV line overnight, PS can have a large disruptive effect on patients' sleep, relationships, work, and social lives; as well as the lives of their families and/or caregivers[6, 7]. One patient from the UK described how having to receive PS makes them feel as though they have:

"become a prisoner in my own home"[8].

Reducing dependence on PS as much as possible is a critical treatment goal for patients.

B.1.3.1 Disease overview

Short bowel syndrome (SBS) is an ultra-rare gastrointestinal condition characterised by a clinically significant reduction in intestinal absorptive capacity. This usually results from surgical resection of large portions of the intestine, commonly due to disease, trauma, complications of surgery, or congenital abnormalities[4, 9]. Typically, patients with SBS will have <200 cm of small intestine remaining[10], whereas an adult's normal small intestine length is 300–800 cm. Loss of absorptive intestinal surface area results in reduced absorption of nutrients, electrolytes and water[11]. Symptoms of SBS therefore include diarrhoea, nutrient deficiencies, electrolyte disturbances, dehydration, malnutrition, and weight loss[12].

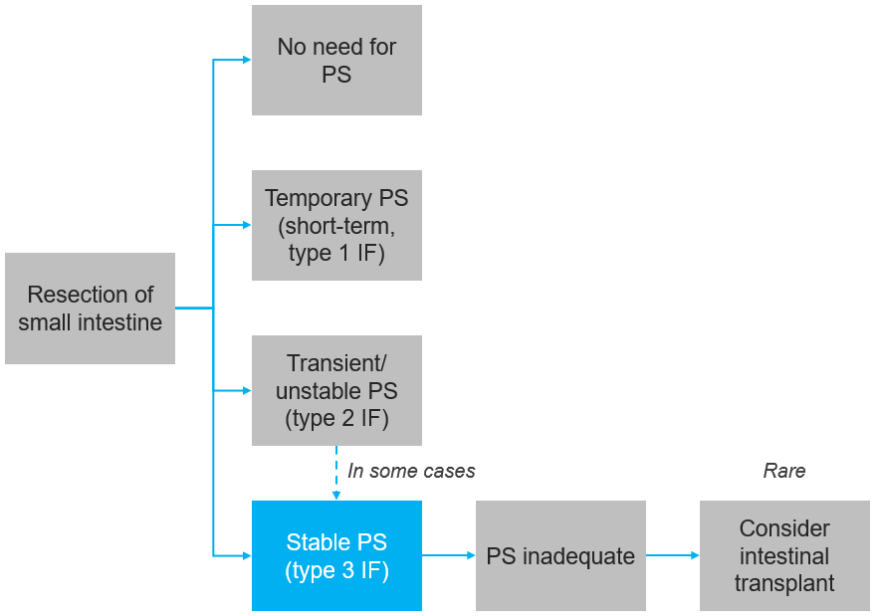
In some cases, the length of intestine remaining will mean that function is reduced below the minimum necessary for the absorption of macronutrients and/or water and electrolytes. This is known as intestinal failure, and intravenous supplementation of fluids and/or nutrients (known as parenteral support, PS) will be required to maintain health (and growth in children)[5]. Intestinal failure can be categorised into three types based on the duration and severity of loss of function (**Table 3**).

Table 3: Functional classification of intestinal failure

Type 1	Acute, short-term, and usually self-limiting condition, which is common in the perioperative setting or in association with critical illness
Type 2	Prolonged acute condition, often in metabolically unstable patients, requiring complex multi-disciplinary care and intravenous supplementation over periods of weeks or months
Type 3	Chronic condition in metabolically stable patients who require intravenous supplementation over months or years. This may be reversible or irreversible
Notes: ESPEN, The European Society for Clinical Nutrition and Metabolism; SBS with type 3 intestinal failure is the indication for teduglutide **Source**: ESPEN guidelines[5]	

Following the initial intestinal resection resulting in intestinal failure, a process of intestinal adaptation occurs. This is a natural process that leads to structural and functional changes to the remaining intestine that increases the absorption of fluids and nutrients. As a result of this process, some patients may be able to gain independence from PS – this defines type 1 or type 2 intestinal failure (**Figure 1**). Intestinal adaptation does not restore or increase the length of the intestine, but instead improves the functionality of what remains. In adults, the majority of intestinal adaptation occurs in the first two years following resection; in children, continued recovery may occur with age[13].

Figure 1 Need for PS following intestinal resection



Abbreviations: ESPEN, The European Society for Clinical Nutrition and Metabolism; PS, parenteral support; IF, intestinal failure

Notes: Intestinal failure can be classified as type 1, 2 or 3 (**Table 3**). This submission focuses on patients with SBS-IF with stable PS needs (type 3)

Source: ESPEN guidelines[5]

Our submission will focus on patients with SBS and type 3 intestinal failure, which we will refer to as SBS-IF. Patients with SBS-IF require PS beyond the period of intestinal adaptation, most often for the remainder of their life, and their PS needs will stabilise over time. No therapeutic options currently available in England allow patients with SBS-IF to alleviate the need for or gain independence from PS. SBS-IF is ultra-rare: there are an estimated 350 patients in England[14, 15], in line with the prevalence estimates of between 0.4 and 40 per million in Europe[16].

SBS-IF typically occurs when the initial resection of the small intestine is extensive, and sometimes includes part or all of the colon. A wide range of underlying diseases may result in SBS-IF (see **Table 4**): the patient population is highly heterogeneous, and patients may have a range of different bowel anatomies, comorbidities, and clinical requirements. Patient quality of life is similarly heterogenous due to the range of potential causes of the disease and their clinical requirements[17].

Table 4: Underlying causes of SBS-IF

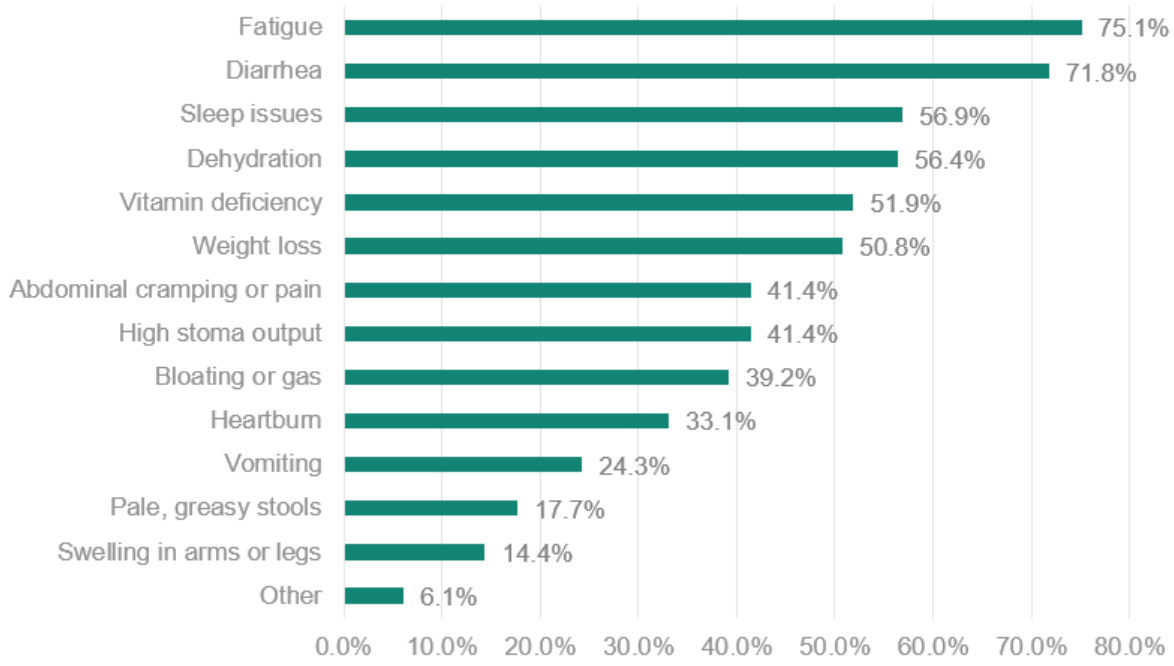
Condition	Description	Adults (n=514)	Children (n=370)
Mesenteric ischaemia	Acute or chronic condition caused by poor blood supply to the intestines	35.8%	-
Crohn's disease	Long-term condition causing inflammation of the lining of the digestive tract	29.0%	-
Radiation enteritis	Irritation and inflammation of the intestines during or after radiation therapy to the abdomen, rectum, or pelvis	9.7%	-
Surgical complications	-	7.8%	-
Familial polyposis	Rare, inherited condition that causes polyps to form in the colon and rectum. If untreated, polyps are likely to become cancerous	4.1%	-
Volvulus	Twisting of the colon, leading to obstruction and possibly resulting in ischemia and gangrene	2.3%	22%
Necrotising enterocolitis	Inflammation and death of intestinal tissue, which can lead to a perforation and allow contents of the intestine to leak into the abdomen	-	30%
Gastroschisis and atresia	Birth defect where intestines are found outside of baby's body	-	19%
Intestinal atresia	Spectrum of birth defects that result in blockage of either the small or large intestine	-	15%

Condition	Description	Adults (n=514)	Children (n=370)
Extensive intestinal aganglionosis	Extensive absence of ganglion cells in the nerve supply of the bowel		6.7%
Trauma	-	-	1%
Others	-	-	11.5%
Abbreviations: SBS-IF, short bowel syndrome with type 3 intestinal failure **Source**: Adult data adapted from ESPEN guidelines and Pironi 2006[5, 18]; paediatric data from Höllwarth 2017[19]			

SBS-IF represents a large burden on patients' lives. Many patients will never eat or drink again without suffering severe gastrointestinal distress[20]. A major complication and burden on quality of life is chronic diarrhoea[21], reported by approximately 70% of adults with SBS-IF[22], which if not appropriately managed can lead to under-nutrition and dehydration. As well as imposing health burden, diarrhoea affects quality of life; clinicians state that patients can have up to 20 bouts of diarrhoea per day[23], and patients report having to be constantly aware of the nearest toilet when out of their house. Parents of children with SBS-IF similarly can feel unable to leave the house due to the number of daily nappy and soiled clothing changes. Dehydration, weight loss and abdominal cramping or pain are also very commonly reported (>40% of patients)[22]. Commonly reported symptoms of SBS-IF are shown in **Figure 2** (next page). In addition to these, patients also experience a number of complications related to the need for parenteral support (see next section B.1.3.2).

Data suggest a substantial mortality impact for SBS. Five-year survival for patients is reported to be between 60–80%[24-27]. The higher figures tend to be reported in more recent data, likely reflecting improved clinical management of the condition. It is worth noting that it is not possible to distinguish SBS with type 3 intestinal failure (which we are terming SBS-IF) from SBS with type 1 or 2 intestinal failure from these data. Survival of patients with SBS and type 3 intestinal failure is likely to be lower, reflecting the severity of the underlying condition. PS may also impact patient survival; this is discussed more in B.1.3.2 below.

Figure 2 Symptoms reported by adult patients with SBS-IF



Abbreviations: SBS-IF, short bowel syndrome with type 3 intestinal failure

Source: Survey of 181 adult patients (from France, Germany, Italy, UK, USA) with SBS-IF[22]

B.1.3.2 Treatment burden

Patients with SBS-IF will die of dehydration or malnutrition without either nutritional support or further treatment for their condition. In the UK, the majority of patients with SBS-IF will be reliant for the rest of their life on parenteral support (PS): intravenous administration of nutrients and fluids[5]. PS is a highly sophisticated and complex treatment that requires an exceptional degree of multidisciplinary collaboration and expertise to ensure that patients' nutritional and hydration needs are kept in balance[5, 20]. While PS allows patients to meet their nutritional and hydration needs, it is not curative and does not restore intestinal function.

After initiation and observation in hospital, patients usually transition to receiving PS at home via an ambulatory pump connected to a central catheter, where they will receive nutrients and fluids for typically 10–14 hours overnight[28]. Patients usually receive PS for 2–7 nights a week, with more severe cases of SBS-IF requiring more nights on treatment. Because patients would not be able to survive without PS, they and their families are typically immensely grateful for the treatment[8]; however it is also highly disruptive, associated with serious complications, and can seriously impede patients' ability to live a normal life.

PS is associated with significant serious and occasionally fatal complications; a number of these are related to the use of a catheter to administer PS. These complications include catheter-related bloodstream infections and sepsis, which may

result in prolonged antibiotic treatment, repeated hospitalisation, replacement of a catheter device, and death if not sufficiently treated[29]. Catheter-related infections are rare (approximately 0.14–0.83 events per catheter-year[20, 30]), however this is dependent on patient education with the device and high levels of hygiene and care in catheter insertion and removal[16, 20]. Central venous catheter thrombosis is also reported (incidence 0.01–0.03 events per catheter-year[20]), which may cause chronic pain and swelling, occlude catheter access points[31], and potentially be fatal. Occluded points of catheter access (reported incidence 0.07 episodes per catheter-year[20]) can prevent patients from receiving life-sustaining PS; this places an enormous burden of stress on patients, particularly when only one or two viable access points remain. Patients in this situation find their lives dependent on a single vein being able to withstand receiving large volumes of fluid.

PS is also associated with metabolic complications. Key among these are decreased kidney function, which may progress to chronic kidney disease[32] and intestinal failure-associated liver disease, which may progress to advanced liver disease and, in 5% to 15% of cases end-stage liver failure[33-35]. Chronic kidney disease and liver failure are both potentially fatal. Chronic kidney disease has been reported in up to 18% of patients after 5 years on PS[32]. Depending on the diagnostic criteria used, incidence of liver disease has been reported in up to 50% of patients with SBS-IF[16], although improvements in the management of SBS-IF have resulted in reduced incidence. Further complications include metabolic bone disease (which may in turn result in a higher incidence of fragility fractures[36]), iron deficiency[37] and manganese toxicity (where patients may present with Parkinson's-like symptoms)[38].

The above complications (particularly catheter-related infections, central venous thrombosis and liver disease) are even more common in children with SBS-IF than adults[35, 39, 40], and clinical feedback suggest that they also result in longer hospital stays than in adults. In addition, children receiving PS experience growth retardation[41], which can manifest as gaining excess weight without gaining height, and gaining fat mass rather than lean mass[42]. Attainment of bone mass is also a concern in children, who are at increased risk of developing metabolic bone disease[43]. Summarily, PS is not conducive to healthy physical growth in children.

There is some evidence that PS itself negatively impacts patient survival, in addition to the negative impact of the underlying SBS-IF. In a cohort of 268 patients with SBS (notably not all with type 3 intestinal failure), 105 deaths were observed over a 25-year period, of which 13 (13%) were attributed to PS-related complications[24]. A similar figure was observed for a cohort of 472 patients with SBS (again, not all with type 3 intestinal failure): 109 deaths over 5-years of follow up with 13 deaths (13%) attributable to PS-related complications[44]. As patients with SBS-IF are dependent on PS to survive (and until recently, no treatments existed to allow patients to gain independence from PS), it is not currently possible to reach any conclusions about survival for patients with SBS-IF on PS compared to off PS. In addition, with the centralisation of SBS-IF care in centres of excellence, clinical feedback suggests patients in the UK would be 'very unlucky' to die of PS-related complications.

Spending nights on PS puts a huge quality of life burden on patients with SBS-IF, and on their caregivers. Patients' livelihoods are severely curtailed[8]: each night spent

on PS usually represents a full evening of social activity lost. This is not simply a 'quiet night in'; patients from the UK describe the impact as follows:

"I'd become a prisoner in my own home"[8]

"[PS] *rules my life and I hate it".*[45]

"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."*[45]

Similarly, patients are much less able to spend nights away from home owing to the difficulty of transporting and cleaning PS equipment, therefore any travel and holidays are challenging. Their lives quite literally revolve around their treatment. Patients from the UK describe it similarly:

"I would just want to be able to go off to wherever for a week or whatever, and I can't do that"[8]

"You've got to plan your whole life around it all the time"[8]

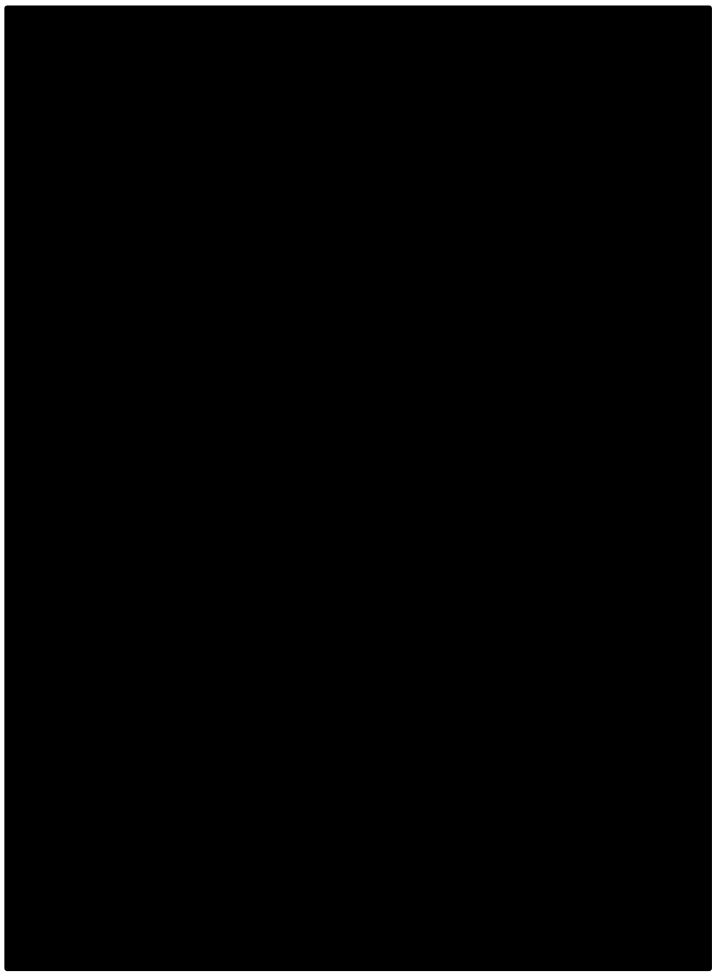
The extent of medical equipment required to administer PS can be seen in the patient photo below (**Figure 3**, next page).

Being connected to a pump overnight is also highly disruptive to sleep due to pump noises, equipment alarms, a need to urinate frequently, and the discomfort of sleeping (and physically rolling over) when connected to IV lines. A patient from the UK described the impact of PS on sleep as:

"…I don't sleep as well, um, one because I go to toilet a little bit more, um, from weeing . . . Unfortunately my bag will leak during the night"[46]

As a result, fatigue is reported by up to 75% of patients with SBS-IF[22]. [redacted].

Figure 3 Patient with home PS equipment



Patient's intimate relationships can also be affected by having to be connected to an IV line at night, and having a stoma bag that may leak[8]. This was described by patients from the UK:

"I would not necessarily have sex if I was on my drip"[8]

"I think he felt like he couldn't touch me or anything"[8]

As a result of the drastic changes it makes to patients' lives, PS is also associated with psychological distress[49, 50]. Anxiety, depression, fear and negative body image are 'universal experiences', and the loss of ability to eat is cited as a major adjustment problem[49]. This latter point was echoed by a patient from the UK:

"it's so hard when you want to eat but you can't eat and you see everybody else eating … it just … your blood just boils"[8]

For children, in addition to the burden already described, PS has been associated with psychological distress and lower social competence compared to population norms. Children receiving PS have been found to be often distressed at being left alone, with parents describing them as anxious, shy, and sensitive[51]. Loneliness,

social isolation and depression are common amongst children and their families[52]. PS has been observed to be associated with behavioural and attention issues in children, which further impacts their development through negative effects at school [53].

Measuring the quality of life of patients with SBS-IF receiving PS is difficult[54], even with the development of disease-specific instruments in recent years[55-57]. This is due in part to the heterogeneity of the patient population. By way of example, patients for whom SBS resulted from an underlying chronic disease (e.g. Crohn's disease) are likely to experience starting PS as a positive given the increased control they gain over their disease. Patients for whom SBS resulted from an acute event (e.g. mesenteric ischaemia) are likely to view starting PS very negatively by comparison with the life they led before[17]. The small patient population further complicates quality of life measurements[56]. Assessing quality of life in children has additional well documented challenges: children may not interpret quality of life questions as intended, and may find completing questionnaires burdensome[58]. Also, children who have had chronic diseases since birth are unlikely to have experienced what their quality of life could be, as their disease is all they have ever known.

SBS-IF and PS requirements are not only a burden to the patient themselves but also to their family and caregivers. Both adults and children with SBS-IF will commonly need an informal caregiver for help with general household chores, shopping, transport to medical appointments, administering PS, and emotional support[59]; [redacted]. Caregivers of patients with SBS-IF often suffer a lack of social activities, difficulties with relationships, lost income and employment difficulties and, in some cases, depression[50]. A survey of 122 caregivers for patients with SBS-IF found that 30% of caregivers report difficulties spending time with family and friends. Caring for a patient on PS affects a caregiver's ability to work full-time, which has an associated financial burden[59]; the same caregiver survey found caregivers report missing on average 40% of work hours in a given week (or 90 days in a 45-week working year)[59]. A caregiver from the UK described how:

"I don't work anymore. I'm fulltime carer for her now . . . [resulting in] *mortgage arrears . . . that is another massive stress"*[46]

For parents, caring for a child who is receiving PS affects their family and social lives: they report feelings of frustration, annoyance, and stress, as well as problems sleeping[60]. It can also restrict the family's' ability to travel and go on holiday[46]. Moreover, the emotional and financial burden of SBS-IF can damage relationships between parents and children with SBS-IF, and result in parents feeling resentment towards their child[61].

B.1.3.3 Treatment goals

Reducing the quality of life burden of PS and minimising associated complications are key treatment goals for both adults and children[5].

A key way to reduce the quality of life burden of PS is to reduce the number of days per week for which a patient has to receive it. For patients, reducing the number of days per week is one the most common asks they have of their treatment.

Unanimously, when three world-renowned experts in the management of SBS-IF were asked, they all stated that a single additional day off PS per week was, in their experience, a meaningful outcome for patients[62].

Using a quality of life instrument designed specifically to capture the effect of PS on everyday life (the PNIQ instrument)[57], reduction in days per week of PS was found to be statistically significantly correlated with improvement in quality of life among patients with type 3 intestinal failure[63]. Similarly, a reduction of a single day of PS per week was associated with a statistically significant improvement in SBS-IF patients' quality of life in two vignette studies[64, 65].

Patients from the UK similarly describe how:

"If I didn't have to be on it 7 nights a week . . . [it would] *just allow me, I suppose to feel normal"*[46]

"I try and get out of it …every time I go [to clinic], *I say, can I have a night off?"* [45]

This treatment goal is echoed by the teduglutide European Public Assessment Report (EPAR), which states:

"One or more days without having to be chained to an i.v. line constitutes a real benefit for the patient."[66]

For children, weaning off PS as quickly as possible and increasing enteral and/or oral nutrition is important to minimise the effect of SBS-IF on growth, both physical and psychological. Increased enteral nutrition in children also improves the process of intestinal adaptation and helps prevent liver disease, underlining the importance of being able to reduce PS and encourage this positive feedback loop[67, 68].

B.1.3.4 Treatment pathway and proposed position of teduglutide

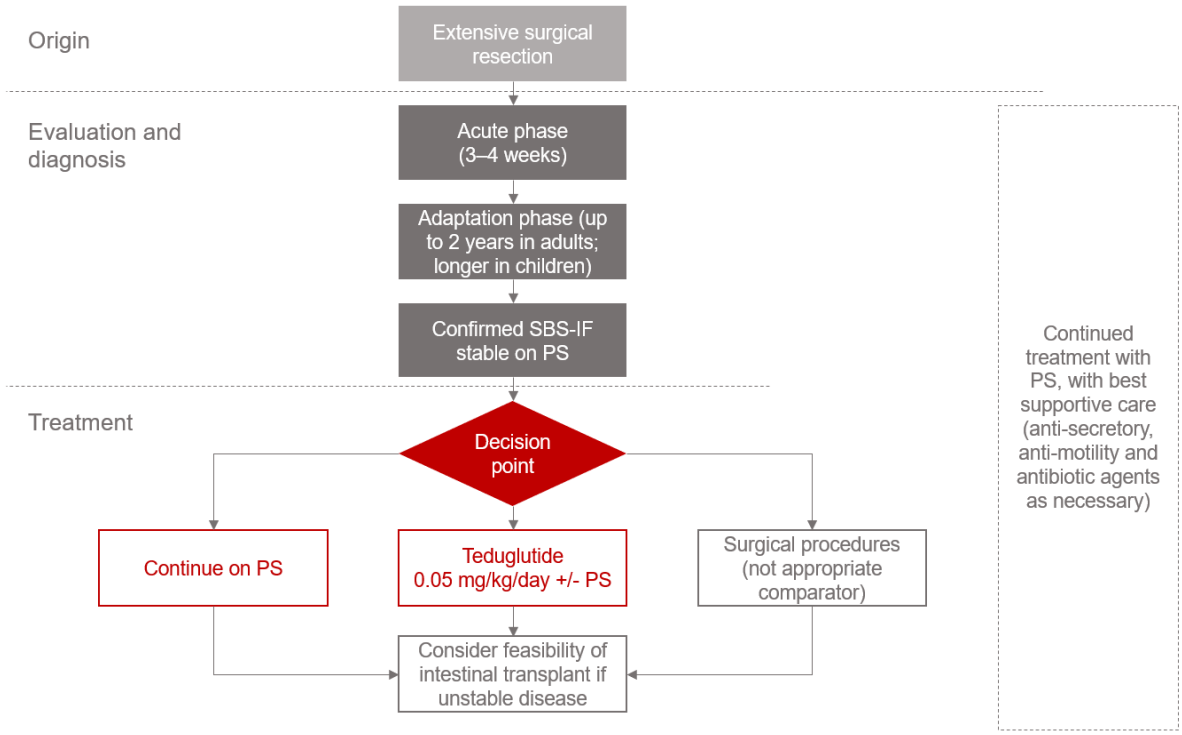
Current pharmacological options for SBS-IF only provide symptomatic relief and do not address the underlying condition[69]; patients dependent on life-sustaining PS therefore currently have no way of reducing or eliminating their PS dependence. There is a need for an effective pharmacological treatment that improves the absorptive capacity of the remaining intestine, in order to restore intestinal function, mitigate the symptoms of SBS-IF, and reduce dependence on PS[70].

Teduglutide is the first (and currently only) licensed pharmacological therapy that has demonstrated an ability to improve the absorptive capacity of the intestine, enhancing intestinal adaptation, increasing nutrient absorption and enabling patients to reduce their reliance on PS. Teduglutide has been granted EMA marketing authorisation for the treatment of patients aged 1 year or above with SBS, who are stable following a period of intestinal adaptation after surgery[1].

As per the licensed indication[1], the suggested place in therapy for teduglutide is for patients aged 1 year and above with SBS-IF who are stable following a period of intestinal adaptation after surgery (**Figure 4**). Furthermore, treatment should be initiated under the supervision of a medical professional with experience in the treatment of SBS. PS optimisation (typically to obtain a target urine output of 1.0 to

2.0 L/day) and stabilisation (typically represented by consistent PS requirements for ≥1 year) should be performed before treatment initiation. Teduglutide should be administered in conjunction with PS and symptom relieving medications (anti-secretory, anti-motility and antibiotic agents) but with the aim of eventually reducing dependence on PS – i.e. by reducing volume and thereby frequency and, if possible, achieving enteral autonomy[1].

Figure 4 Treatment pathway and positioning of teduglutide for adults and children with SBS-IF



Abbreviations: ESPEN, The European Society for Clinical Nutrition and Metabolism; PS, parenteral support; SBS-IF, short bowel syndrome with type 3 intestinal failure

Notes: Rationale for not considering surgical procedures as an appropriate comparator is discussed in the paragraph below this figure

Source: ESPEN guidelines[5]

As shown in **Figure 4**, surgical procedures are an option following confirmed diagnosis of SBS-IF. These include the Bianchi procedure, serial transverse enteroplasty and spiral intestinal lengthening and tailoring – all are performed with the aim of lengthening the remaining bowel and/or increasing transit time. The European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines recommend these procedures only in 'selected' patients[5], however due to the risk of anastomotic breakdown, stricture and vascular injury associated with these procedures, they are rarely performed in practice[16]. Intestinal transplant is only recommended in patients who cannot be managed with standard care, and those at

high risk of death due to the underlying disease. This is because intestinal transplant has been observed to reduce patient survival[24, 33, 71].

B.1.4 Equality considerations

None identified.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

Several systematic literature reviews (SLRs) were performed to identify relevant clinical studies. These were performed in line with NICE guidance in the methods of technology appraisal, using a pre-prepared search strategy and multiple reviewers assessing results. For the present submission a clinical SLR, covering clinical trial data and real-world evidence for adults and children treated with teduglutide for short bowel syndrome with type 3 intestinal failure (SBS-IF) was performed on 21st May 2021.

See Appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

B.2.2 List of relevant clinical effectiveness evidence

B.2.2.1 Overview of the clinical effectiveness evidence

A large body of evidence exists to support the effectiveness of teduglutide. This includes a number of interventional clinical trials, open-label extensions to these trials, and a body of non-interventional real-world evidence (the latter is extensive as marketing authorisation for teduglutide was first granted in 2012). There is also data from the Australian Takeda Patient Support Programme (PSP), which has collected real-world data on teduglutide following marketing authorisation and reimbursement in Australia.

All the studies identified by the clinical systematic literature reviews (SLRs), both clinical trials and real-world evidence, are presented in **Table 5**,

Table 6 and

Table 7:

- **Table 5** lists sources of data that we use in our economic model; methodology and results of these studies are discussed in detail in this dossier
-

- **Table 6** lists clinical trials identified by our SLRs that are not used in our economic model
-

- **Table 7** lists real-world evidence identified by our SLRs (which we have not included in our economic model)

B.2.2.2 Tabulated summary of clinical evidence

Table 5: Clinical evidence used in our economic model

Name	Other identifiers	Design	Population	Intervention	Comparator	Relevant outcomes
STEPS[72]	CL0600-020; NCT00798967	Phase 3, multi-national, randomised, double-blind, placebo-controlled, 24-week study	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 Safety
STEPS-2[73]	CL0600-021; NCT00930644	Two-year, open-label, multi-national, extension study for patients screened or treated in STEPS	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 Safety
PSP data	REVESTIVE atHOME	A non-interventional Patient Support Programme in Australia	Real-world patients receiving teduglutide in Australia	Teduglutide 0.05 mg/kg/day [redacted]	None	Days per week of PS Volume of PS

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

Notes: The PSP data are unpublished and were therefore not identified in our clinical SLR

Source: STEPS[72]; STEPS-2[73]; Teduglutide SMPC[1]; Revestive atHOME PSP Blueprint[74]

Table 6 shows clinical studies identified by our SLRs that were not used in our economic model, and gives the rationale for their exclusion.

Table 6: Clinical study evidence not used in our economic model

Study name	Other identifiers	Study design	Population	Intervention	Comparator	Rationale for exclusion
STEPS-3[75]	TED-C11-001; NCT01560403	Up to one year, open-label extension study for patients in STEPS-2 at 5 US sites	Adults (≥18 years old) with SBS-IF who completed STEPS-2	Teduglutide 0.05 mg/kg/day (n=12)	None	STEPS-3 is analysed in three cohorts (see section B.2.6.2.2), and the cohort of relevance for the model only has 5 patients. This is too few patients to meaningfully base the model on post-STEPS-2
004[76]	CL0600-004; NCT00081458	Phase 3, multi-national, randomised, double-blind, placebo-controlled, 24-week study	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)	004 and 005 have weak external validity owing to the unduly restrictive PS weaning algorithm used. This algorithm is far removed from the more liberal PS weaning used in current clinical practice.
005[77]	CL0600-005; NCT00172185	28-week, open-label, multi-national, extension study for patients treated with teduglutide or placebo in 004	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)	None	
SHP633-301[78]	NCT03571516	Phase 3, multi-national, open-label, randomised, 24-week study	Infants (aged 4 to 12 months) with SBS with 1 month of stable PS	Teduglutide 0.05 mg/kg/day (n=5)	Standard care (PS; n=5)	Children < 1 year old are outside the scope of the present marketing authorisation and decision problem
C14[79]	TED-C14-006; NCT02682381	Phase 3, multi-national, open label, non-randomised, 24-week study	Children (aged 1 to 17 years old) with ≥12	Teduglutide 0.025 mg/kg/day (n=24) Teduglutide 0.05 mg/kg/day (n=26)	Standard care (PS; n=9)	C14 and C13 included a small number of patients receiving the licensed dose of

			month history of SBS			teduglutide; SHP633-304 and -303 allowed non-continuous treatment with teduglutide*. Given the adult data do not have these issues, and children are likely to derive even more benefit from teduglutide than adults (discussed further in B.2.12), we believe it is justified to model paediatric patients with adult data (modelling approach described more in B.3.2.1)
SHP633-304[80]	NCT02954458	Open-label, multi-national, long-term extension study to C14 and SHP633-301	Patients with SBS who completed C14 or SHP633-301	Teduglutide 0.05 mg/kg/day (n=61)	None	
C13[81]	TED-C13-003; NCT01952080	Phase 3, open label, non-randomised, 12-week study in the UK and US	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)	
SHP633-303[82]	NCT02949362	Open-label, long-term extension study to C13	Patients with SBS who completed C13	Teduglutide 0.05 mg/kg/day (n=29)	None	
SHP633-302[83]	NCT02980666	Phase 3, open-label, non-randomised, 24-week study	Japanese children (4 months to 15 years old) with SBS-IF	Teduglutide 0.05 mg/kg/day (n=10)	None	Japanese population deemed less applicable to the UK
TED-C14-004[84]	NCT02340819	Open-label, 24-week study with a long-term extension	Adult Japanese patients with SBS-IF	Teduglutide 0.05 mg/kg/day (n=11)	None	
REVE study[85]	NCT03562130	Single French centre, open-label, 48-week study	Children with SBS and ≥2 years on PS	Teduglutide 0.05 mg/kg/day (n=17)	None	11 of 17 patients in the REVE study did not have SBS with type 3 IF, so are outside the

						scope of the marketing authorisation and present decision problem
Iturrino *et al*. 2016[86]	NCT02099084	Randomised, double-blind, placebo-controlled, crossover pilot study in a single US centre involving 7 days of treatment, followed by >7 days washout	Adults with SBS who were dependent on PS	Teduglutide 0.05 mg/kg/day (n=8)	Placebo	Iturrino *et al*. reported the effects of teduglutide on gut transit, intestinal absorption, gut permeability to mannitol/lactulose, stool weight and urine volume. These are not outcomes relevant to this submission

Abbreviations: SBS, short bowel syndrome; SBS-IF, short bowel syndrome with type 3 intestinal failure; PS, parenteral support; US, United States; UK, United Kingdom

Notes: *At the beginning of each 28 week cycle, patients and investigators (in SHP633-303 and -304) could opt for 24 weeks of teduglutide treatment followed by 4 weeks of no treatment, or for 28 weeks of no treatment

Source: C14[79]; SHP-633-304[80]; C13[81]; SHP-633-303[82]; SHP633-301[78]; TED-C14-004[84]; REVE study[85]; Iturrino *et al.* 2016[86]; Teduglutide SMPC[1]

The clinical development programme for teduglutide has featured two phase 3 randomised controlled trials (STEPS and 004) and subsequent extension studies to these (STEPS-2/STEPS-3 and 005, respectively). Chronologically, 004 was the first study initiated but it used an unduly restrictive parenteral support (PS) weaning algorithm where PS volumes could only be reduced by a maximum of 10% of baseline volumes at each visit. This limits the external validity of results from 004 (and 005 which applied the same algorithm). In follow-up STEPS was initiated as a randomised controlled trial with a very similar design to 004, however in STEPS PS volumes could be reduced by a maximum of 30% of baseline volume at each visit (see section B.2.6.1.3 for more discussion on the weaning algorithms used in 004 and STEPS and their effect on study results).

Of note, the PS weaning algorithm used in STEPS (and its extension studies STEPS-2 and STEPS-3) is still more conservative than would be used in clinical practice – real world evidence indicates that PS volume reductions are often attempted earlier, more frequently and reach a larger magnitude than was seen in the STEPS program of studies (see B.2.6.4 and B.2.8)[87, 88].

While we have not included the studies listed in

Table 6 in our economic model, we will present evidence in this dossier from some of them:

- We will present efficacy data from STEPS-3, which demonstrates that teduglutide has continued clinical benefit beyond 24 months of treatment
- We will present efficacy data from 004. While the unduly restrictive PS weaning algorithm used in 004 means that the trial has limited applicability to real-world practice, 004 is a randomised controlled trial that provides high quality evidence for the superiority of teduglutide over placebo. We will also present safety data from 004 (and extension 005), pooled with safety data from STEPS and STEPS-2
- We will present efficacy data from the C14 and C13 clinical trials in children to demonstrate that results with teduglutide in children are comparable, if not better than, results in adults
- We will also present pooled safety data from C13, C14, SHP633-303 and SHP633-304 to demonstrate that no new safety signals were identified in children

Table 7 lists published non-interventional real-world evidence studies identified by our SLRs. These studies are not included in our economic model as we were not able to access robust patient-level data. We will present select effectiveness and safety results from the studies in this list that have been published as full manuscripts (rather than presented as abstracts/posters at conferences only), as more and better quality data are available in manuscripts. We will use these data to make the case that in the real-world, results with teduglutide are generally equal to or better than those seen in the STEPS programme (see B.2.6.4.1. and B.2.8).

Table 7: Real-world studies identified by clinical and real-world evidence SLRs

Study name	Location	Data collection dates (index to cut-off)	Population*	Number of patients receiving teduglutide	Discussed in further detail in section B.2.6.4.1?
Abdulla 2019	USA, single centre	Jan 2010 – May 2018	Patients with SBS-IF	17	No – abstract only
Allard 2021a and Allard 2021b	Multi-country (North America and Northern/Western Europe)	Jun 2014 – Jun 2020	Patients of any age with SBS-IF	328 (and 675 patients with SBS-IF who never received teduglutide)	No – abstracts only. While this registry contains a large number of patients, the complexity of the data collection requirements and narrow timepoints of assessment (which do not align with variability in real-world clinical visitation schedules) result in huge drop-off rates (<25% of patients report data at each time point) which imposes significant bias. Our ability to interpret these data is therefore heavily limited
Averianova 2019	Russia, single centre	NR	Children with SBS*	5	No – abstract only
Chen 2019	USA, single centre	Q1 2013 – Q2 2017	Adults with SBS-IF	23	No – abstract only
Chiplunker 2020	USA, single centre	NR	Patients with SBS* from Crohn's disease	9	No – abstract only
Corey 2021	USA, multi-centre (number of centres not reported)	Jan 2018 – Dec 2019	Patients who discontinued teduglutide	230	No – abstract only
Cruz 2020	USA, single centre	Jan 2013 – Dec 2018	Adults with ultra-SBS†	9	No – while published as a full manuscript, ultra SBS is a subgroup of the population of interest

Gondolesi 2020	Argentina, multi-centre (number of centres not reported)	Mar 2006 – Aug 2018	Adults with SBS-IF who had undergone ARGIS (surgery)	8	No – while published as a full manuscript, teduglutide post-ARGIS is a subgroup of the population of interest
He 2019	Australia, single centre	NR	Adults with SBS-IF	5	No – abstract only
Joly 2020 (also Joly 2017)	France, multi-centre (15 centres)	Oct 2015 – Sep 2017	Patients with SBS-IF	54	**Yes**
Kochar 2017 (also Kochar 2016 abstract)	USA, multi-centre (3 centres)	2007 – 2014	Patients with SBS* from Crohn's disease	13	No – while published as a full manuscript, SBS from Crohn's disease is a subgroup of the population of interest
Kurin 2020	USA, single centre	NR	Patients with SBS-IF from IBD	7	No – while published as a full manuscript, SBS from IBD is a subgroup of the population of interest
Lam 2018	USA, single centre	2009 – 2015	Adults with SBS-IF	18	**Yes**
Martin 2021 (also Martin 2020)	France, single centre	2009 – Dec 2019	Patients with SBS-IF	31	**Yes**
Martinez 2019	Argentina, single centre	NR	Children with SBS*	4	No – abstract only
Micic 2016	USA, single centre	NR	Patients with IF*	8	No – abstract only
Pevny 2019b	Germany, single centre	Sep 2014 – May 2017	Patients with SBS-IF	19	**Yes**
Pevny 2020 (also Pevny 2019a)	Germany, multi-centre (6 centres)	NR	Patients with SBS-IF	52	No – abstract only
Puello 2020	USA, single centre	Mar 2013 – May 2019	Adults with SBS-IF	18	**Yes**
Ramos Boluda 2020	Spain, multi-centre (8 centres)	Feb 2017 – Jun 2019	Children with SBS-IF	17	**Yes – although not presented in our summary of real-world evidence (section B.2.6.4.1)**

					but presented alongside data from children (section B.2.6.5)
Regano 2019	Italy, single centre	NR	Patients with SBS-IF	3	No – abstract only
Schoeler 2018	Germany, single centre	From Nov 2014	Adults with SBS*	14	**Yes**
Singh 2019	USA, single centre	Jan 2013 – Oct 2018	Patients with SBS*	17	No – abstract only
Solar 2020a	Argentina, multi-centre (number of centres not reported)	Jun 2014 – Mar 2020	Patients with SBS-IF who had undergone ARGIS (surgery)	17	No – while published as a full manuscript, teduglutide post-ARGIS is a subgroup of the population of interest
Solar 2020b	Argentina, multi-centre (12 centres)	2017 – 2020	Patients with SBS*	9	No – abstract only
Tamara 2020	Spain, single centre	Jan 2018 – Mar 2020	Adults with SBS*	4	**Yes**
Ukleja 2018	USA, single centre	Apr 2013 – Jun 2016	Adults with SBS*	6	**Yes**

Abbreviations: ARGIS, autologous gastrointestinal reconstructive surgery; NR, not reported; IBD, inflammatory bowel disease; SBS, short bowel syndrome; SBS-IF, short bowel syndrome with type 3 intestinal failure; SLR, systematic literature review

Notes: *In the literature, the terms SBS-IF, SBS and IF are used interchangeably, but in this instance all refer to SBS with type 3 IF (the population of interest in this dossier); †Ultra-SBS is defined as having <50 cm of small intestine remaining (SBS is usually defined as <200 cm small intestine remaining)

Source: Clinical SLR (Appendix D)

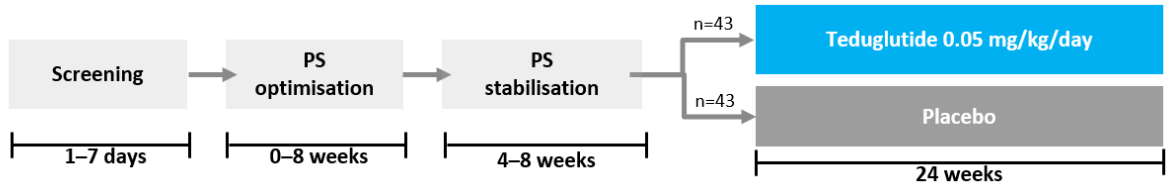
B.2.3 Summary of the methodology of the relevant clinical effectiveness evidence

B.2.3.1 Methodology of the randomised trials comparing teduglutide and placebo in adults

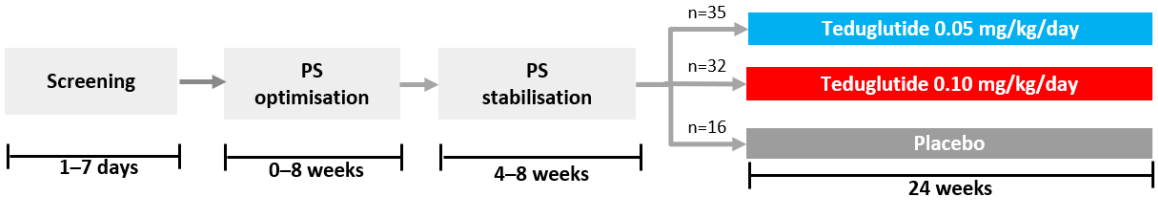
The two randomised controlled trials comparing teduglutide and placebo (STEPS and 004) were very similar in their overall design, with the principle differences being the investigation of two teduglutide doses in 004 (0.05 mg/kg/day and 0.10 mg/kg/day) versus only the licensed dose (0.05 mg/kg/day) in STEPS, and an unduly restrictive parenteral support (PS) weaning algorithm used in 004 compared to STEPS (the PS weaning algorithm used in STEPS still being more conservative than applied in real-world clinical practice). STEPS was initiated after 004 in part to investigate the efficacy of teduglutide with a more clinically relevant PS weaning algorithm. An overview of the two study's designs can be seen in **Figure 5** a more detailed summary of their methodology is provided in **Table 8**.

Figure 5 Overview of randomised controlled trial designs: A) STEPS and B) 004

A



B



Abbreviations: PS, parenteral support

Notes: Teduglutide was administered subcutaneously into abdomen, thigh, or arm

Source: STEPS primary publication[72]; STEPS CSR[89]; 004 primary publication[76]; 004 CSR[90]

Table 8: Summary of the methodology of randomised controlled trials STEPS and 004

Trial name	**STEPS** (NCT00798967) Initiated November 2008	**004** (NCT00081458) Initiated May 2004
Study rationale	Investigate the efficacy (in terms of PS reduction), safety and tolerability of teduglutide in adults with SBS-IF	Investigate the efficacy (in terms of PS reduction), safety and tolerability of teduglutide in adults with SBS-IF
Trial design summary	STEPS was a multi-national, phase 3, randomised, double-blind, parallel group, placebo-controlled 24-week trial.	004 was a multi-national, phase 3, randomised, double-blind, parallel group, placebo-controlled 24-week trial
PS optimisation and stabilisation period (Stage 1)	After screening, patients underwent PS optimisation (for 0–8 weeks, to achieve target urine output of 1.0–2.0 L/day) and PS stabilisation (for 4–8 weeks: PS use to match prescribed use; and oral fluid intake and urine output were not to deviate >25% from target)	After screening, patients underwent PS optimisation (for 0–8 weeks, to achieve target urine output of 1.0–2.0 L/day) and PS stabilisation (maintain urine output of 1.0–2.0 L/day for 4–8 weeks)
Randomisation and treatment period (Stage 2)	Patients were randomised (1:1) by computer-generated interactive response system to teduglutide or placebo for 24 weeks Randomisation was stratified by baseline PS volume (more or less than 6 L/week) Patients and investigators were blinded to treatment received	Patients were randomised (2:2:1) by computer-generated interactive response system to teduglutide 0.05 mg/kg/day, teduglutide 0.10 mg/kg/day or placebo for 24 weeks Randomisation was stratified by baseline PS use (IV fluids and electrolytes only; nutrients and fluids 3–5 times weekly; and nutrients and fluid 6–7 times weekly) Patients and investigators were blinded to treatment received
Weaning protocol used during Stage 2	**Condition:** if urine volumes during the preceding 48 hours were ≥10% above baseline	**Condition:** if urine volumes during the preceding 48 hours were ≥10% above baseline

Trial name	**STEPS** (NCT00798967) Initiated November 2008	**004** (NCT00081458) Initiated May 2004
	Magnitude: PS volume could be reduced by between 10–30% of baseline PS volume at each timepoint **Timepoints at which reduction could be made:** study visits on weeks 2, 4, 8, 12, 16, 20 and 24	**Magnitude:** PS volume could be reduced by up to 10% of baseline PS volume at each timepoint **Timepoints at which reduction could be made:** study visits on weeks 4, 8, 12, 16, 20 and 24 (and reduced on no more than 5 of these 6 timepoints) If, in addition, urine volume was over 2.0 L/day, PN volume could be reduced by ≥10% of baseline PS volume (as clinically appropriate).
Eligibility criteria for participants	• Aged ≥18 • SBS resulting from intestinal failure caused by a major intestinal resection • Receiving PS continuously for ≥12 months • Receiving PS for ≥3 days per week in 2 weeks prior to baseline • BMI ≥15 kg/m^2 • Naïve to teduglutide • No use of native GLP-2 or human growth hormone within last 6 months • No more than 4 hospital admissions related to SBS within last 12 months • No hospital admission 30 days before screening • Patients with Crohn's disease must have been in clinical remission for ≥12 weeks • No history of cancer within last 5 years • For patients with inflammatory bowel disease, no change in immunomodulator therapy within last 3 months and no biologic therapy in last 6 months	• Aged ≥18 • SBS resulting from intestinal failure caused by a major intestinal resection • Receiving PS continuously for ≥12 months • Receiving PS for ≥3 days per week in 2 weeks prior to baseline • BMI between 18 and 27 kg/m2 • Naïve to teduglutide • No use of native GLP-2 or growth hormones/factors within last 12 weeks • No hospital admission one month before screening • No patients with active Crohn's disease • No use of systemic corticosteroids, methotrexate, cyclosporine, tacrolimus, sirolimus, octreotide, intravenous glutamine or any investigational drug within last 30 days • Use of antimotility, anti-diarrhoeal, H2 receptor antagonists, proton pump inhibitors, bile sequestering agents, oral glutamine, diuretics and oral rehydration solutions were required to be

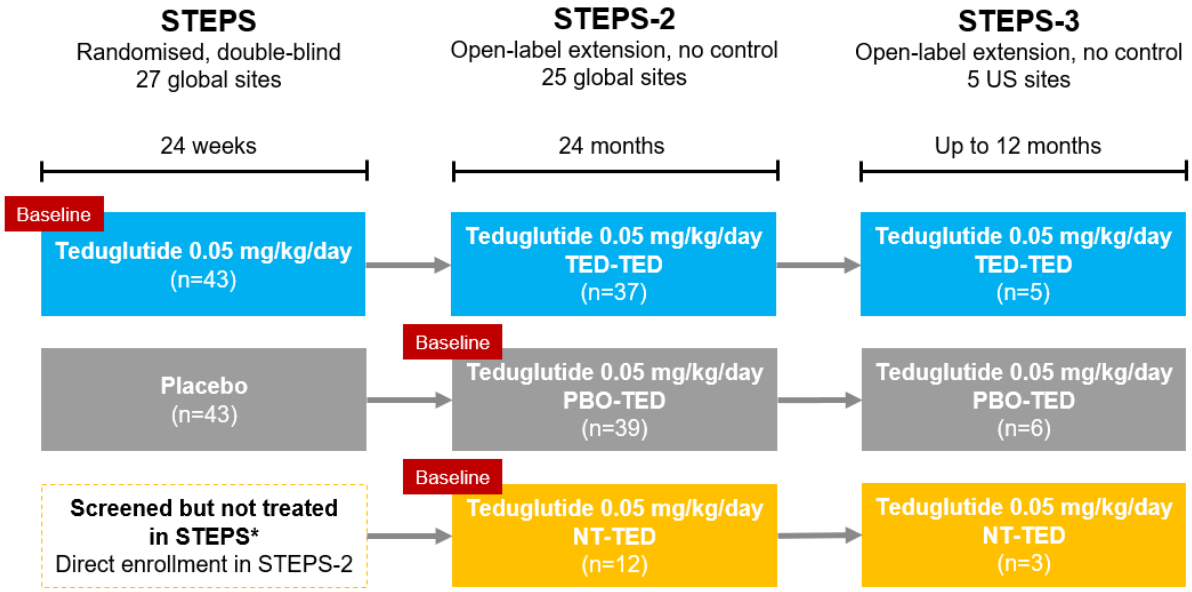
Trial name	**STEPS** (NCT00798967) Initiated November 2008	**004** (NCT00081458) Initiated May 2004
		stable for ≥4 weeks prior to baseline evaluations and remain stable during the study
Settings and locations where the data were collected	27 sites: Canada 4, Denmark 1, France 2, Germany 2, Italy 3, Netherlands 1, Poland 4, Spain 2, UK 2, and USA 6	32 sites: Belgium 1, Canada 4, Denmark 1, Germany 3, France 3, Netherlands 1, Poland 3, UK 1 and USA 15
Trial treatment	• Teduglutide subcutaneous 0.05 mg/kg/day (n=43) for 24 weeks • Placebo (n=43) for 24 weeks	• Teduglutide subcutaneous 0.05 mg/kg/day (n=35) for 24 weeks • Teduglutide subcutaneous 0.10 mg/kg/day (n=32) for 24 weeks • Placebo (n=16) for 24 weeks
Permitted and disallowed concomitant medication	No specific concomitant medications were administered. Administration of any concomitant medication was captured in the electronic case report form Only for reasons of medical necessity could concomitant medications be initiated after screening. Concomitant medications used prior to screening could be continued	No specific concomitant medications were administered. Administration of any concomitant medication was captured in the electronic case report form Medications commonly used to treat SBS must have been used at a stable dose for at least 4 weeks prior to baseline Only for reasons of medical necessity could concomitant medications be initiated after screening. Concomitant medications used prior to screening could be continued
Primary endpoint (including scoring methods and timings of assessments)	• % of patients who demonstrated a response (≥20% reduction in weekly PS volume) at week 20 and maintained to week 24 'PS volume' at a given timepoint was defined as the mean volume from the previous 14 days	• Graded response score (a combination measure of magnitude of response and duration at weeks 16–24), described in more detail in section B.2.6.1.2 'PS volume' at a given timepoint was defined as the mean volume from the previous 14 days

Trial name	**STEPS** (NCT00798967) Initiated November 2008	**004** (NCT00081458) Initiated May 2004
Other endpoints measured in the study and used in the economic model/specified in the scope	• Change in days per week of PS from baseline • Change in volume of PS from baseline • Safety	• Change in days per week of PS from baseline • Change in volume of PS from baseline • Safety
Pre-planned subgroups	Results were analysed by: • Country • Gender • Age category (<45, 45–64, >64 years) • Colon-in-continuity (yes/no) • Presence of ileocaecal valve (yes/no) • Presence of stoma (yes/no) • Race • Randomisation stratification variable: ≤6 L/week, >6 L/week	Results were analysed by: • Parenteral fluid volume use in three categories: PS consisting of IV fluid and electrolytes only (3 to 7 times per week), PS (3 to 5 times per week), PS (6 to 7 times per week), • Colon in continuity (yes/no) • Presence of ileocecal valve (yes/no) • Percent colon (summarized by quartiles)
Abbreviations: CSR, clinical study report; GLP, glucagon-like peptide; PS, parenteral support; SBS-IF, short bowel syndrome with type 3 intestinal failure **Source**: STEPS primary publication[72]; STEPS CSR[89]; 004 primary publication[76]; 004 CSR[90]		

B.2.3.2 Methodology of STEPS extension studies investigating the longer-term efficacy and safety of teduglutide in adults

Two extension studies to the original STEPS trial were performed; STEPS-2 and STEPS-3. An overview is shown in **Figure 6**.

Figure 6 Overview of STEPS clinical programme



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[72]; STEPS-2 primary publication[73]; STEPS-3 primary publication[75]

Both STEPS-2 and STEPS-3 were open label extension studies, with the primary aim being to investigate the long-term safety and efficacy of teduglutide 0.05 mg/kg/day. STEPS-2 allowed for up to 24 months further treatment with teduglutide beyond STEPS, STEPS-3 for up to 12 months beyond STEPS-2. Due to the STEPS-3 study being open for a year (rather than allowing a year of additional treatment), the amount of follow-up per patient was variable and very few patients completed a full additional 12 months of treatment in STEPS-3.

To enrol in STEPS-2, patients had to have completed STEPS (receiving teduglutide or placebo) or completed screening in STEPS but without being enrolled due to full study enrolment. To enrol in STEPS-3, patients had to have completed STEPS-2.

PS weaning in STEPS-2 and STEPS-3 followed the same algorithm used in STEPS in terms of the maximum PS reductions that could be made (10%–30% of baseline

PS volume at each timepoint, see **Table 8** in section B.2.3.1 for more details), however as study visits were less regular, PS reductions could be made less frequently during the follow-up studies. In STEPS, PS reductions could be made every 2–4 weeks, whereas in STEPS-2, PS reductions could only be made at week 2, month 1, month 2, month 3 and every 3 months thereafter. Reductions in STEPS-3 could be made every 3 months.

Endpoints of relevance in these studies were change in days per week of PS from baseline, change in PS volume from baseline and safety. Endpoints were assessed at the same timepoints as PS reductions could be made (week 2, month 1, month 2, month 3 and every 3 months thereafter in STEPS-2; every 3 months in STEPS-3). Baseline in STEPS-2 and STEPS-3 was defined as the initiation of teduglutide treatment equating to entry to STEPS for patients treated with teduglutide in STEPS (TED-TED cohort) and initiation of STEPS-2 for patients treated with placebo or not treated in STEPS (PBO-TED and NT-TED cohorts; see **Figure 6** above).

B.2.3.3 Methodology of the Patient Support Programme (PSP)

Following the reimbursement of teduglutide for patients with short bowel syndrome with type 3 intestinal failure (SBS-IF) in Australia, a Takeda-sponsored patient support programme (PSP) was set up (starting November 2019 and ongoing) to provide training and guidance to patients, nurses and clinicians on the use of teduglutide and the process of PS weaning in patients with SBS-IF. As part of this PSP, home nursing services support the monitoring and reporting of patients' PS reductions whilst on teduglutide.

[redacted]

A Takeda-sponsored homecare service will also be available in England if teduglutide is approved and this will similarly provide patients with the option to receive regular visits by homecare nurses to offer support and assistance as teduglutide is introduced and PS weaning occurs. The homecare nursing team will also similarly provide frequent reporting and communication of patient progress to the clinical team in order to optimise patient management. As such, the care pathway established by the Australian PSP can be considered akin to that which would exist were teduglutide to be approved in England[74].

B.2.3.4 Methodology of trials conducted in children

Table 9: Summary of methodology of paediatric studies C14 and C13

Trial number	**C14** (NCT02682381) Initiated June 2016	**C13** (NCT01952080) Initiated November 2013
Study rationale	To determine the safety and pharmacodynamics/efficacy of teduglutide in children with SBS-IF	To determine the safety and pharmacodynamics/efficacy of teduglutide in children with SBS-IF
Trial design	C14 was an open-label, dose-finding 24-week study conducted in paediatric patients with SBS-IF. All patients were screened for a minimum of 2 weeks before initiating on study treatment to establish baseline PS volume. Patients (and/or their families) could choose between receiving teduglutide or standard care (PS) only; no randomisation between teduglutide and PS was performed. Patients who chose treatment with teduglutide were randomised to one of two doses (0.025 mg/kg/day or 0.05 mg/kg/day).	C13 was an open-label, dose-finding, non-randomised 12-week trial conducted in paediatric patients with SBS-IF. All patients were screened for a minimum of 2 weeks before initiating on study treatment to establish baseline PS volume. Patients were enrolled to one of three doses of teduglutide (0.0125 mg/kg/day, 0.025 mg/kg/day or 0.05 mg/kg/day). The doses were administered sequentially; if no unexpected safety signals were observed for ≥6 patients in one dose cohort, the next dose cohort could be initiated. A fourth observational cohort received standard care treatment (PS) only. No randomisation was performed, patients could choose whether they received teduglutide or standard care.
PS weaning protocol	Decisions regarding PS reduction were ultimately at the discretion of the investigator, although guidelines were provided. Guidelines suggested that PS volume could be decreased by ≥10% if all of the following were met: • urine output ≥25 mL/kg/day	Decisions regarding PS reduction were ultimately at the discretion of the investigator, although guidelines were provided. Guidelines suggested that PS volume could be decreased if fluid intake exceeded output by >400 mL/m^2

Trial number	**C14** (NCT02682381) Initiated June 2016	**C13** (NCT01952080) Initiated November 2013
	• urine specific gravity <1,020 • weight had been gained • <10 stools per day (if not in nappies) or stool/mixed output <75 mL/kg/day (if in nappies) or ostomy output <80 mL/kg/day	
Eligibility criteria for participants	• Aged 1–17 • ≥12 month history of SBS • Dependent on PS for ≥30% of caloric intake • No substantial change in PS use (or enteral nutrition) for ≥3 months • Body weight ≥10 kg and above fifth percentile for age • No gastrointestinal obstruction within 6 months of screening • No major gastrointestinal surgery within 3 months of screening • No history of cancer of clinically significant lymphoproliferative disease (excluding non-aggressive or surgically resected cancer) • No biologic therapy for Crohn's disease within 6 months of screening • No current immunosuppressant therapy for inflammatory bowel disease • No evidence of pseudo-obstruction of dysmotility syndrome • No use of native GLP-2, GLP-1 or human growth hormone within 3 months of screening • No prior use of teduglutide • No more than 3 SBS- or PS-related hospital admissions within 3 months of screening	• Aged 1–17 • ≥12 month history of SBS • Dependent on PS for ≥30% of caloric intake • No substantial change in PS use (or enteral nutrition) for ≥3 months • Body weight ≥10 kg and above fifth percentile for age • No gastrointestinal obstruction within 6 months of screening • No major gastrointestinal surgery within 3 months of screening • No history of cancer of clinically significant lymphoproliferative disease (excluding non-aggressive or surgically resected cancer) • No biologic therapy for Crohn's disease within 6 months of screening • No current immunosuppressant therapy for inflammatory bowel disease • No evidence of pseudo-obstruction of dysmotility syndrome • No use of native GLP-2, GLP-1 or human growth hormone within 3 months of screening • No prior use of teduglutide • No more than 3 SBS- or PS-related hospital admissions within 3 months of screening

Trial number	**C14** (NCT02682381) Initiated June 2016	**C13** (NCT01952080) Initiated November 2013
	• No unscheduled hospital admission within 1 month of screening	• No unscheduled hospital admission within 1 month of screening
Settings and locations where the data were collected	24 sites in North America and Europe	17 sites in the US and UK
Trial treatment	• Teduglutide subcutaneous 0.025 mg/kg/day (n=24) for 24 weeks • Teduglutide subcutaneous 0.05 mg/kg/day (n=26) for 24 weeks • Standard care for 24 weeks (n=9)	• Teduglutide subcutaneous 0.0125 mg/kg/day (n=8) for 12 weeks • Teduglutide subcutaneous 0.025 mg/kg/day (n=14) for 12 weeks • Teduglutide subcutaneous 0.05 mg/kg/day (n=15) for 12 weeks • Standard care for 12 weeks (n=5)
Permitted and disallowed concomitant medication	No specific concomitant medications were administered, and no specific medications were prohibited whilst receiving study treatment	No specific concomitant medications were administered, and no specific medications were prohibited whilst receiving study treatment
Primary endpoints (including scoring methods and timings of assessments)	The study analysis was descriptive in nature and was not powered to analyse a primary endpoint	The study analysis was descriptive in nature and was not powered to analyse a primary endpoint
Other endpoints used in the economic model/specified in the scope	• Change in volume of PS • Change in days per week of PS Patients were assessed for PS volume every week.	• Change in volume of PS • Change in days per week of PS

Trial number	**C14** (NCT02682381) Initiated June 2016	**C13** (NCT01952080) Initiated November 2013
		Patients were assessed for PS volume every week for the first 4 weeks, and then every 2 weeks until week 12. A final study visit occurred at week 16.
Pre-planned subgroups	None	None
Abbreviations: CSR, clinical study report; GLP, glucagon-like peptide; PS, parenteral support; SBS-IF, short bowel syndrome with type 3 intestinal failure **Source**: C14 primary publication[79]; C14 CSR[91]; C13 primary publication[81] C13 CSR;[92]		

B.2.3.5 Baseline characteristics from randomised trials comparing teduglutide and placebo in adults

The baseline characteristics of patients in STEPS and 004 are presented in **Table 10**. In general, the patient population in the STEPS and 004 trials were broadly similar to the UK population (see Appendix L.1.1.1), despite only three patients in each trial being recruited from the UK.

Table 10: Baseline characteristics of patients in the randomised trials of teduglutide in adults

	STEPS		**004**		
	Teduglutide 0.05mg/kg/day (N=43)	**Placebo (N=43)**	**Teduglutide 0.10mg/kg/day (N=32)**	**Teduglutide 0.05mg/kg/day (N=35)**	**Placebo (N=16)**
Age, years, mean (SD) [range]	50.9 (12.6) [22–78]	49.7 (15.6) [18–82]	50.3 (14.0) [19-79]	47.1 (14.2) [20-68]	49.4 (15.1) [20-72]
BMI, kg/m^2, mean (SD) [range]	22.5 (3.2) [17.6–29.8]	22.3 (3.1) [17.5–28.6]	21.7 (2.6) [17.0-26.4]	21.2 (3.0) [15.6-26.7]	22.0 (2.9) [17.4-28.4]
Women, n (%)	22 (51)	24 (56)	19 (59.4)	18 (51.4)	9 (56.3)

	STEPS		004		
	Teduglutide 0.05mg/kg/day (N=43)	**Placebo (N=43)**	**Teduglutide 0.10mg/kg/day (N=32)**	**Teduglutide 0.05mg/kg/day (N=35)**	**Placebo (N=16)**
Cause of major intestinal resection, n (%)					
Vascular disease	13 (30)	16 (37)	8 (25)	14 (40)	3 (19)
Crohn's disease	10 (23)	8 (19)	13 (41)	10 (29)	7 (44)
Volvulus	3 (7)	6 (14)	4 (13)	5 (14)	2 (13)
Injury	4 (9)	4 (9)	2 (6)	3 (9)	1 (6)
Cancer	1 (2)	2 (5)	NR	NR	NR
Other	12 (28)	7 (16)	5 (16)	3 (9)	3 (19)
Intestinal anatomy or remnant small bowel length unknown, n (%)	3 (7)	3 (7)	2 (6)	1 (3)	0
Patients with stoma, n (%)	21 (49)	17 (40)	NR	NR	NR
Types of stoma, n (%)					
Jejunostomy	11 (52)	5 (29)	4 (13)	6 (17)	4 (25)
Ileostomy	6 (29)	9 (53)	7 (22)	2 (6)	1 (6)
Colostomy	4 (19)	1 (6)	NR	NR	NR
Other (duodenostomy; jejunostomy + ileostomy)	0 (0)	2 (12)	NR	NR	NR
Colon in continuity, n (%)	26 (61)	23 (54)	19 (59)	26 (74)	11 (69)
Overall remnant small bowel length, cm					
n	40	40	27	31	15
Mean (SD)	84.4 (64.6)	68.7(63.9)	68 (43)	58 (44)	77 (53)
Mean time receiving PS, years (SD)	6.8 (6.3)	5.9 (5.7)	7.3 (5.9)	6.6 (6.5)	7.9 (7.5)
Mean parenteral volume, mL/day (SD)	1,844 (1,057)	1,929 (1,026)	1,816 (1,008)	1,374 (639)*	1,531 (874)
Mean days per week of PS (SD)	5.6 (1.7)	5.9 (1.5)	5.5 (1.4)	5.1 (1.6)*	5.3 (1.7)

	STEPS		004		
	Teduglutide 0.05mg/kg/day (N=43)	**Placebo (N=43)**	**Teduglutide 0.10mg/kg/day (N=32)**	**Teduglutide 0.05mg/kg/day (N=35)**	**Placebo (N=16)**
Concomitant medication					
Antidiarrhoeals, n (%)	22 (51)	16 (37)	19 (59)	22 (63)	8 (50)
Antisecretory agents, n (%)	25 (58)	22 (51)	17 (53)	19 (54)	7 (44)

Abbreviations: BMI, body–mass index; PS, parenteral support; SD, standard deviation.

Notes: *n=34 as baseline PS data were not provided for one patient

Source: STEPS primary publication[72]; STEPS CSR[89]; 004 primary publication[76]; 004 CSR[90]

The baseline characteristics of patients included in the adult extension studies (STEPS-2, STEPS-3 and 005), and baseline characteristics from the clinical studies in children (C13 and C14) and are available in Appendix L.1.1.6. Baseline characteristics from the Australian Takeda Patient Support Programme are provided in section B.2.6.4.2.

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

A summary of the statistical analyses conducted for the randomised controlled trials STEPS and 004 are presented in **Table 11**.

Table 11: Summary of statistical analyses in STEPS and 004

Study	STEPS	004
Hypothesis objective	The objectives of this clinical study were to evaluate the efficacy, safety, and tolerability of teduglutide 0.05 mg/kg/day compared with placebo in patients with SBS who are dependent on PS. The primary objective was to compare the percentage of patients treated with teduglutide versus placebo who demonstrated a response at week 20 maintained to week 24. A response was defined as the achievement	The objective of this clinical study was to evaluate the efficacy, safety, tolerability, and pharmacokinetics of daily subcutaneous administration of teduglutide compared with placebo in subjects with PS-dependent SBS. The primary objective was to compare subjects treated with teduglutide vs. placebo with respect to a graded response score that accounted for both intensity and duration of a response at the end of the 24-week treatment period. Patients were assigned a score of 0 to 5, with higher scores

Study	STEPS	004
	of a 20% to 100% reduction from baseline in weekly PS volume.	indicating a greater magnitude and/or duration of response (scoring system described in section B.2.6.1.2)
Populations for analysis	• Intent-to-treat population: all patients randomised in the study (n=43 teduglutide, n=43 placebo). All efficacy analyses were conducted in this population • Safety population: all patients who received at least one dose of double-blinded study treatment (n=42 teduglutide, n=43 placebo). All safety analyses were conducted in this population • Per-protocol population: all patients who completed the study without major prespecified protocol violations (n=37 teduglutide, n=38 placebo). Efficacy analyses in this population were used to support analyses in the intent-to-treat population	• Intent-to-treat population: all patients who received at least one dose of study drug (n=35 teduglutide 0.05 mg/kg/day, n=32 teduglutide 0.10 mg/kg/day, n=16 placebo). Efficacy and safety analyses were conducted in this population • Per-protocol population: all patients who completed the study without major protocol violations (n=26 teduglutide 0.05 mg/kg/day, n=29 teduglutide 0.10 mg/kg/day, n=15 placebo). Efficacy analyses in this population were used to support analyses in the intent-to-treat population
Statistical analysis	Analysis of the primary endpoint compared the event rates for the two treatment groups using the Cochran–Mantel–Haenszel test statistics adjusted for the randomisation stratification variable (≤6 or >6L/week of PS volume at baseline). Analysis was conducted in the intent-to-treat population Other efficacy endpoints were summarised using descriptive statistics	For the primary efficacy endpoint, the ordered categorical response variable was summarised for each treatment group using descriptive statistics. Pairwise treatment comparisons were made using a rank analysis of covariance (an extension of the Wilcoxon rank sum test) with strata for the baseline PS consumption level used for the stratification of the randomisation and treatment group with the baseline weekly PS volume as a covariate, and a step-down procedure for multiple comparisons Other efficacy endpoints were summarised using descriptive statistics
Sample size, power calculation	Eighty-six patients were randomised in a 1:1 ratio to detect differences in responder rates between teduglutide 0.05 mg/kg/day and placebo groups of 35% versus 6%, respectively, based on the response rates reported in the 004 randomised controlled trial (α = 0.05, 2-sided rest and power= 90%). Grounded on these assumptions, nQuery Advisor (version 6.0,	A sample size of 80 randomised subjects (32 subjects in each of the teduglutide treatment groups and 16 subjects in the placebo group) was to provide at least 90% power to detect an increase in the percentage of subjects who had the protocol-defined minimum response (20% decrease for both weeks 20 and 24), from 5% in the placebo treatment group to 50% in the teduglutide treatment groups (80%

Study	STEPS	004
	Statistical Solutions, Saugus, MA, USA) based on the Fisher exact test was used to calculate the power.	power to detect an increase to 44%). The power calculations were based on two-sided tests of significance using Fisher's Exact test.
Data management, patient withdrawals	This study did not include any follow-up to assess the duration of effect of teduglutide after discontinuation. This study had a Data and Safety Monitoring Board No patients were lost to follow-up.	This study did not include any follow-up to assess the duration of effect of teduglutide after discontinuation. This study had a Data and Safety Monitoring Board No patients were lost to follow-up.
Abbreviations: PS, parenteral support; SBS, short bowel syndrome **Source**: STEPS CSR[89]; 004 CSR[90]		

No formal hypothesis testing was conducted in the single-arm extension studies STEPS-2, STEPS-3 and 005. Descriptive statistics were used to analyse all efficacy and safety endpoints. Due to the small eligible patient pool for trials C13 and C14 (children with SBS and PS dependency), no formal hypothesis testing was planned for these studies, and descriptive statistics were used to analyse PS volume and safety endpoints. Descriptive statistics were used to analyse the Patient Support Programme.

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

No quality issues were noted for either of the randomised controlled trials in adults (STEPS and 004). Quality issues for the two controlled trials in children (C13 and C14) relate to the lack of randomisation between teduglutide and standard care arms. Appendix D provides the complete quality assessment for each trial.

B.2.6 Clinical effectiveness results of the relevant trials

B.2.6.1 Teduglutide versus placebo efficacy in adults

Results from the two phase 3 randomised controlled trials of teduglutide (STEPS and 004) provide high-quality evidence that show the superiority of teduglutide 0.05 mg/kg/day to placebo. We will report the results of the primary endpoint from STEPS and 004 to make this point, and we will also show that teduglutide allows patients to reduce days per week of parenteral support (PS; an important treatment goal, see B.1.3.3) more than placebo (the difference is statistically significant).

We will also discuss two points that limit interpretation of these data:

- The nature of the PS weaning algorithms used, which did not allow PS weaning as early, as regularly, or of a magnitude seen in real-world clinical practice (see B.2.6.1.3)
- The high placebo response seen in STEPS, which does not reflect results with standard care in clinical practice. This is an artefact of the PS weaning algorithm and led to patients receiving placebo risking dehydration and losing weight. The principal investigator of the trial stated this should be viewed as a protocol violation[93] (see B.2.6.1.4)

B.2.6.1.1 Results from STEPS

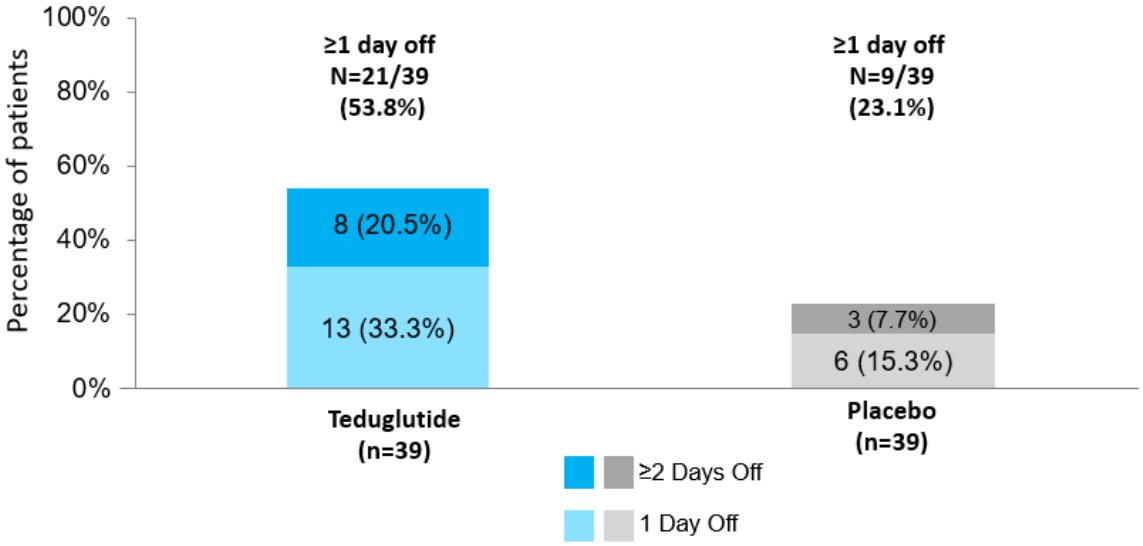
The STEPS trial met its primary endpoint: a statistically significant improvement in the number of patients achieving a clinical response (≥20% reduction in parenteral support [PS] volume) at week 20, maintained to week 24[72]:

- Teduglutide arm: **63%** (n=27/43) achieved a clinical response
- Placebo arm: **30%** (n=13/43) achieved a clinical response
- Risk ratio 2.077 (95% CI 1.25 to 3.46); *p*=0.002

This analysis was performed in all patients randomised to treatment (the intent-to-treat cohort).

Patients receiving teduglutide were statistically significantly more likely to achieve days off PS. Among patients who completed 24 weeks of treatment (n=39 in each arm), more patients in the teduglutide arm than the placebo arm reported achieving at least one day off PS per week (53.8% vs 23.1%, *p*=0.005; **Figure 7**).

Figure 7 Patients achieving days off PS per week in teduglutide and placebo arms by week 24; STEPS trial



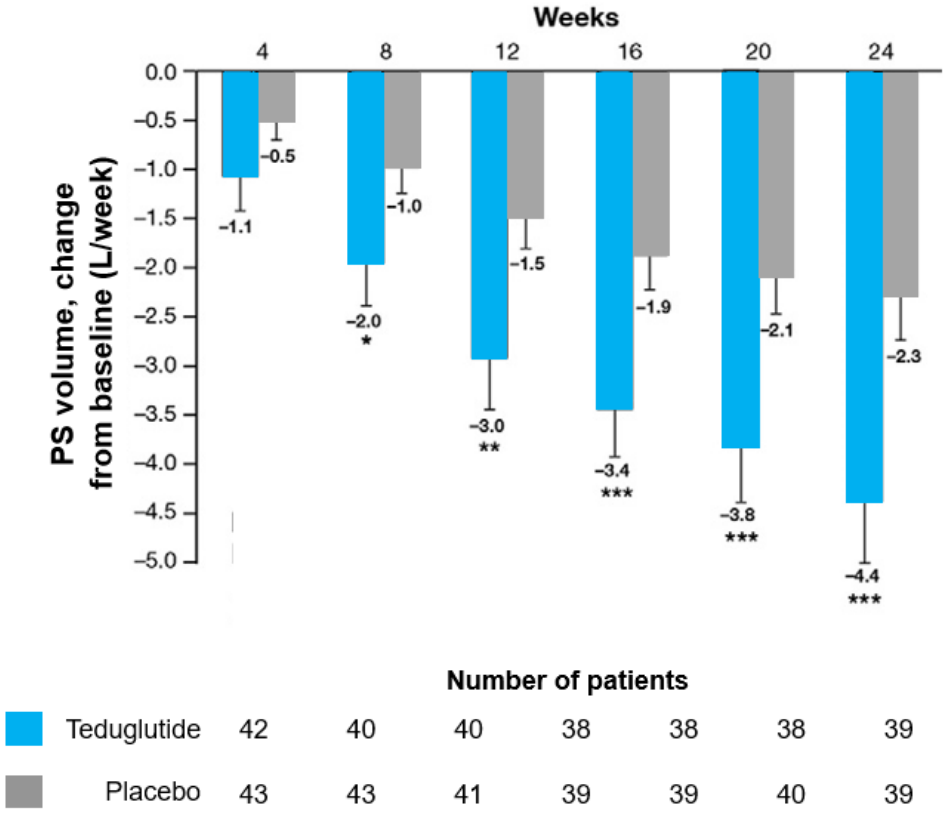
Abbreviations: PS, parenteral support

Notes: *p*=0.005 for teduglutide vs placebo

Source: STEPS primary publication[72]; STEPS CSR[89]

Furthermore, at every observation time point, patients receiving teduglutide had a greater reduction in PS volume than patients receiving placebo (-1.1 L/week vs -0.5 L/week at week 4; -4.4 L/week vs -2.3 L/week at week 24). This difference reached the threshold for statistical significance at week 8 and remained significant for the remaining period of 24 weeks (**Figure 8**).

Figure 8 Change in PS volume from baseline in teduglutide and placebo arms; STEPS trial



Abbreviations: PS, parenteral support

Notes: *$p \leq 0.05$ vs placebo; **$p \leq 0.01$ vs placebo; ***$p \leq 0.001$ vs placebo
Blue bars = teduglutide 0.05 mg/kg/day arm; grey bars = placebo arm

Source: STEPS primary publication[72]; STEPS CSR[89]

B.2.6.1.2 Results from 004

Study 004, like STEPS, provides evidence of the comparative efficacy of teduglutide versus placebo in adults. The primary endpoint in 004 was a graded response score, which took into account both the magnitude and durability of PS volume reduction. The graded response score was assessed in the intent-to-treat population (all patients randomised). The scoring system is described in

Table 12 and results are shown in **Figure 9**. Higher response scores represented a greater magnitude and/or durability of PS volume reduction versus lower scores. A graded response score of 1 or more indicated a ≥20% reduction in PS volume at week 20 sustained to week 24 (equivalent to the primary endpoint in STEPS).

Table 12: Graded response scoring system used in 004

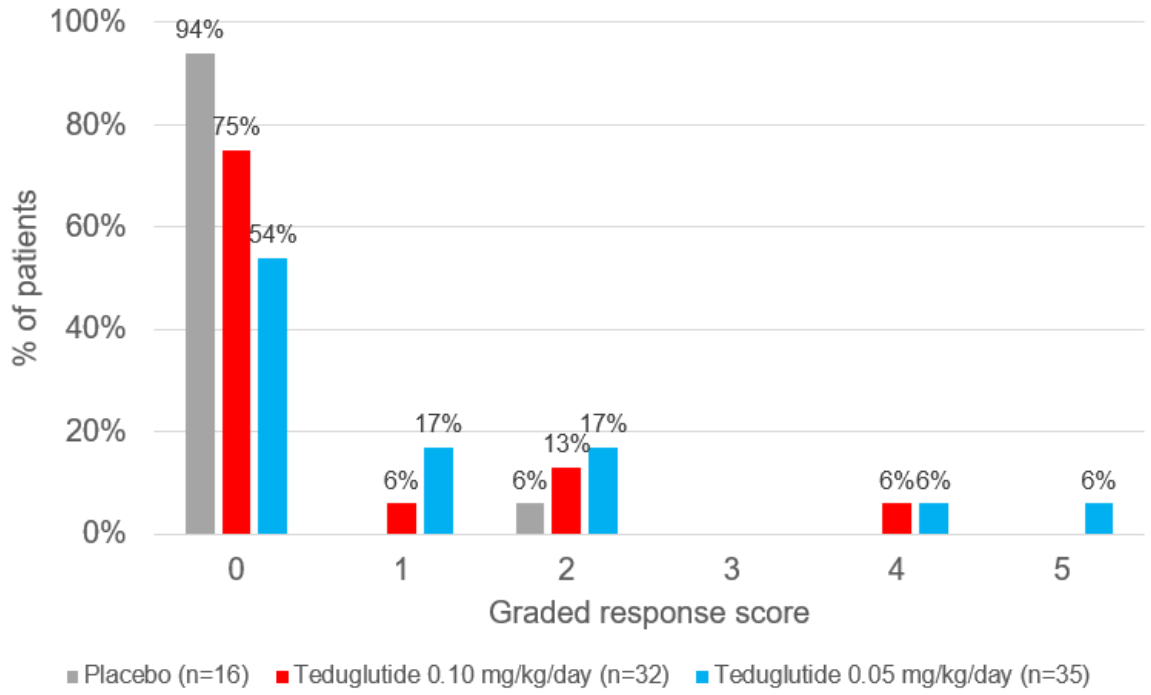
		Reduction in weekly PS volume at week 20 and maintained to week 24			
		<20%	**20–39%**	**40–99%**	**100%**
Reduction in weekly PS volume at week 16 and maintained to week 20	**<20%**	*0*	*1*	*2*	*3*
	20–39%	*0*	*2*	*3*	*4*
	>40%	*0*	*3*	*4*	*5*

Abbreviations: PS, parenteral support

Note: The numbers in *italics* are the graded response scores assigned to patients who fall into the criteria described by the row and column

Source: 004 primary publication[76]; 004 CSR[90]

Figure 9 Graded response score results in two teduglutide arms and placebo arm; 004 study



Abbreviations: PS, parenteral support

Notes:
p=0.16 for comparison of teduglutide 0.10 mg/kg/day vs placebo;
p=0.007 for comparison of teduglutide 0.05 mg/kg/day vs placebo;

A graded response score of 1 or more indicates a ≥20% reduction in PS volume at week 20 sustained to week 24 (equivalent to the primary endpoint in STEPS). The responder rates in 004, using the STEPS primary endpoint, were:
• 6% in placebo arm

• 25% in teduglutide 0.10 mg/kg/day arm • 46% in teduglutide 0.05 mg/kg/day arm One patient receiving teduglutide 0.10 mg/kg/day weaned off PS at week 24 with a graded response score of 4 **Source:** 004 primary publication[76]; 004 CSR[90]

[redacted]

Further data from 004 are presented in Appendix L.1.1.4. While study 004 provides further evidence for the superior efficacy of teduglutide 0.05 mg/kg/day compared to placebo, the study has weak external validity and is not reflective of current clinical practice (see section B.2.6.1.3 below).

B.2.6.1.3 PS weaning algorithms in STEPS and 004

Both STEPS and 004 used a PS weaning algorithm that restricted the magnitude and speed at which investigators could reduce patients' PS volumes. These algorithms are described in **Table 13**.

Table 13: Weaning algorithms used in STEPS and 004

	STEPS	**004**
Condition	PS volumes could be reduced if urine volumes during the preceding 48 hours were ≥10% above baseline	PS volumes could be reduced if urine volumes during the preceding 48 hours were ≥10% above baseline
Magnitude	Between 10–30% of baseline PS volume at each timepoint	Up to 10% of baseline PS volume at each timepoint
Timepoints at which reductions could be made	Study visits on weeks 2, 4, 8, 12, 16, 20 and 24	Study visits on weeks 4, 8, 12, 16, 20 and 24 (and reduced on no more than 5 of these 6 timepoints)
Other	None	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)
Abbreviations: PS, parenteral support **Source:** STEPS primary publication[72]; 004 primary publication[76]		

The weaning algorithms used limit the external validity of both studies. This is highlighted in the discussion of a real-world evidence study on teduglutide effectiveness published by lead author Professor Francisca Joly, a world-renowned expert in the management of SBS-IF:

"In our "real-life" experience of the weaning process, fluid intake and urine output monitoring could be less strict than in the published trials, allowing more freedom in PS reduction"[87]

Furthermore, three UK-based expert clinicians with extensive experience of SBS-IF supported the above statement by Joly *et al*., confirming that PS reductions in the real-world are likely to be more rapid than could be undertaken in STEPS and 004[62]. This is partly because weaning in the real-world is likely to be based on a more holistic assessment of patients – while urine volume is appropriate for guiding PS weaning in a clinical trial setting, it is not the only factor considered in real-world practice.

While the weaning algorithm used in STEPS (allowing PS volume reductions of up to 30% of baseline volume) is conservative relative to real-world practice, the weaning algorithm applied in 004 (allowing PS volume reductions of up to only 10% of baseline volume) should be considered unduly restrictive. This can be further illustrated by comparing response rates between 004 and STEPS. The more restrictive PS weaning algorithm used in 004 is reflected in the lower response rates and mean PS volume reductions for both the teduglutide 0.05 mg/kg/day arm and placebo arm compared to STEPS (**Table 14**). Furthermore in the real-world, where PS weaning algorithms are not used, we see better results with teduglutide than in either of these clinical trials (section B.2.6.4).

Table 14: 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[72]; STEPS CSR[89]; 004 primary publication[76]; 004 CSR[90]			

In summary, while STEPS and 004 demonstrate the superior efficacy of teduglutide over placebo in a randomised and controlled setting, the trials both lack external validity on account of the conservative PS weaning algorithms used in STEPS and

unduly restrictive algorithm used in 004. As STEPS is a better approximation of real-world practice, we will use results from STEPS (and extension study STEPS-2) in our economic model, but we will not use results from 004 (or extension study 005).

B.2.6.1.4 Placebo response in STEPS

A feature of the STEPS results is the apparent efficacy of placebo: a response rate of 30%, an average PS reduction of -2.3 L/week and 23.1% (n=9/39) of patients reaching an additional day per week off PS (all measured at week 24 and relative to baseline).

Teduglutide improves intestinal absorption, allowing patients to reduce PS and increase oral fluid/nutrition intake. It should be noted first that the PS reductions in the placebo arm of STEPS are not likely due to increased intestinal absorption. All patients entering STEPS underwent a process of PS optimisation (to achieve suitable urine output) and stabilisation (to ensure PS volume received matched PS volume prescribed). Furthermore patients in the placebo arm of STEPS had been receiving PS for on average 5.9 years (SD 5.7) after which time spontaneous adaptation of the intestine is

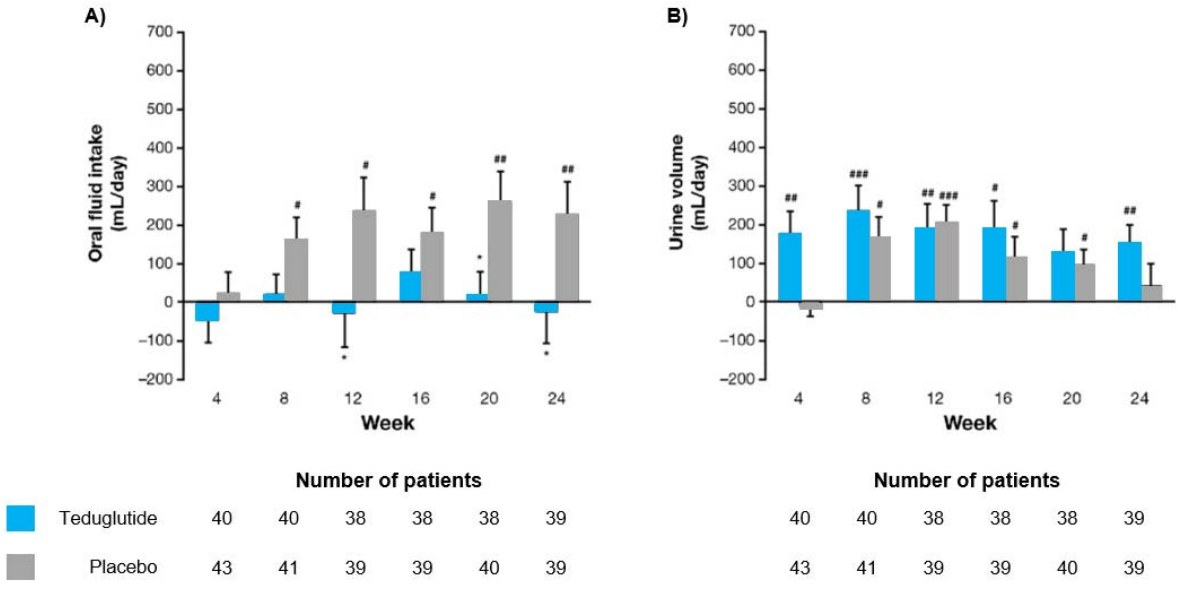
In clinical practice, a patient would only be able to reduce their PS if the absorptive capacity of their intestine improved, such that they could effectively receive more nutrients and fluid by mouth and meet their nutritional demands. Improved intestinal absorption can be observed through decreased faecal wet weight (as more fluid is absorbed by the intestine), and in phase 2 studies of teduglutide, decreased faecal wet weight was seen to correlate with increased urine volume. As urine volume was more feasible to measure, subsequent clinical trials used urine volume as a marker of intestinal adaptation and as a guide to reducing PS volume. Therefore, in STEPS, PS volumes could be reduced (by up to 30% of baseline) if urine volume was ≥10% above baseline.

Whilst urine volume fluctuations may explain the placebo response rate, we should also consider to what degree weaning in the teduglutide arm of STEPS was also driven by these fluctuations rather than reduced PS need, and therefore may also have not been appropriate.

[redacted] As PS volume (which contains IV fluids for hydration) decreased in both arms over the study, patients in the placebo arm had to significantly increase their oral fluid intake ([redacted]; **Error! Not a valid bookmark self-reference.A**, below) in order to compensate for this loss of IV fluid (the increased oral fluid intake was not lost as increased urine production, see **Error! Not a valid bookmark self-reference.B** below). Patients receiving teduglutide did not increase their oral fluid intake as their IV fluid intake decreased; we can infer this was because their intestine was able to absorb more fluid from their existing oral intake. For a graphical illustration of this situation, see**Figure 11** (next page). Urine production in both arms increased from baseline but otherwise stayed fairly constant over the study, supporting the above interpretation (**Error! Not a valid bookmark self-reference.B,** below).

[redacted]

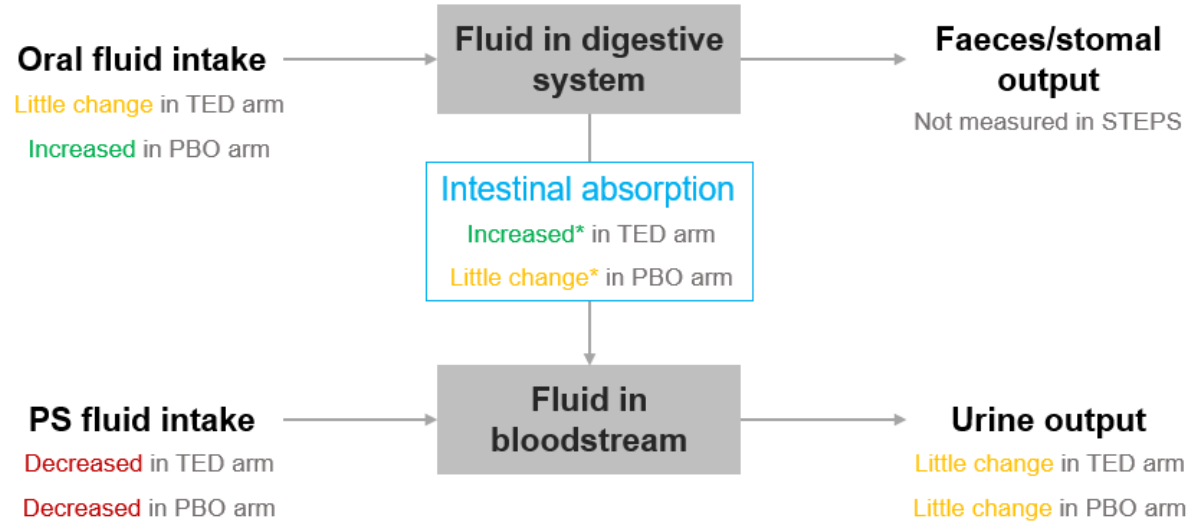
Figure 10 Change in A) oral fluid intake and B) urine volume from baseline in teduglutide and placebo arms; STEPS trial



Notes:
**p*≤0.05 vs placebo; ***p*≤0.01 vs placebo; ****p*≤0.001 vs placebo
#*p*≤0.05 vs baseline within group; ##*p*≤0.01 vs baseline within group; ###*p*≤0.001 vs baseline within group

Source: STEPS primary publication[72]; STEPS CSR[89]

Figure 11 Graphical overview of patient fluid balance in patients treated with teduglutide and placebo during STEPS



Abbreviations: PBO, placebo; PS, parenteral support; TED, teduglutide

Notes: *Intestinal absorption was not directly measured, but can be inferred from the changes in oral fluid intake, PS fluid intake and urine output

Source: STEPS primary publication[72]; STEPS CSR[89]; Expert statement from Professor Jeppesen[93]

[redacted]

[redacted]

B.2.6.2 Teduglutide longer-term efficacy in adults

STEPS-2 represents the largest overall patient exposure to teduglutide 0.05 mg/kg/day in a clinical trial (n=88 patients for up to 24 months). STEPS-3 also provides longer-term efficacy data, however the study was small (n=14) and patients had varied follow-up times due to rolling study start dates but a fixed end date.

We will use data from STEPS-2 and STEPS-3 to highlight that the clinical benefit observed with teduglutide in STEPS is enhanced with longer-term treatment.

B.2.6.2.1 Results from STEPS-2

Data from STEPS-2 were analysed by prior treatment and therefore split into three cohorts:

- The TED-TED cohort (n=37), who were previously treated with teduglutide in STEPS and continued teduglutide in STEPS-2 (total 30 months of teduglutide treatment)
- The PBO-TED cohort (n=39), who received placebo in STEPS, and commenced teduglutide at the start of STEPS-2 (total 24 months of teduglutide treatment)
- The NT-TED cohort (n=12), who were screened but not treated in STEPS, and commenced teduglutide at the start of STEPS-2 (total 24 months of teduglutide treatment)

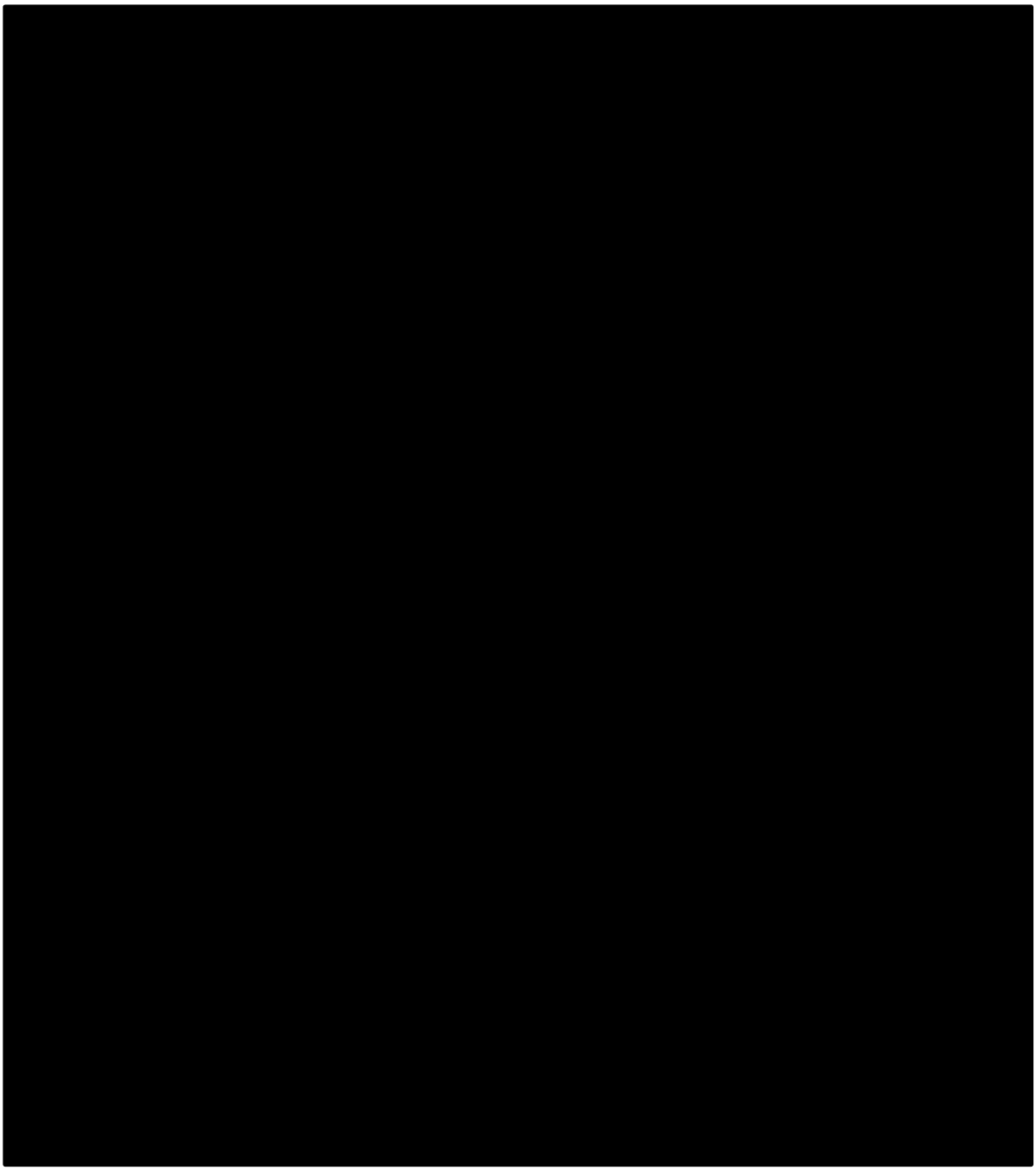
STEPS-2 used the same conservative parenteral support (PS) weaning algorithm as STEPS (discussed further in B.2.6.1.3), although in STEPS-2 patients had fewer opportunities to reduce their PS volume (every ~3 months in STEPS-2, compared to every ~4 weeks in STEPS). In routine clinical practice, clinical visits are likely to be more frequent, and so the weaning algorithm used in STEPS limits the external validity of the study, and STEPS-2 is limited even more so. The TED-TED cohort experienced the more clinically relevant STEPS algorithm whilst receiving teduglutide, and so these data have the highest external validity (the PBO-TED and NT-TED cohorts only experienced weaning on teduglutide using the less valid STEPS-2 algorithm). Three UK-based expert clinicians with direct experience of teduglutide supported the idea that the TED-TED cohort represented the most clinically relevant data[62]. For these reasons, we will focus throughout this dossier on the TED-TED cohort. Data from the PBO-TED and NT-TED cohorts are presented in Appendix L.

Longer-term treatment with teduglutide in STEPS and STEPS-2 resulted in sustained, continued reductions in PS requirements, as measured by days per week of PS and PS volume (PS volume data in Appendix L). At the start of STEPS, patients receiving teduglutide spent a mean of [redacted] days per week on PS. After 30 months of teduglutide treatment, this had decreased to [redacted] days per week on PS (**Figure 12**, next page)

Figure 12 Mean days per week of PS during STEPS/STEPS-2 in the TED-TED cohort

(**Figure 13**, next page) and 33% (n=10/30) achieved complete independence from PS. This demonstrates the continued clinical benefit teduglutide provides over longer term treatment.

Figure 13 Proportion of patients achieving at least 1 day off PS per week in STEPS and STEPS-2 for patients in the TED-TED cohort



B.2.6.2.2 Results from STEPS-3

Data from STEPS-3 are supplementary to the results seen in STEPS-2 due to the weaker internal validity of STEPS-3.

STEPS-3 was a small trial (n=14) conducted only in the USA. Furthermore, although STEPS-3 collected additional data for 'up to 1 year of treatment', the confluence of the rolling study start dates and a fixed study end date means that the number of

patients available at a given assessment timepoint is variable; not all patients received 12 months of additional teduglutide treatment. As per STEPS-2, data from STEPS-3 are presented in three cohorts by treatment received in STEPS (TED-TED, PBO-TED, NT-TED; see B.2.6.2.1 above)[75].

Results from STEPS-3 further reinforce that teduglutide has longer-term efficacy in adults with SBS-IF and continued treatment is associated with a sustained response. Of the 5 patients in the TED-TED cohort who entered STEPS-3, the mean reduction in days per week of PS was 3.0 days [redacted].

It is particularly notable that two patients [redacted] gained independence from PS during the STEPS-3 study. One patient gained independence after 126 weeks of teduglutide treatment, one after 130 weeks. This demonstrates that teduglutide can continue to provide clinical benefit after over 2 years of treatment[75]. [redacted]

Taken together, data from STEPS-2 and STEPS-3 reinforce that teduglutide continues to provide clinical benefit beyond 2 years of treatment.

Further data from STEPS-3 are presented in Appendix L.1.1.3.

B.2.6.3 Teduglutide quality of life data from clinical trials in adults

Quality of life data comparing teduglutide with placebo were captured in 004 and STEPS, however none of the data collected provides a meaningful assessment of the impact of reducing parenteral support (PS) on patient quality of life.

In 004, no difference was reported for any of the instruments used (SF-36, EQ-5D and IBDQ) when comparing results for the teduglutide arm at week 24 vs baseline or vs placebo arm at week 24. We will not further discuss quality of life results of 004 here: in the EPAR, it was noted that these quality of life/utility measures had not been developed to assess the quality of life of patients with short bowel syndrome with type 3 intestinal failure (SBS-IF) and were unlikely to be sensitive enough (considering both the small number of patients and heterogeneity in symptoms between patients; both factors that make assessment of quality of life in SBS difficult to measure). At the time of 004's initiation, no disease-specific quality of life measures were available[66].

STEPS assessed patients' quality of life using an SBS-specific quality of life scale (SBS-QoL), which was designed and developed specifically to measure quality of life changes over time in patients with SBS (however, measuring quality of life driven by PS was not a goal in developing the SBS-QoL)[56]. The SBS-QoL asks patients to rate the influence of their disease on 17 items (general wellbeing; everyday activities; working-life; leisure activities; social life; energy level; physical health; mobility and self-care activities; pain; diet, eating and drinking habits; emotional life; sleep;

gastrointestinal symptoms; fatigue/weakness; diarrhoea; skeleton/ muscle symptoms; and other symptoms/discomfort) using a visual-analogue scale. Each item is scored from 0 to 10, giving overall scores from 0 (perfect) to 170 (worst).

STEPS did not demonstrate any statistically significant quality of life differences between the teduglutide and placebo groups after 24 weeks of treatment[89, 95]:

- Patients receiving teduglutide experienced a reduction (improvement) in mean SBS-QoL score of **-11.7** (SD 26.8)
- Patients receiving placebo experienced a reduction (improvement) in mean SBS-QoL score of **-6.3** (SD 30.5)
- Mean difference **-5.4** in favour of teduglutide; ***p*=0.407**

[redacted]. It is also contrary to quality of life findings using the PNIQ: an instrument designed specifically to capture the effect of PS on everyday life[57]. Using the PNIQ, a reduction in days per week of PS was found to be statistically significantly correlated with improvement in quality of life among patients with type 3 intestinal failure[63].

There are a number of potential reasons why SBS-QoL data from STEPS did not demonstrate a statistically significant quality of life difference between teduglutide and placebo:

- As the EMA acknowledged when reviewing these results in the teduglutide EPAR, there is notable heterogeneity in the SBS-IF population, which makes differences in quality of life between treatment arms difficult to detect[66]. This heterogeneity can arise from the underlying condition that gives rise to SBS: patients for whom SBS resulted from a chronic disease are likely to experience PS positively given the disease control it offers, but patients for whom SBS resulted from an acute condition are likely to view PS negatively by comparison with their previous state[17].
- Randomisation was not intended to balance the 17 SBS-QoL items between the treatment groups, and so the teduglutide and placebo arms may have had differing quality of life concerns at baseline.
- The teduglutide EPAR suggests that the SBS-QoL instrument may not be sensitive enough to detect difference between teduglutide and placebo[66].
- STEPS was not powered to detect statistically significant changes in the SBS-QoL score[72].

As stated in the EPAR, the CHMP considered that the absence of statistically significant difference between teduglutide and placebo in SBS-QoL scores was related to the heterogeneity of the study population as well as the lack of sensitivity of the SBS-QoL instrument. Therefore, these results were not considered to undermine the clinical relevance of the observed effect on reduction in PS volume[66].

B.2.6.4 Teduglutide effectiveness in adults in a real-world setting

Results from a real-world setting show that the effectiveness of teduglutide is likely to surpass the efficacy observed in the STEPS clinical trials. Here, we will present data from published real-world studies of teduglutide and from the Australian Takeda Patient Support Programme (PSP); both of which support this point. In B.2.8, we will use a meta-analysis to formally compare these sources of data.

B.2.6.4.1 Results from published studies

Our clinical systematic literature review (SLR) identified 20 non-interventional studies of teduglutide; we will consider eight of them here, and use them to make the point that in the real-world, teduglutide is at least as effective, if not more effective, than demonstrated in the phase 3 trial STEPS and its extension, STEPS-2.

These eight studies all investigated teduglutide 0.05 mg/kg/day in adults with SBS-IF and were published as full papers, as opposed to presented only at congresses (see section B.2.2.2,

Table 7 for the rationale for our focus on them). Although not included in our model, these eight studies are relevant to the decision problem because they provide data on the real-world effectiveness of teduglutide, and therefore are representative of the outcomes that could be expected were teduglutide available on the NHS. They also illustrate the effectiveness of teduglutide outside of the artificial constraints of a clinical trial environment, and notably in an environment where restrictive PS weaning algorithms are not used.

We will present data from these eight studies alongside data from patients treated with teduglutide in STEPS and STEPS-2. This allows a descriptive comparison of teduglutide's effectiveness in environments where parenteral support (PS) weaning algorithms are used (STEPS/STEPS-2) and not used (the real-world). This comparison is only appropriate if the baseline characteristics of the populations are comparable. The degree of heterogeneity in the age, sex and underlying cause of disease between patients in these eight studies and STEPS/STEPS-2 is no more than would be expected given the heterogenous nature of the short bowel syndrome with type 3 intestinal failure (SBS-IF) population and small numbers of patients involved (**Table 15**).

Table 15: Baseline characteristics of patients in real-world studies and STEPS

	Joly 2020	Lam 2018	Martin 2021	Pevny 2019	Puello 2020	Schoeler 2018	Tama-ra 2020	Ukleja 2018	STEPS TED arm
Number of patients	54	18	31	27	18	14	4	6	43
Age, years, mean (SD) *unless otherwise stated as median* or (min – max)*	52.3 (2.1)	47* (20–81)	51* (IQR 37–59)	51 (17)	54.4* (28–74)	49.1 (18.7)	53 (20–74)	46.3 (18.1)	50.9 (12.6)
Female, %	35%	61%	35%	52%	56%	64%	50%	67%	51%
Primary cause of disease, %									
Inflammatory bowel disease	30%	NR	32%	15%	67%	50%	0%	33%	23%
Radiation enteritis	6%	NR	3%	0%	0%	7%	0%	0%	0%
Volvulus	13%	NR	13%	0%	0%	0%	0%	0%	7%
Vascular disease	39%	NR	32%	44%	17%	36%	50%	0%	30%
Injury	0%	NR	10%	11%	0%	0%	0%	0%	9%
Other	13%	NR	10%	30%	17%	7%	50%	33%	30%
Bowel features									
Colon-in-continuity, %	65%	83%	52%	78%	50%	64%	25%	50%	61%
Remaining small bowel length, cm, mean (SD) *unless otherwise stated as median* or (min–max)*	61.8 (5.9)	55* (6–180)	74* (IQR 34–100)	NR	100* (40–240)	64.5 (20–150)	70 (60–80)	75 (32)	84.4 (64.6)
PS consumption									
Duration of PS dependency, years, mean (SD) *unless otherwise stated as median* or (min–max)*	9.8 (1.2)	3.0* (0.3–8)	4.8* (IQR 2.3–8.3)	4.3 (5.8)	NR	NR	3.5 (NR)	4.6 (4.8)	6.8 (6.3)
PS volume, L/wk, mean (SD) *unless otherwise stated as median* or (min–max)*	11.2 (1.1)	9.9* (2.7–30)	7.5* (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)	12.6 (7.4)
PS days per week, mean (SD) *unless otherwise stated as median* or (min–max)*	4.4 (0.2)	NR	4* (IQR 3–5)	5 (2)	6.1 (95%CI 5.2–6.9)	5.6 (NR)	5 (0)	4.8 (2)	5.6 (1.7)

Abbreviations: 95%C, 95% confidence interval; med, median; NR, not reported; R, range; SD, standard deviation; SEM, standard error of the mean

Notes: * represents median (min – max)

Source: STEPS primary publication[72]; STEPS CSR[89]; STEPS-2 primary publication[73]; STEPS-2 CSR[94]; real-world study publications[87, 88, 96-101]

Ukleja 2018 and Martin 2021 should perhaps be considered outliers as these studies included patients with particularly low PS needs at baseline (baseline PS volume 7.7 L/wk in Ukleja 2018 and 7.5 L/wk in Martin 2021). This is relevant as previously published data have suggested that patients on lower baseline PS volumes are more likely to gain independence from PS with teduglutide[102]. However, across the other real world studies, there is no reason to consider the included patients to represent an 'easier to treat' population considering key characteristics such as: the proportion of patients with a colon in continuity (range: 25% to 83% versus 61% in STEPS/STEPS-2); mean remnant small bowel length (range: 61.8–70 cm versus 84.4 cm in STEPS/STEPS-2); or mean volume of PS consumption (range: 9.9–13.6 L/wk versus 12.6 L/wk in STEPS/STEPS-2).

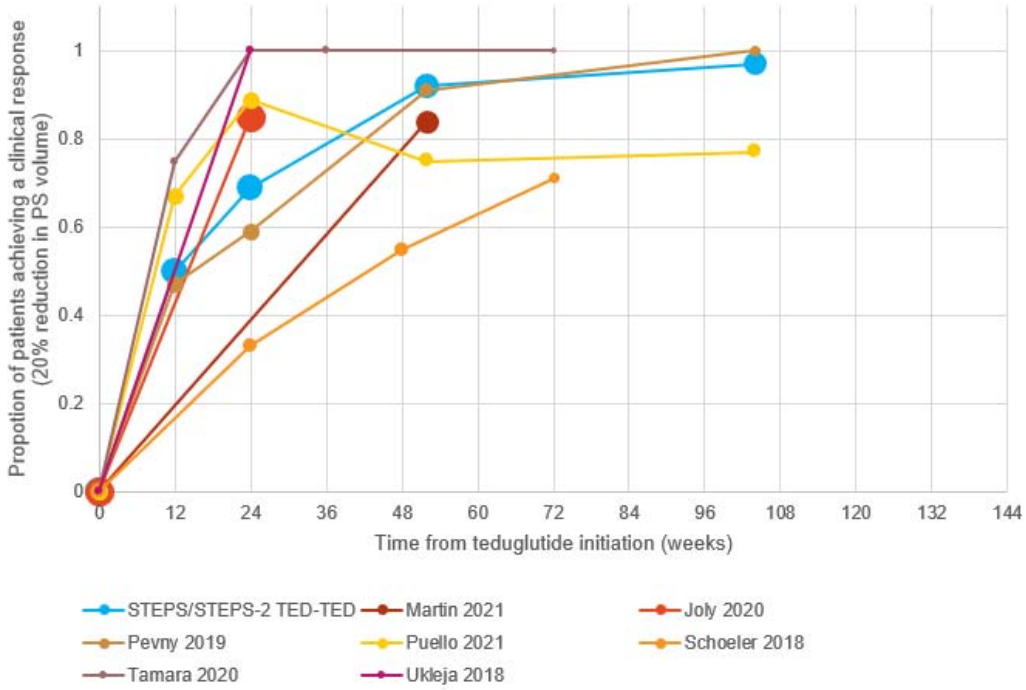
For the purpose of this descriptive comparison to STEPS and STEPS-2, we have chosen to present two outcomes from the eight real-world studies because they were the most consistently reported across the eight studies:

- Percentage of patients achieving clinical response (≥20% reduction in PS volume from baseline)
- Percentage of patients gaining independence from PS (100% reduction in PS volume from baseline)

The percentage of patients achieving a clinical response over time in the real-world studies and STEPS/STEPS-2 is shown in **Figure 14** (next page). In general, clinical response was similar when comparing real-world studies to STEPS/STEPS-2; clinical response rates at week 24 were [redacted] in STEPS and 33% to 100% in the real world. At week 52, response rates were [redacted] in STEPS-2 and 55% to 100% in the real world. It is worth noting that the authors of the Schoeler 2018 paper (which showed the lowest clinical response amongst the real-world studies at all timepoints) specifically mentioned that:

"…due to the lack of experience with this novel treatment approach and because of patient safety reasons, parenteral support was intentionally reduced slowly"[99]

Figure 14 Percentage of patients achieving a clinical response over time in real-world studies and STEPS/STEPS-2



Abbreviations: PS, parenteral support; TED-TED, the subgroup of patients from STEPS-2 who were previously treated with teduglutide in STEPS (see B.2.3.2)

Notes:

Size of marker is proportional to number of patients on teduglutide at given timepoint

% indicates the number clinical responders as a proportion of the number of patients receiving teduglutide at the time for all studies.

Schoeler 2018 publication reported clinical response data for 7 patients at '>12 months'; we have plotted this at 72 weeks for convenience

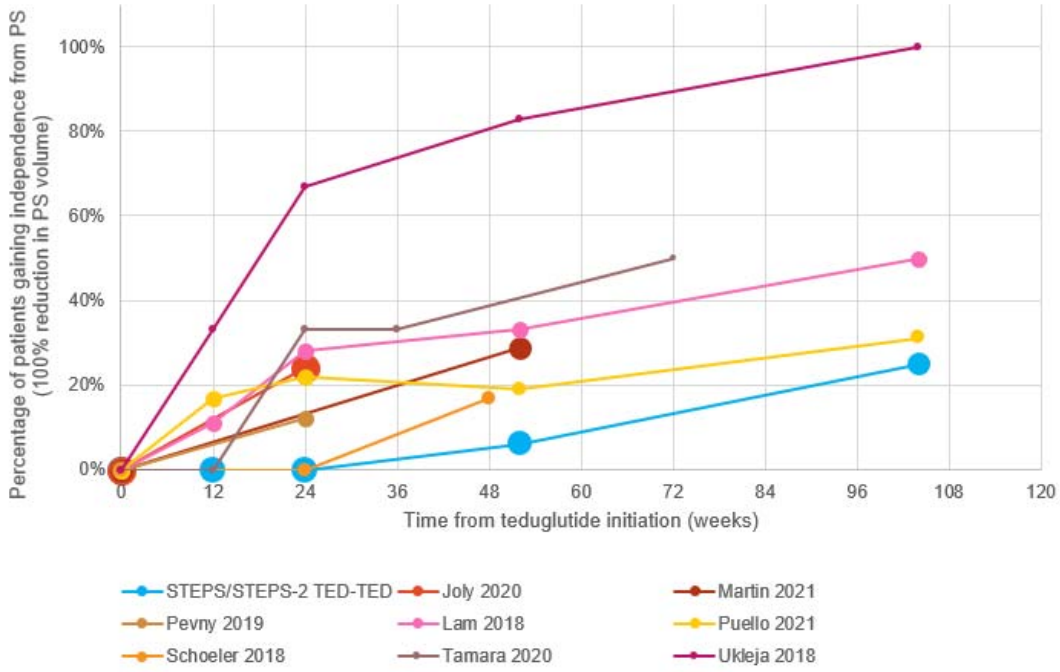
The definition of clinical response used here (≥20% reduction in PS volume from baseline) is different to the definition used in STEPS (≥20% reduction at week 20 maintained to week 24), hence the clinical response at week 24 for STEPS data reported here (69%) is higher than the value reported in B.2.6.1 (63%)

Source: STEPS primary publication[72]; STEPS CSR[89]; STEPS-2 primary publication[73]; STEPS-2 CSR[94]; real-world study publications[87, 88, 97-101]

Figure 15 shows the percentage of patients gaining total independence from PS in real-world studies and in STEPS/STEPS-2. Whilst the results from Ukleja 2018 and Martin 2021 should be considered outliers due to included patients' low baseline PS consumption (this is discussed above), the percentage of patients gaining independence from PS at a given time point in STEPS and STEPS-2 consistently lags behind that seen in the real-world. In the real-world, up to 33% of patients gain independence from PS after 24 weeks of teduglutide (compared 0% in STEPS), and between 17% and 40% of patients gain independence after 52 weeks of teduglutide

(compared to [redacted] in STEPS-2). Of particular note, after 52 weeks of treatment the percentage of patients gaining independence from PS in STEPS/STEPS-2 lag behind equivalent results from Schoeler 2018, who (as quoted above) *"intentionally reduced PS slowly"*[99]. Finally, it is also noteworthy that some real-world studies reported patients gaining independence from PS as early as 12 weeks into treatment with teduglutide; the first patient to gain independence from PS in STEPS/STEPS-2 did so after [redacted] of treatment[90].

Figure 15 Percentage of patients gaining independence from PS over time in real-world studies and STEPS/STEPS-2



Abbreviations: PS, parenteral support; TED-TED, the subgroup of patients from STEPS-2 who were previously treated with teduglutide in STEPS (see B.2.3.2)

Notes:

Size of marker is proportional to number of patients on teduglutide at given timepoint

% indicates (number gaining independence from PS) / (number receiving teduglutide at the time) for all studies. An exception here is Lam 2018, which does not provide patient numbers at each timepoint of assessment; we have therefore assumed all 18 patients remained on teduglutide throughout follow-up as this gives the most conservative estimate of complete response rate

Results from Ukleja 2018 and Martin 2021 should be considered an outlier, this is discussed in reference to baseline characteristics above

Source: STEPS primary publication[72]; STEPS CSR[89]; STEPS-2 primary publication[73]; STEPS-2 CSR[94]; real-world study publications[87, 88, 96-101]

Even considering the aforementioned outliers, we can conclude that in real-world practice, it appears that a similar number of patients achieve a clinical response

compared to in STEPS/STEPS-2, but a higher proportion of patients gain independence from PS. These conclusions are supported by our meta-analysis (see B.2.8). These results are likely due to the lack of PS weaning algorithms in real-world practice; whereas in STEPS/STEPS-2 these algorithms likely limited the extent and speed with which patients could reduce PS and thereby the reported efficacy of teduglutide. This point is discussed further in B.2.13.3.

B.2.6.4.2 Results from the Patient Support Programme (PSP)

[redacted]

[redacted]

Table 16: Baseline characteristics of patients treated with teduglutide in the PSP and in STEPS

Characteristic	[redacted]	**STEPS TED arm (n=43)**
Cause of disease, n (%)		
Crohn's disease	[redacted]	10 (23.3)
Ischaemia/vascular disease	[redacted]	13 (30.2)
Small bowel atresia	[redacted]	0
Radiation enteritis	[redacted]	0
Gastroschisis	[redacted]	0
Gastric cancer	[redacted]	1 (2.3)
Other	[redacted]	19 (44.2)
Average remnant small bowel length, cm (SD)	[redacted]	84.4 (64.6; data for n=40)
Colon in continuity, n (%)	[redacted]	26 (60.5)
Average time on PS, years (SD)	[redacted]	6.8 (6.3)
Weekly PS volume at baseline, L (SD)	[redacted]	12.6 (7.4)
Days per week of PS at baseline (SD)	[redacted]	5.6 (1.7)
Abbreviations: PS, parenteral support; PSP, patient support programme; SD, standard deviation; TED, teduglutide		

Notes: age and sex data were not available for PSP data

Source: STEPS primary publication[72]; STEPS CSR[89]; Revestive atHOME PS reduction report[103]

[redacted]

Figure 16 Percentage of patients achieving days off PS per week in the PSP (green) and STEPS/STEPS-2 (blue)

[redacted]

[redacted]

[redacted]

Table 17: Percentage of patients achieving clinical response and gaining independence from PS in the PSP and STEPS/STEPS-2 TED-TED cohort

	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]			
[redacted]			

[redacted]

B.2.6.5 Teduglutide efficacy in children

Results from the two phase 3 trials conducted in children with short bowel syndrome (SBS), C13 and C14, provide evidence of the efficacy of teduglutide in a paediatric population. We will use these data to illustrate that the efficacy of teduglutide in children is similar to, if not better than, its efficacy in adults.

B.2.6.5.1 Results from C14

In C14, 26 patients received teduglutide 0.05 mg/kg/day and 11 patients received standard care for 24 weeks. Importantly, there was no randomisation when allocating patients to teduglutide or standard care. No statistical hypothesis testing was pre-specified in C14, and the study was not powered for any analyses beyond descriptive statistics.

The primary endpoint in C14 was the percentage of patients achieving a clinical response, defined as a ≥20% reduction in parenteral support (PS) volume at week 24 in the intent-to-treat population (all enrolled patients)[79]:

- Teduglutide 0.05 mg/kg/day group: **69%** (n=18/26) achieved a clinical response
- Teduglutide 0.025 mg/kg/day group: **54%** (n=13/24) achieved a clinical response
- Standard care group: **11%** (n=1/11) achieved a clinical response

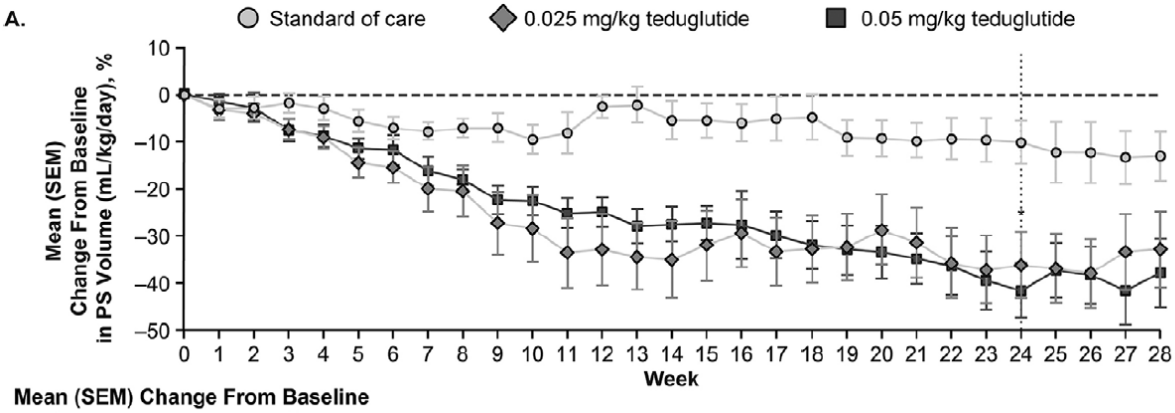
Patients receiving teduglutide achieved reductions of days per week on PS (mean -1.3 days per week at week 24 for patients receiving teduglutide 0.05 mg/kg/day) whilst standard care patients did not (**Table 18**). Reductions in PS volume over the course of the study were recorded for patients receiving both teduglutide doses (**Figure 17**, next page).

Table 18: Change in days per week of PS in C14

Mean days per week on PS (± SD)	Baseline (days per week)	Change from baseline at week 24 (days per week)
Teduglutide 0.05 mg/kg/day (n=26)	6.6 ± 0.79	-1.3 ± 0.79
Teduglutide 0.025 mg/kg/day (n=24)	6.5 ± 1.10	-0.9 ± 1.78
Standard care (n=11)	6.6 ± 1.33	0
Abbreviations: PS, parenteral support; SD, standard deviation **Notes:** None **Source:** C14 primary publication[79]		

In addition, 3 patients (12%) in the teduglutide 0.05 mg/kg/day cohort and 2 patients (8%) in the teduglutide 0.025 mg/kg/day cohort gained independence from PS during the study. None of the patients who received standard care were able to reduce days per week of PS.

Figure 17 Change in PS volume from baseline by treatment arm; study C14



Mean (SEM) Change From Baseline in PS Volume (mg/kg/d), %

Week	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28
SOC[a]	0	–3	–3	–7	–7	–10	–3	–5	–6	–5	–9	–9	–10	–12	–13
	(0)	(2)	(3)	(2)	(2)	(3)	(2)	(4)	(4)	(5)	(4)	(4)	(5)	(7)	(5)
0.025 mg/kg teduglutide[b]	0	–4	–9	–16	–21	–29	–33	–35	–30	–33	–29	–36	–36	–38	–33
	(0)	(2)	(2)	(3)	(5)	(7)	(8)	(8)	(7)	(7)	(7)	(7)	(7)	(7)	(8)
0.05 mg/kg teduglutide[c]	0	–3	–9	–12	–18	–23	–25	–28	–28	–32	–34	–36	–42	–38	–38
	(0)	(3)	(2)	(3)	(2)	(3)	(3)	(4)	(7)	(5)	(6)	(6)	(6)	(6)	(7)

Abbreviations: PS, parenteral support; SEM, standard error of the mean; SOC, standard of care

Notes:
[a]n=9 (except n=8 week 4–9; n=7 week 10, 25–26, 28)
[b]n=20 (except n=19 week 1, 11, 14, 16, 17, 20, 22, 23, 25, 26; n=18 week 28; n=17 week 27)
[c]n=25 (except n=24 week 1, 11, 12, 26; n=23 week 20, 22, 23, 25; n=22 week 27, 28)

Source: C14 primary publication[79]

Our clinical SLR also identified a single published study that focused specifically on the real-world experience of teduglutide 0.05 mg/kg/day in children with SBS (a Spanish non-interventional study in 8 sites including 17 patients). Akin to C14, this study provided guidance for PS weaning, however implementation of the guidance was at the discretion of the investigator. Results are shown in **Table 19** (next page) and baseline characteristics in Appendix L.

A naïve comparison of paediatric data (from C14 and the real world study) with adult data (from STEPS) suggests that a similar proportion of adults and children receiving teduglutide 0.05 mg/kg/day achieve a clinical response (≥20% PS volume reduction), but it appears that at week 24 children are more capable than adults of gaining complete independence from PS within that time (**Table 19**, next page).

Table 19: Comparison of results in C14, a real-world study in children and STEPS for patients receiving teduglutide 0.05 mg/kg/day

	C14	Real-world study in children	STEPS
% of patients with ≥20% PS volume reduction at week 24	69% (n=18/26)	87% (n=13/15)	69% (n=27/39)
Mean % change in PS volume at week 24 compared to baseline	-42% ([redacted])	Not reported	-32% (SD 19%)
Mean reduction in days per week of PS at week 24 compared to baseline	-1.3 (SD 2.24)	Not reported	[redacted]
% of patients gaining independence from PS by week 24 (100% PS volume reduction)	12% (n=3/26)	44% (n=7/16)	0%

Abbreviations: PS, parenteral support; SD, standard deviation; SEM, standard error of the mean

Source: C14 primary publication[79]; Ramos Boluda *et al.* 2020[104]; STEPS primary publication[72]

Additionally, in the real world study, 11 of 16 children (69%) who completed 12 months of teduglutide treatment achieved total independence from PS. These results were specifically highlighted by the NHS England Paediatric Medicine Clinical Reference Group[105]:

"Real life data in children has been published to show that outcomes in children are more favourable than that seen in published clinical trials and no new safety concerns have been reported"

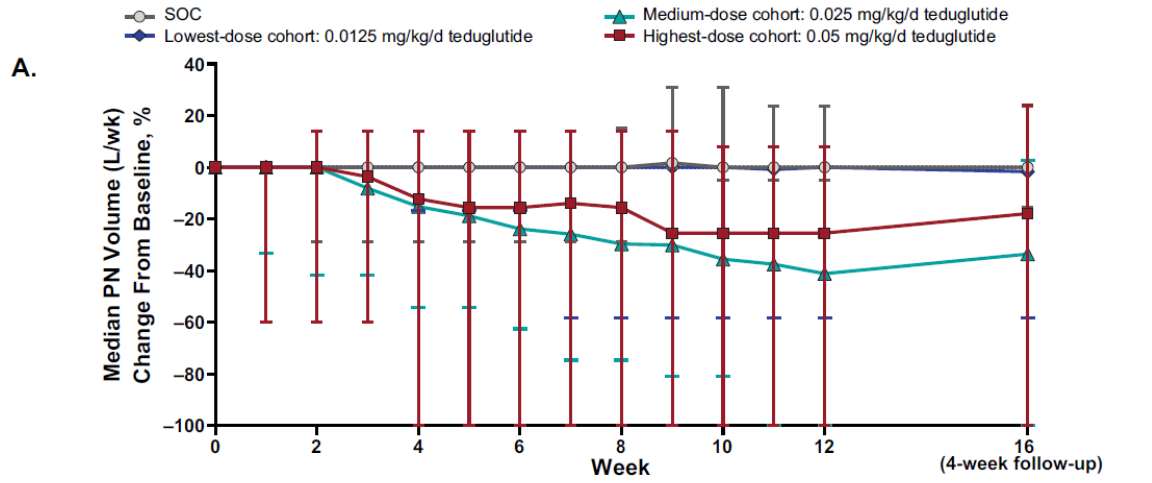
B.2.6.5.2 Results from C13

Study C13 recruited fewer patients to receive teduglutide 0.05 mg/kg/day than C14 (n=15 vs n=26 respectively), and was also of shorter duration (12 weeks vs 24 weeks), but still illustrates the efficacy of teduglutide in children with SBS-IF.

[redacted]

The study also showed reductions in PS volume over the course of 12 weeks (**Figure 18**, next page), consistent with results from C14.

Figure 18 Change in PS volume from baseline split by teduglutide dose received; C13



Week	0	1	2	3	4	5	6	7	8	9	10	11	12	16
Median PN Volume (L/wk), % Change From Baseline (min, max)														
SOC*	0 (0, 0)	0 (0, 0)	0 (−29, 0)	0 (−29, 0)	0 (−29, 0)	0 (−29, 0)	0 (−29, 0)	0 (−29, 0)	0 (−29, 15)	1.7 (0, 31)	0 (−5, 31)	0 (−5, 24)	**0 (−5, 24)**	0 (−15, 24)
0.0125 mg/kg/d†	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 1)	0 (−17, 0)	0 (−17, 1)	0 (−17, 0)	0 (−58, 0)	0 (−58, 0)	0 (−58, 0)	0 (−58, 0)	−1 (−58, 0)	**0 (−58, 0)**	−2 (−58, 0)
0.025 mg/kg/d‡	0 (0, 0)	0 (−33, 0)	0 (−42, 0)	−8 (−42, 0)	−15 (−54, 0)	−19 (−54, 0)	−24 (−63, 0)	−26 (−75, 0)	−30 (−75, 0)	−30 (−81, 0)	−36 (−81, 0)	−38 (−100, 0)	**−41 (−100, 0)**	−34 (−100, 3)
0.05 mg/kg/d§	0 (0, 0)	0 (−60, 0)	0 (−60, 14)	−4 (−60, 14)	−12 (−100, 14)	−16 (−100, 14)	−16 (−100, 14)	−14 (−100, 14)	−16 (−100, 14)	−25 (−100,14)	−25 (−100, 8)	−25 (−100, 8)	**−25 (−100, 8)**	−18 (−100, 24)

Abbreviations: PN, parenteral nutrition; SOC, standard of care

Notes:
*n=5 (except n=4 at week 5)
†n=8 (except n=6 at week 11 and n=7 at weeks 1, 4–10, 12, and 16)
‡n=14 (except n=13 at week 12)
§n=15 (except n=14 at weeks 7, 9–12, and 16)

Source: C13 primary publication[81]

Further efficacy data from C13 can be found in Appendix L, along with data from the two paediatric extension studies (SHP633-303 and SHP633-304).

B.2.7 Subgroup analysis

Analyses of subgroups likely to derive greater benefit from teduglutide have produced mixed results. As discussed above (B.2.6.5.1), children appear to have more potential to gain independence from parenteral support (PS) with teduglutide, although no published studies address this question. Real-world evidence[87] and a post-hoc analysis of STEPS[106] found that higher baseline PS volume was a predictor of better response to teduglutide. A second post-hoc analysis of the STEPS, STEPS-2 and STEPS-3 studies found that patients with lower baseline PS needs were more likely to wean off PS[102]. On the other hand, a pooled analysis of data from STEPS, STEPS-2, STEPS-3, 004 and 005[107] found no characteristics to be predictive of weaning off PS.

The teduglutide European Public Assessment Report (EPAR) states: *"Considering the rarity and heterogeneity of the disease it was not considered useful to define subgroups of patients. The experts advised that patients with higher volume requirements can possibly benefit from a significant reduction of PN/I.V*. [PS] *fluid and patients with lower requirements might have the chance to be weaned off completely."*[66]

In line with the EPAR, we have not presented any further subgroup data. Our model also does not define subgroups of patients with short bowel syndrome with type 3 intestinal failure (SBS-IF) that may derive additional benefit from teduglutide (with the exception of performing a paediatric-specific base case analysis, see B.3.2.1).

B.2.8 Meta-analysis

Results from a real-world setting show that the effectiveness of teduglutide is likely to surpass the efficacy observed in the STEPS clinical trials. In B.2.6.4, we descriptively presented data from published real-world evidence and Patient Support Programme (PSP) data, alongside data from STEPS and STEPS-2 for reference. To provide a robust statistical comparison of the efficacy of teduglutide in clinical trials and effectiveness in the real-world, we performed a meta-analysis to provide a pooled estimate from published real-world evidence and formally compare this to results from the PSP and STEPS/STEPS-2.

To estimate the effectiveness of teduglutide in the real-world, we used eight published studies identified by our clinical/real-world systematic literature reviews (SLRs; see B.2.2.2;

Table 7); the same ones as were used in our descriptive comparison (B.2.6.4.1). The outcomes of interest were the percentage of patients achieving a clinical response (≥20% reduction in parenteral support [PS] volume) and the percentage of patients gaining independence from PS (100% reduction in PS volume), evaluated at 6 months and 12 months. We chose these outcomes and timepoints as they were the most widely reported across the eight studies. The eight studies were meta-analysed using a generalised linear mixed model to obtain pooled estimates using both fixed-effect and random-effect models. The pooled summary results of the published real-world studies from the meta-analysis were statistically compared to equivalent results from STEPS/STEPS-2 and from the PSP.

[redacted]

[redacted]

Figure 19 Summary of meta-analysis results: ≥20% reduction in PS volume at month 12

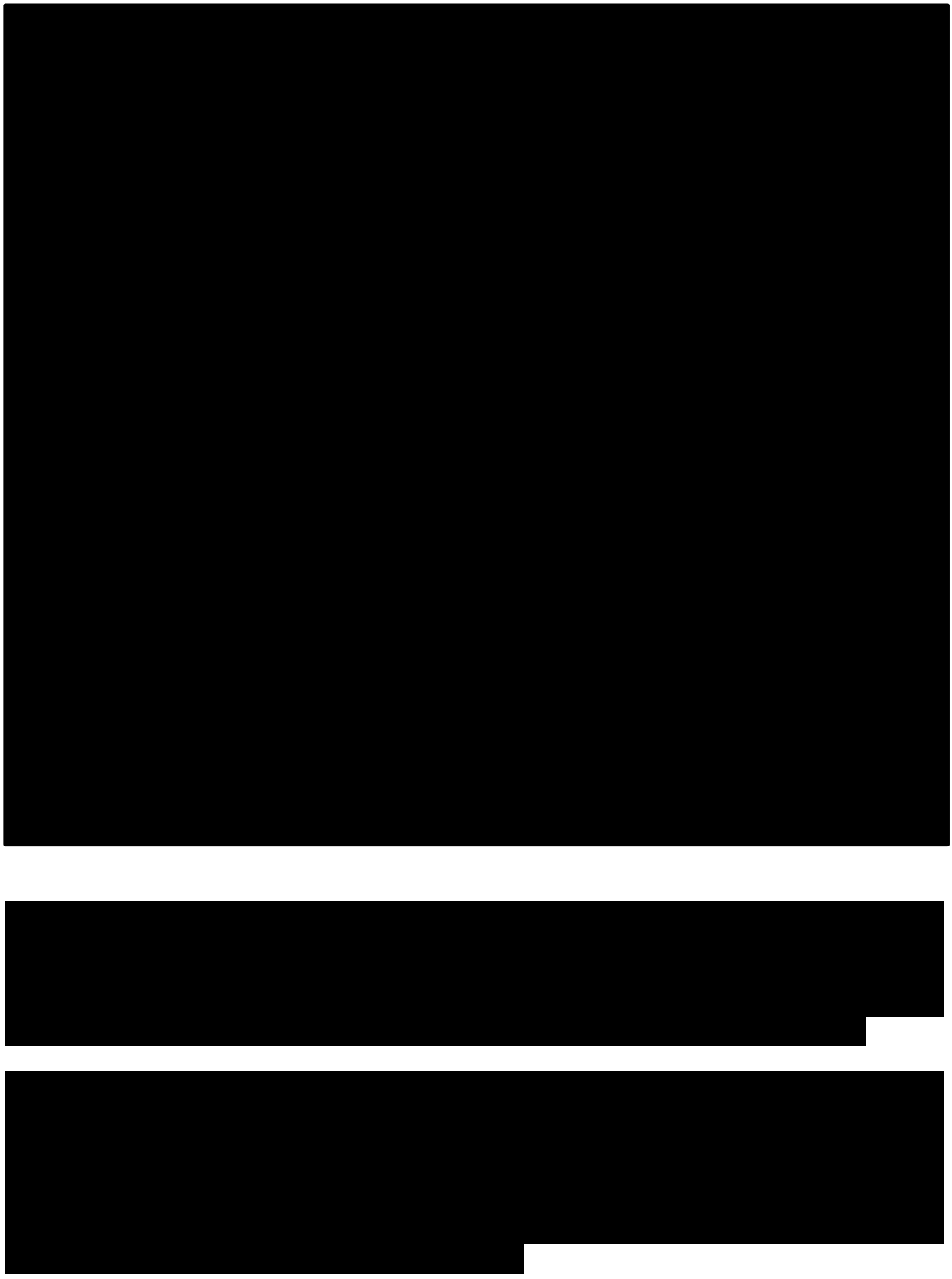
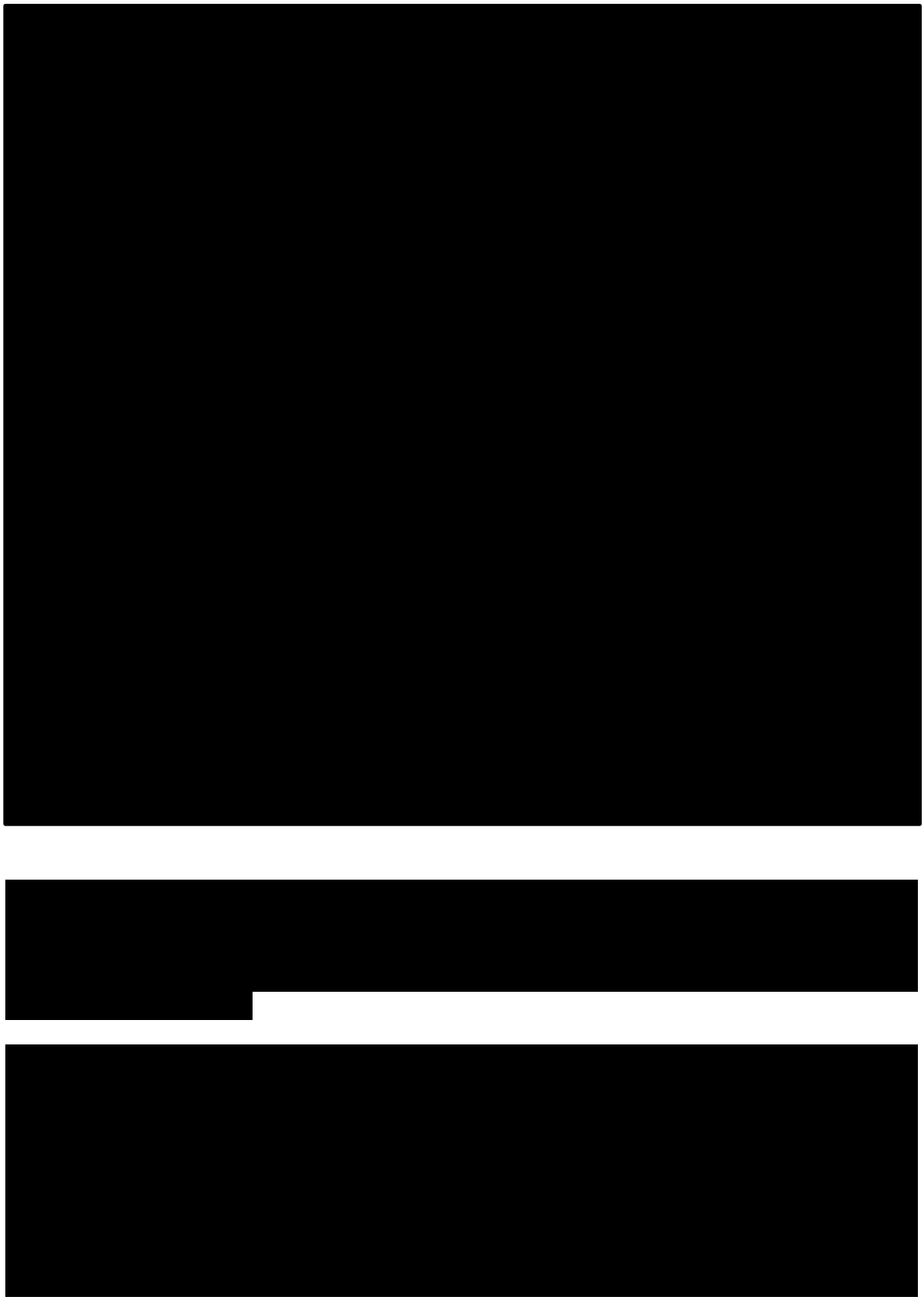


Figure 20 Summary of meta-analysis results: 100% reduction in PS volume at month 12



[redacted]

[redacted]

B.2.9 Indirect and mixed treatment comparisons

We did not perform any indirect or mixed treatment comparisons. This is because the only relevant comparator to teduglutide is standard care (PS), and data from STEPS and 004 (see B.2.6.1) directly compare teduglutide and standard care. We did not indirectly compare STEPS and 004 as the comparator groups are not equivalent due to the different weaning algorithms used (see B.2.6.1.3).

B.2.10 Adverse reactions

In general, teduglutide is well tolerated in adults and children, with a safety profile that clinicians consider manageable.

B.2.10.1 Safety results with teduglutide in adults

In clinical trials, teduglutide was well-tolerated in adult patients, with a broadly similar adverse event profile compared to patients treated with placebo[109]. **Table 20** shows data pooled from STEPS, STEPS-2, 004 and 005, representing exposure to teduglutide for 173 patients (134 received 0.05 mg/kg/day, 39 received 0.10 mg/kg/day) totalling 222 person-years. Overall the frequency and severity of adverse events and serious adverse events were similar between patients treated with teduglutide and patients treated with placebo.

Table 20: Safety outcomes with teduglutide in adults; pooled data from STEPS, STEPS-2, 004 and 005

	Teduglutide group, RCT + extensions (STEPS, STEPS-2, 004, 005)	**Teduglutide group, RCTs (STEPS + 004) only**	**Placebo group, RCTs (STEPS + 004) only**
	N=173	**N=109**	**N=59**
Safety parameter, n (%)			
At least one adverse event	167 (96.5)	99 (90.8)	49 (83.1)
Adverse event severity*			
Mild	151 (87.3)	84 (77.1)	45 (76.3)
Moderate	140 (80.0)	74 (67.9)	34 (57.6)
Severe	83 (48.0)	31 (28.4)	16 (27.1)
Any serious adverse event	101 (58.4)	39 (35.8)	17 (28.8)
Serious adverse event severity*			
Mild	29 (16.8)	13 (11.9)	5 (8.5)

	Teduglutide group, RCT + extensions (STEPS, STEPS-2, 004, 005)	Teduglutide group, RCTs (STEPS + 004) only	Placebo group, RCTs (STEPS + 004) only
	N=173	**N=109**	**N=59**
Moderate	59 (34.1)	18 (16.5)	7 (11.9)
Severe	56 (32.4)	16 (14.7)	8 (13.6)
Adverse events leading to discontinuation	34 (19.7)	10 (9.2)	4 (6.8)
Adverse events leading to death	3 (1.7)	0	0
Adverse event grouping† or adverse event preferred term occurring in at least 5% of patients in teduglutide RCT + extension group, n (%)			
Gastrointestinal stoma complications‡	31 (45.6)	17 (37.8)	3 (13.6)
Abdominal pain†	72 (41.6)	42 (38.5)	16 (27.1)
Upper respiratory tract infection†	50 (28.9)	30 (27.5)	8 (13.6)
Catheter sepsis events†	47 (27.2)	17 (15.6)	10 (16.9)
Nausea†	46 (26.6)	29 (26.6)	12 (20.3)
Headaches†	35 (20.2)	18 (16.5)	9 (15.3)
Asthenic conditions†	35 (20.2)	14 (12.8)	7 (11.9)
Injection site reactions†	33 (19.1)	22 (20.2)	7 (11.9)
Abdominal distension	32 (18.5)	18 (16.5)	1 (1.7)
Urinary tract infections†	32 (18.5)	17 (15.6)	10 (16.9)
Catheter site–related reactions†	29 (16.8)	9 (8.3)	8 (13.6)
Febrile disorders†	29 (16.8)	10 (9.2)	7 (11.9)
Vomiting	26 (15.0)	15 (13.8)	6 (10.2)
Weight decreased†	26 (15.0)	2 (1.8)	6 (10.2)
Musculoskeletal pain†	25 (14.5)	8 (7.3)	6 (10.2)
Diarrhoea†	24 (13.9)	7 (6.4)	7 (11.9)
Fluid overload†	23 (13.3)	11 (10.1)	4 (6.8)
Hypersensitivity†	21 (12.1)	9 (8.3)	3 (5.1)
Flatulence	19 (11.0)	9 (8.3)	4 (6.8)
Cognition and attention disorders and disturbances†	17 (9.8)	5 (4.6)	4 (6.8)
Dehydration	17 (9.8)	4 (3.7)	5 (8.5)
Arthralgia	15 (8.7)	7 (6.4)	3 (5.1)
Muscle spasms	15 (8.7)	4 (3.7)	4 (6.8)
Appetite disorders†	14 (8.1)	8 (7.3)	2 (3.4)
Biliary tract disorders†	14 (8.1)	4 (3.7)	1 (1.7)
Lower respiratory tract infection†	13 (7.5)	6 (5.5)	3 (5.1)
Skin haemorrhage†	13 (7.5)	5 (4.6)	1 (1.7)
Gastrointestinal stenosis and obstruction†	12 (6.9)	6 (5.5)	0
Sleep disturbances†	10 (5.8)	6 (5.5)	0

	Teduglutide group, RCT + extensions (STEPS, STEPS-2, 004, 005)	Teduglutide group, RCTs (STEPS + 004) only	Placebo group, RCTs (STEPS + 004) only
	N=173	**N=109**	**N=59**
Depressive disorders†	10 (5.8)	2 (1.8)	1 (1.7)
Coughing and associated symptoms†	9 (5.2)	5 (4.6)	0
Hepatic enzyme increased†	9 (5.2)	4 (3.7)	2 (3.4)
Pancreatic disorders NEC†	9 (5.2)	3 (2.8)	1 (1.7)
Contusion	9 (5.2)	2 (1.8)	0
Peripheral embolism and thrombosis†	9 (5.2)	1 (0.9)	2 (3.4)
Hot flush	9 (5.2)	1 (0.9)	0
Blood bicarbonate decreased	9 (5.2)	0	0

Abbreviations: AE, adverse events; NEC, not elsewhere classified; RCT, randomised controlled trial

Notes:

*Mild AEs were usually transient, requiring no special treatment and generally did not interfere with daily activities. Moderate AEs impaired usual activities and required simple therapeutic action. Severe AEs resulted in an interruption of usual activities and required vigorous therapeutic intervention.

†The preferred terms in the AE groupings represent medically similar terms.

‡Percentages calculated based on number of patients with a stoma (n = 45 for the RCT teduglutide group; n = 68 for the RCT/extension teduglutide group; n = 22 for the RCT placebo group).

Sources: Pape 2020[109]

The most commonly reported adverse events in the 173 patients pooled from four clinical studies were gastrointestinal stoma complication (n=31 of 68 patients with stoma; 45.6%), abdominal pain (n=72; 41.6%), upper respiratory tract infection (n=50; 28.9%) and nausea (n=46; 26.6%). 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 adverse events observed were believed to be mainly related to either the pro-absorptive and intestinotrophic effects of teduglutide, insufficient parenteral support (PS) weaning or the underlying nature of short bowel syndrome with type 3 intestinal failure (SBS-IF).

Three deaths occurred in adult patients receiving teduglutide; one was deemed possibly treatment related. The treatment-related death was a case of metastatic adenocarcinoma which may have been secondary to Hodgkin's lymphoma treated with chemotherapy and radiotherapy. A causal relationship with teduglutide treatment could not be ruled out; as a result, this malignancy was reported as related to treatment. The other two deaths, neither deemed treatment-related, were due to lung cancer and to catheter-related sepsis with urinary tract infection. A third instance of cancer (in addition to the adenocarcinoma and lung cancer described

above) was reported: a case of planocellular carcinoma of the lung in which a causal relationship with teduglutide could not be ruled out.

Although there were only three cancer reports in 222 person-years with teduglutide treatment, it was not possible to determine if this rate of events was higher than could be expected for a similar teduglutide-treated population. From the theoretical point of view, teduglutide being a growth factor (and inducing epithelial hyperplasia) raises some concern of induction and/or promotion of benign and/or malignant tumours. As a result, a risk management plan is in place to minimise the risks presented by any adverse events associated with teduglutide use and to closely monitor patients for any signs of gastrointestinal cancer[66].

B.2.10.1 Safety results with teduglutide in children

In general, the safety profile observed with teduglutide in children is similar to that observed in adults. **Table 21** shows data pooled from C13, SHP633-303, C14 and SHP633-304, representing exposure to teduglutide for 89 children. The authors of the publication describing this pooled data in children concluded:

"*The spectrum of adverse events was also similar to that reported in a recent integrated analysis of safety data from the adult clinical studies of teduglutide"* [Pape *et al.* 2020, presented in the above section B.2.10.1]

Table 21: Safety outcomes with teduglutide in children; pooled data from C13, SHP633-303, C14 and SHP633-304

	Children receiving teduglutide (N=89)
Safety parameter, n (%)	
Any adverse event	89 (100.0)
Adverse event severity	
Mild	17 (19.1)
Moderate	36 (40.4)
Severe	36 (40.4)
Any adverse event related to teduglutide	35 (39.3)
Any serious adverse event	69 (77.5)
Any serious adverse event related to teduglutide	3 (3.4)
Adverse events leading to discontinuation	2 (2.2)
Adverse events leading to death	1 (1.1)
Adverse events occurring in at least 5% of patients	
Vomiting	46 (51.7)
Pyrexia	39 (43.8)
Upper respiratory tract infection	37 (41.6)
Cough	30 (33.7)
Device-related infection*	26 (29.2)
Abdominal pain	23 (25.8)
Diarrhoea	23 (25.8)
Headache	18 (20.2)
Nasopharyngitis	18 (20.2)
Viral infection	18 (20.2)

Alanine aminotransferase increased	18 (20.2)
Nausea	15 (16.9)
Rash	15 (16.9)
Influenza	14 (15.7)
Dehydration	13 (14.6)
C-reactive protein increased	13 (14.6)
Device breakage*	13 (14.6)
Abdominal pain upper	12 (13.5)
Blood bicarbonate decreased	12 (13.5)
Abdominal distension	11 (12.4)
Device occlusion*	10 (11.2)
Fatigue	10 (11.2)
Rhinorrhea	10 (11.2)

Abbreviations: PS, parenteral support

Notes:

Serious adverse events were defined as any medical event that required inpatient hospitalisation or prolongation of hospitalisation, resulted in persistent or significant disability, was life-threatening, resulted in death, or was judged by the investigator as an important medical event.

The medical assessment of severity was determined by using the following definitions. Mild – a type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living. Moderate – a type of adverse event that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject. Severe – a type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

*All device-related events were related to central venous catheters used to administer PS, not to the teduglutide injection device.

Source: Hill 2020[110]

Compared with safety results from the adult studies, upper respiratory adverse events (cough, upper respiratory tract infection, nasopharyngitis, rhinorrhea, rhinitis, nasal congestion), pyrexia, vomiting, and catheter complications (device breakage, occlusion, and dislocation) were more common in the paediatric studies[110], as might be expected in a younger population[111].

The most commonly reported adverse events in children were vomiting in 51.7% of patients, pyrexia in 43.8%, upper respiratory tract infection in 41.6%, cough in 33.7%, and device-related (central venous catheter) infection 29.2%. Two patients (2.2%) discontinued teduglutide treatment because of an adverse event; neither event was considered related to teduglutide. Although pyrexia was reported frequently (28.1%) as a serious adverse event, no instances of pyrexia were deemed treatment-related. The most common adverse events considered related to treatment were vomiting and abdominal pain.

One patient died during the paediatric clinical programme. In the context of severe comorbid conditions and lack of response to teduglutide, treatment was discontinued and the family also electively withdrew enteral and parenteral fluid and nutritional

support. This death was considered by the investigator to be unrelated to teduglutide treatment.

B.2.11 Ongoing studies

Two Takeda-sponsored studies with teduglutide in short bowel syndrome with type 3 intestinal failure (SBS-IF) are ongoing:

- **NCT04883606** (T-Rex): retrospective study of teduglutide in adults with SBS-IF in Spain
- **NCT03268811**: an open-label study of teduglutide in Japanese children with SBS. Extension study to SHP633-302 (see

- **Table 6**, B.2.2.2)

B.2.12 Innovation

Teduglutide is the first and only pharmacological treatment approved to treat short bowel syndrome with type 3 intestinal failure (SBS-IF) in the UK[5]. Unlike existing therapies for SBS-IF that only manage symptoms of the disease, teduglutide has demonstrated an ability to enhance intestinal adaptation, improve the absorptive capacity of the intestine, increase nutrient absorption and enable patients to reduce their reliance on parenteral support (PS)[1].

B.2.12.1 Teduglutide is a step-change in SBS-IF management

For patients with SBS-IF, PS is currently a life-long and permanent restriction in most patients' lives, and offers no opportunity for restoration of the natural physiological function of the intestine. There are no pharmacological options for SBS-IF which address the underlying condition. Teduglutide is innovative as the first pharmacological treatment to have been approved that improves the absorptive capacity of the remaining intestine in order to reduce dependence on PS. Clinical trials show that a third of patients (33%) are able to gain complete independence from PS with teduglutide treatment for 30 consecutive months[73]. In real-world studies, PS independence occurred sooner than in STEPS: between 17% and 40% of patients gained independence within a year of treatment[87, 88, 96-101]. For patients, gaining independence from PS means a huge improvement in their ability to socialise, travel, work and sleep; better mental wellbeing; a reduced burden on intimate relationships; and freedom from medical issues and stress resulting from serious PS-associated complications. It also means a huge improvement in the quality of life of caregivers, who as a result of the care they provide suffer a lack of social activities, difficulties with relationships, lost income and employment difficulties and, in some cases, depression[50].

Representatives of patient advocacy groups talk of how gaining independence from PS, *"must feel like freedom has come at last"*.

In children, the step-change that teduglutide represents is, if anything, greater. SBS-IF, and its management with PS, is severely damaging to children's physical[41-43] and mental[51, 52] development. Reducing children's dependence on PS at a critical stage of their growth gives them the best chance to develop into healthy adults as well as to enjoy childhood. Reducing PS by even just one day per week provides the opportunity to have a 'sleepover' with a friend or commit to an after-school activity; we hear anecdotally of children getting excited about being able to take up weekly ballet lessons for the first time. Gaining independence from PS and having their central line removed provides even more freedom from the risk of infection and the opportunity to enjoy childhood; families tell us this means their child can do things like have swimming lessons for the first time, go paddling in the sea, and have a 'normal' child's bedroom free from medical equipment.

B.2.12.2 Benefits of treatment not captured by our model

B.2.6.12.1 Underestimated benefit to children

Our economic model is likely to underestimate the benefits of teduglutide in children. Our approach to modelling paediatric patients is discussed in more detail in section B.3.2.1; in summary we have assumed the same extent and rate of PS weaning as in adults, but longer survival times, two caregivers per patient (rather than one as for adults) and higher costs for certain complications. This approach likely results in an underestimated treatment benefit, underestimated cost saving and overestimated treatment cost.

As discussed in B.2.6.5, efficacy results with teduglutide in children are likely to be greater than those seen in adults; we see greater proportions of children gain independence from PS, and more quickly in C14 than in STEPS. This is because in children, increasing enteral nutrition further promotes intestinal adaptation[67, 68]. As our model links PS consumption with caregiver requirements and clinical feedback suggests that children are likely to have higher caregiver requirements, our model also underestimates the utility gain for children's caregivers. Furthermore, clinical feedback suggests that children are likely to suffer from more complications related to the use of PS (e.g. liver disease) and spend longer in hospital while these resolve, compared to adults. In addition, our model assumes all children use the teduglutide 5 mg vial, whereas in the real-world, children who weigh less than 20 kg would be able to use the smaller 1.25 mg vial[1], which has 50% lower cost. Taken together, it is likely that our model underestimates cost savings, overestimates treatment costs and underestimates the treatment benefit of teduglutide in children.

B.2.6.12.2 Reductions in PS volume but not days

Our economic model focuses only on reductions in days per week of PS, because this is a highly relevant outcome correlated with improvement in quality of life for patients with SBS-IF[63, 64]. It is likely however that reducing volume of PS, and therefore time each night hooked up to a machine, will also be of benefit to patients. Considering data from STEPS and STEPS-2, after 30 months of continuous teduglutide treatment, n=21/30 patients reduced PS by at least one day per week, whereas n=28/30 had achieved a 20% or greater reduction in PS volume. [redacted]. Our model assumes no benefit for these patients, even though some treatment benefit is likely. There may even be some patients who would prefer to spend fewer hours connected to a machine each night than to receive a full day off PS entirely, although feedback from our advisory board suggested that this desire was uncommon. The benefits of teduglutide to these patients will also be underestimated by our model.

B.2.6.12.3 Productivity gains

By reducing PS, and the associated burdens that go with it (such as fatigue), patients work productivity is likely to improve (productivity gains are not part of the NICE reference case, and so not captured in our model[112]). A notable example would be work productivity or school performance for patients, and also work productivity for caregivers. [redacted]

[redacted]. It is worth noting that adults with SBS-IF are typically in their 50s, which is for many the peak years of their career. Carers report missing 90 days per working year[59]. School performance in children is also adversely affected by their disease[53]; and furthermore children have their whole adult lives ahead of them to provide contributions to society.

B.2.6.12.4 General wellbeing

At an advisory board three expert UK-based clinicians with experience of teduglutide stated that their patients report an increased feeling of wellbeing and greater muscle mass with teduglutide treatment[62]. One clinician described a young patient who went from having a dirty nappy 12 times a day to 4 times a day after starting teduglutide [62]. The disruption that changing nappies and soiled outfits this regularly caused to their parents was immense, to the point that they didn't feel as though they could leave the house. These 'general wellbeing' improvements achieved among patients treated with teduglutide and their caregivers are unlikely to be captured because quality of life instruments for this population are not sensitive enough to these issues.

B.2.13 Interpretation of clinical effectiveness and safety evidence

Parenteral support (PS) is a critical life-extending treatment for patients with short bowel syndrome and type 3 intestinal failure (SBS-IF). It is a high-tech, sophisticated and complex treatment that requires multidisciplinary input and expertise to administer. On the one hand, PS allows patients with SBS-IF to manage a condition that would otherwise be fatal. On the other, patients receiving PS typically spend over ten hours per night connected to a disruptive medical device for a number of (if not all) nights of the week. PS severely impairs the social lives, sleep, ability to work and ability to maintain relationships of those who receive it. Despite its life-extending capacity, PS represents a large quality of life burden for patients with SBS-IF, and for their caregivers and families.

Each day per week that patients with SBS-IF spend free of PS results in a statistically significant improvement in their quality of life[113]. Reducing days of PS per week (while maintaining a healthy nutritional and fluid balance) is therefore a key treatment goal. When asked at an advisory board, three leading clinicians in the management of SBS in the UK stated that what patients with SBS-IF will ask for is an extra day free of PS. For patients, gaining independence from PS means a huge improvement in their ability to socialise, travel, work and sleep; better mental wellbeing; a reduced burden on intimate relationships; and freedom from medical issues and stress resulting from serious PS-associated complications.

In the clinical data we have presented, teduglutide was able to consistently achieve a reduction in days per week of PS for patients with SBS-IF. In particular, the data demonstrates five key points, which we elaborate on below:

- Teduglutide is more effective than placebo in reducing the PS requirements of adults with SBS-IF; this difference is statistically significant and clinically meaningful

- With longer-term treatment, the efficacy of teduglutide is enhanced in adults

- In a real-world setting, patients receiving teduglutide are able to reduce PS intake to a greater extent than observed in clinical trials, and more patients are able to achieve complete independence from PS

- Teduglutide has a manageable safety profile and is well-tolerated in adults

- In children teduglutide shows a similar safety profile, and evidence suggests children are more capable than adults of gaining independence from PS with teduglutide

B.2.13.1 Teduglutide is more effective than placebo in adults with SBS-IF

In STEPS teduglutide 0.05 mg/kg/day was associated with a statistically significant improvement in the trial's pre-defined primary endpoint compared to placebo:

- **63%** of patients achieved a ≥20% reduction in PS volume at week 20 maintained until week 24 with teduglutide 0.05 mg/kg/day

- vs **30%** with placebo (risk ratio 2.077 [95% CI 1.25 to 3.46]; *p*=0.002 for comparison)

In 004, a post-hoc analysis of the primary endpoint comparing placebo to only the licensed dose of teduglutide (0.05 mg/kg/day) met the threshold for statistical significance:

- **46%** of patients receiving teduglutide 0.05 mg/kg/day had a graded response score ≥1 (graded response score ≥1 is equivalent to the primary endpoint of STEPS; in section B.2.6.1.2, see

- **Table 12** for details of the graded response score and **Figure 9** for results)
- vs **6%** with placebo (p=0.007 for comparison)

These are high-quality randomised controlled trials, which pass all items on the Centre for Reviews and Dissemination 2008 criteria for assessment of risk of bias in randomised controlled trials (see Appendix D). The studies have high internal validity, and enable us to confidently say that the difference in outcomes between the placebo and teduglutide 0.05 mg/kg/day arms relates to the treatment effect of teduglutide.

The teduglutide European Public Assessment Report (EPAR) considered the results of 004 'hypothesis generating' on the basis that the primary endpoint (involving the unlicensed dose) was not met[66]. Given this, and coupled with the unduly restrictive PS weaning algorithm which severely limits the external validity of the study (see B.2.6.1.3 for more discussion), we believe it is appropriate to not focus on 004 in this review of the clinical evidence.

Data from STEPS have better external validity. In relation to the present decision problem, the STEPS data show that teduglutide 0.05 mg/kg/day (the intervention of interest) is more efficacious than placebo (a substitute for the comparator of interest, standard care) in a primary subpopulation of interest (adults with SBS-IF). The adult population enrolled in STEPS was similar in characteristics, disease aetiology and baseline PS consumption to the adult SBS-IF population in the UK (see Appendix L.1.1.1 for comparison), suggesting these results are applicable to the NHS.

However, STEPS underestimates the benefit of teduglutide with respect to standard care for two reasons. Firstly the PS weaning algorithm used in STEPS imposed significant constraints on the magnitude and timing of PS reductions, and is conservative relative to real world practice (see B.2.6.1.3 for more discussion). This was confirmed by clinicians with both clinical trial and real-world experience of teduglutide at an advisory board[62]. Correspondingly, we see patients gain independence from PS more rapidly when treated with teduglutide in the real world (see B.2.6.4.1), a finding confirmed by other global leaders in SBS-IF management:

"In our "real-life" experience of the weaning process, fluid intake and urine output monitoring could be less strict than in the published trials, allowing more freedom in PS reduction"[87]

"When compared with the STEPS study series, in which enteral independence required >6 months of teduglutide therapy, we have demonstrated more rapid gains in PS reduction and achievement of enteral independence likely as a result of the less strict optimization protocols when compared with the clinical trials."[88]

Secondly, the placebo results in STEPS overestimate the benefit that would be expected for patients receiving standard care. Patients receiving placebo in STEPS reduced their PS requirements which would not be expected in stable patients who are no longer capable of spontaneous intestinal adaption. [redacted]

[redacted]. As a result, it is not appropriate to base assumptions with regards to standard care on the placebo data from STEPS.

Given the efficacy of teduglutide in STEPS, it is perhaps surprising that no significant differences (compared to placebo) in patient quality of life were directly observed. In STEPS, the SBS-QoL tool was used to evaluate patient quality of life. While it was noted in the EPAR that this was the best tool available to assess quality of life for patients with SBS-IF, it was also noted that the tool was not sensitive and may not adequately capture quality of life in a small and highly heterogenous population[66] (see B.2.6.3 for further discussion).

In line with the primary endpoint, patients receiving teduglutide in STEPS were significantly more likely to achieve ≥1 day per week off PS by the end of the trial (week 24) than those receiving placebo; 53.8% (n=21/39) with teduglutide vs 23.1% (n=9/39) for placebo (p=0.005). A reduction in days being 'hooked up' to an IV line is an enormous benefit for patients. It principally represents days during which a patient can feel like they have a normal social, family or personal life, and have improved sleep uninterrupted by equipment alarms or the need to urinate. A reduction of a day per week of PS represents a measurable quality of life gain for patients[63, 65, 113]. Three national expert clinicians at an advisory board unanimously confirmed that patients with SBS-IF consistently seek an extra day free of PS, and that this result from STEPS is highly meaningful[62].

B.2.13.2 With longer-term treatment, the efficacy of teduglutide is enhanced in adults

In STEPS-2, which provided a further 24 months of teduglutide treatment (up to a total of 30 months), patients continued to reduce their PS requirements and a substantial proportion gained total independence from PS (see section B.2.6.2.1).

[redacted]. Compared to 24 weeks of treatment in STEPS, where 54% (n=21/39) of patients achieved at least one day off PS and no one gained independence, STEPS-2 shows that teduglutide can continue to provide substantial clinical benefit with longer-term treatment.

The follow-up data from STEPS-2 can be interpreted with similar confidence to the teduglutide data from STEPS. STEPS-2 included the same population as STEPS (37 of 43 patients who were enrolled in the teduglutide arm of STEPS enrolled in STEPS-2), and the intervention and endpoints were in-line with those specified by the present decision problem. The internal validity of STEPS-2 is somewhat limited by the lack of a comparator arm. However, given that we would not expect patients receiving standard care to be able to reduce their PS, we can attribute the continued PS reductions observed in STEPS-2 to teduglutide treatment.

STEPS-2 also used the same conservative PS weaning algorithm as applied in STEPS, although the timepoints at which reductions could be made were less frequent in STEPS-2 (every ~4 weeks in STEPS and every ~3 months in STEPS-2). This conservative PS weaning algorithm limits the external validity of STEPS, and the problem is therefore more acute with STEPS-2. With real-world teduglutide treatment, clinicians commonly wean patients off PS earlier and more aggressively than was seen in either STEPS or STEPS-2.

Data from STEPS-3 are supplementary to the above conclusions drawn from STEPS-2. STEPS-3 was a small, single-arm trial (n=12) and patients had varying lengths of follow-up, limiting the internal validity of the study and the conclusions that can be drawn about PS volume reductions over up to an additional 12 months treatment (see B.2.6.2.2). However, reductions in PS volume continued [redacted], suggesting that teduglutide offers clinical benefit beyond 2 years of treatment.

B.2.13.3 In a real-world setting, patients receiving teduglutide are able to reduce PS intake to a greater extent than observed in clinical trials, and more patients are able to achieve complete independence from PS

[redacted]

An explanation for the difference in results when considering the proportion of patients achieving clinical response and gaining independence from PS may be found in considering the PS weaning algorithm used in STEPS and STEPS-2. The algorithm for reducing PS volume was[72, 73]:

***Condition**: if urine volumes during the preceding 48 hours were ≥10% above baseline, PS volume could be reduced*

***Magnitude**: PS volume could be reduced by between 10–30% of baseline PS volume at each visit (every ~4 weeks in STEPS and every ~12 weeks in STEPS-2)*

In real-world practice, PS weaning is at the discretion of the treating clinician in consultation with their patient[87, 88].

Following the STEPS algorithm, a clinical response (≥20% reduction from baseline PS volume) could be achieved in a single study visit, assuming the urine volume condition was met. The STEPS algorithm therefore was unlikely to inhibit achieving clinical response, and so it follows that clinical response results seen in STEPS/STEPS-2 are in line with real-world evidence (**Figure 14**). However, to achieve complete independence from PS following the STEPS algorithm took a minimum of four study visits (the fastest possible means of gaining independence from PS required reductions of 30%, 30%, 30% and 10% [all percentages of baseline PS]) with the urine volume condition having to be met on each occasion. This algorithm prohibited patients gaining independence from PS before at least week 12 and is likely to have inhibited achieving PS independence even beyond that

timepoint; correspondingly we see that the proportions of patients weaning completely off PS in STEPS and STEPS-2 are lower than the equivalent proportions achieving independence in the real-world (**Figure 15**).

The real-world studies and PSP data support our assertion that the conservative PS weaning algorithm used in STEPS and STEPS-2 inhibited the observed efficacy of teduglutide, and that the effectiveness of teduglutide is greater in real-world practice where weaning is at the discretion of clinicians in consultation with their patients. The international expert authors of Joly 2020 and Puello 2020 validate this in their conclusions:

"In our "real-life" experience of the weaning process, fluid intake and urine output monitoring could be less strict than in the published trials, allowing more freedom in PS reduction" [87]

"When compared with the STEPS study series, in which enteral independence required >6 months of teduglutide therapy, we have demonstrated more rapid gains in PS reduction and achievement of enteral independence likely as a result of the less strict optimization protocols when compared with the clinical trials." [88]

The better results obtainable in real-world settings were also noted in a recent review of PS weaning in patients with SBS-IF:

"The number of patients fully weaned from [PS] *was much higher in the retrospective studies* [real-world] *(20%–61%) versus phase 3 clinical trials (<15%)."* [114]

This published real-world evidence and PSP data is highly relevant to the decision problem as it illustrates how the intervention of interest (teduglutide 0.05 mg/kg/day) is likely to perform in a primary subpopulation of interest (adults with SBS-IF) in a real-world setting akin to the UK. Indeed, the PSP data represents an unbiased reflection of real-world outcomes for an entire national population of patients treated with teduglutide; furthermore, a population that is a relevant comparator to the UK. The PSP data therefore can be considered to have a very high level of external validity (further confirmed results of the meta-analysis as described above). These results also support our rationale for including the PSP data in our economic model (alongside STEPS/STEPS-2 data). This is because the PSP data are more reflective than STEPS/STEPS-2 of the results that are attainable with teduglutide in the real-world, and therefore the results that could be expected were teduglutide available on the NHS. This approach strikes an appropriate balance between leveraging rigorous randomised controlled trial data and leveraging data with higher external validity (see B.3.3.1 for further discussion).

The main limitation of these real-world data are the lack of comparator arms, the size of the real-world studies (as many as 54 and as few as 4 patients) and the heterogeneity of their patient populations. However, with the SBS-IF population itself being small and heterogenous, considering the body of real-world evidence as a whole somewhat lessens this concern.

In summary, our analyses suggests that the real-world effectiveness of teduglutide is likely to surpass the efficacy observed in clinical trials.

B.2.13.4 Teduglutide has a manageable safety profile and is well-tolerated in adults

Overall, teduglutide was generally well tolerated, with a broadly similar overall adverse event profile in the two phase 3 randomised controlled trials in adults (STEPS and 004, see B.2.10.1, **Table 20**), compared with placebo-treated patients. Furthermore, across the long-term extension studies in adults, the reported safety profile was in line with the initial randomised controlled trials.

The most notable adverse events in adults were related to the gastrointestinal tract (including abdominal pain, constipation, bowel obstruction, stoma complications, and ileus) and biliary problems including cholecystitis. These adverse events would be expected given the mechanism of action of teduglutide and nature of SBS-IF. The risks are well-known and considered manageable as described in the risk management plan.

In a pooled analysis of STEPS, STEPS-2, 004 and 005, the authors concluded that the overall occurrence of adverse events was similar with teduglutide and placebo (in STEPS and 004). They also concluded that the most common adverse events with teduglutide were gastrointestinal in nature, consistent with the underlying disease, it's management, and the intestinotrophic action of teduglutide. The authors noted that gastrointestinal adverse events tended to be more frequent earlier in the course of teduglutide treatment[109].

In reference to the observed safety profile in adults, the CHMP noted: *"effects obviously directly related to the pharmacodynamic action of the compound may lead to a relatively high burden of treatment withdrawals, and serious, and sometimes severe adverse events. Considering the serious and disabling nature of condition with a considerable impact on quality of life and only limited symptomatic treatment options, this adverse event profile is considered acceptable."*[66]

B.2.13.5 In children, teduglutide shows a similar safety profile, and evidence suggests children are more capable than adults of gaining independence from PS with teduglutide

Data for paediatric patients are drawn primarily from the phase 3 trial C14. This study has high external validity: the inclusion and exclusion criteria of C14 define a subpopulation in line with the decision problem of this submission (children with SBS-IF), the study considers the intervention of interest (teduglutide 0.05 mg/kg/day), and no PS weaning algorithm was enforced, reflective of real-world practice. However, for patient safety and ethical reasons, C14 was not designed with to facilitate a robust comparison with standard care, limiting the internal validity of the

study and our ability to draw firm conclusions from these data. A standard care cohort does feature, however entry in to this cohort was by patient (/family) choice rather than by randomisation, and few patients/families (n=11) opted to receive standard care. The number of patients receiving teduglutide 0.05 mg/kg/day was also small (n=26), in part because C14 also investigated a second dose of teduglutide (0.025 mg/kg/day). No formal statistical analyses were planned as limited patient enrolment was expected to lead to a small patient population size.

Bearing in mind these limitations, C14 did show clinically meaningful reductions in days per week of PS (mean reduction -1.3 days per week) and PS volume (mean reduction of -42%) over the 24-week study duration for children receiving the licensed dose of teduglutide (see full results in B.2.6.5.1). Three patients receiving the licensed dose of teduglutide in C14 (12%) completely weaned off PS during the 24-week study. It is particularly notable that these results are all superior to equivalent results from the 24-week STEPS study in adults with SBS-IF, where teduglutide patients achieved a mean reduction in days per week of PS of [redacted], a mean reduction in PS volume of -32% and no patients gained independence from PS. This likely reflects children's enhanced capacity for intestinal adaptation, but also demonstrates the particular value of teduglutide to this patient population. A second phase 3 trial in children, C13, provides evidence corroborating the results of C14.

While the data from C13 and C14 have limitations, the CHMP stated:

"*…the durability and further course of the beneficial effects of teduglutide in paediatric patients comprised by the indication can be reasonably assumed from the effect seen in adults based on the totality of data in this rare disease*."[115]

As in adults, better results for teduglutide in children have been seen in the real-world[104]. Of particular note, 7 of 16 (44%) patients gained independence within 24 weeks, rising to 11 of 16 (69%) at one year. As previously stated, gaining independence from PS is life changing for any patient. For children with SBS-IF, this effect is greater: gaining independence from PS gives a child the opportunity to properly grow and develop, both physically and psychologically, without the debilitating constraint of being chained to an IV line overnight.

When the data from C14 and C13 were pooled alongside interim results from their extension studies (SHP633-304 and SHP633-303, respectively) for the purpose of safety evaluation, the authors noted that teduglutide was well tolerated in this population. Compared to results in adults, upper respiratory adverse events (such as cough, upper respiratory tract infection and nasopharyngitis), pyrexia, vomiting and catheter complications were more common in children. The authors concluded that:

"The spectrum of adverse events was also similar to that reported in a recent integrated analysis of safety data from the adult clinical studies of teduglutide"[110], referencing Pape *et al.* 2020[109] (discussed in B.2.13.4).

Based on these results we believe that, as in adults, teduglutide is well-tolerated in children. Teduglutide also appears to be more effective in children than in adults, and allows children a real chance to gain independence from PS at a critical stage in their lives.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

Several systematic literature reviews (SLRs) were performed to identify relevant cost-effectiveness studies. These were performed in line with NICE guidance in the methods of technology appraisal, using a pre-prepared search strategy and multiple reviewers assessing results (detailed in Appendix G). For the present submission, an economic SLR, covering economic and healthcare resource use data for adults and children with SBS-IF, was performed on 21st May 2021. Published cost effectiveness studies are shown in **Table 22**.

Two of the identified studies, Raghu *et al.* 2020a and the 2016 CADTH recommendation for teduglutide, both reported cost per QALY gained for teduglutide compared to standard care for adult patients with SBS-IF, in line with the present decision problem and NICE reference case. However, the populations of these studies and costs used in the models are not in line with the NICE reference case. Therefore, a *de novo* economic model was developed to assess the cost-effectiveness of teduglutide compared to the current standard care from the perspective of the UK NHS, in line with the criteria outlined in the NICE reference case.

Table 22. Summary of published cost-effectiveness studies

Study	Summary of model	Patient population	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Roskott *et al.* 2015	Cohort-based discrete event model Model compared survival for PS vs intestinal transplant over 10 years	Adults with type 3 intestinal failure (not SBS-specific)	Not reported – reported life-year gains only	PS: €13,276 at initiation and €77,652 annually Intestinal transplant: ~€73,000 at initiation and €13,000 annually	Not reported – reported as cost per life-year gained
Midliaccio-Walle *et al.* 2006	Discrete event simulation model Model compared costs for PS vs somatropin (+PS) over 2 years	Patients with SBS-IF	Not reported	PS: $251,033 over 2 years Somatropin: $165,559 over 2 years (USD, 2004)	Not reported
CADTH 2016 (Canadian Drug Expert Committee Final Recommendation: Teduglutide)	Markov state-transition model with 8 health states (PS0 to PS7 + dead) Model compared incremental cost-utility ratio for teduglutide (+PS) vs PS over a 40-year time horizon	Adults with SBS-IF	Teduglutide: 3.82 years PS: 2.35 years	Teduglutide: $3,584,110.57 PS: $1,227,500.40 (CAD, 2019)	$1,600,145 per QALY gained
Raghu *et al.* 2020a	Markov model with 8 health states (PS0 to PS7 + dead)	Adults with SBS-IF were simulated to start at age 40 years	No treatment: 6.7675 years	No treatment: $660,894	ICER (cost/QALY)

	Model compared teduglutide to no treatment over a lifetime time horizon	and requiring 7 days per week of PS	Teduglutide: 7.7665 years	Teduglutide: $1,609,853 (USD, 2018)	TED vs no treatment: $949,910
Raghu *et al*. 2020b	Markov model with 4 health states (PS7, intestinal transplant, post-transplant, PS0 + dead) Model compared 4 permutations of teduglutide/no teduglutide and transplant/no transplant	Children with SBS-IF were simulated to start at age 5 years and requiring 7 days per week of PS	*Incremental QALYs* • TED + transplant vs no TED + transplant (reference strategy): 8.95 • TED + no transplant vs TED + transplant: 0.17	• No TED + transplant (reference strategy): $439,728 • TED + transplant: $1,553,225 • TED + no transplant: $1,735,213 (USD, 2018)	• TED + transplant vs no TED + transplant (reference strategy): $124,353 • TED + no transplant vs TED + transplant: $1,094,249 • No TED + no transplant vs no TED + transplant (reference strategy): dominated by reference strategy

Abbreviations: CAD, Canadian dollar; ICER, incremental cost-effectiveness ratio; PS, parenteral support; PS0, 0 days per week of PS; PS7, 7 days per week of PS; QALY, quality-adjusted life year; SBS, short bowel syndrome; SBS-IF, short bowel syndrome with type 3 intestinal failure; TED, teduglutide; USD, United States Dollar

Sources: Studies identified by economic SLR[116-120]

B.3.2 Economic analysis

A *de novo* economic model was constructed to assess the economic value of teduglutide + parenteral support (PS) compared to standard care alone in the population for which teduglutide is licensed (patients aged 1 year and above with SBS-IF who are stable following a period of intestinal adaptation after surgery). The economic analysis was developed to align with the NICE reference case by conducting the analysis from a UK NHS perspective with costs and benefits discounted at an annual rate of 3.5%. The design of the model is described in the sections below.

B.3.2.1 Patient population

The analyses performed using the economic model aim to assess the cost-effectiveness of teduglutide in the licensed population, as outlined in its marketing authorisation[1]: patients aged 1 year and above with SBS-IF who are stable following a period of intestinal adaptation after surgery.

Two separate base case analyses are presented to demonstrate the cost-effectiveness of teduglutide in the adult (aged ≥18 years) and paediatric (aged 1–17 years) populations, respectively. This approach is appropriate as SBS-IF is a disease with different aetiologies in children and adults, and the potential for intestinal adaptation is greater in children (see B.1.3.3).

There is overlap in terms of the model inputs in the adult and paediatric base case analyses. Mainly, the primary data sources used to inform the effectiveness of teduglutide are the same in both. Both analyses use:

- The STEPS clinical trial programme, which recruited adults with SBS-IF on PS ≥3 days per week (see B.2.3.1)
- Patient Support Programme data from Australia, which include adults with SBS-IF (see B.2.3.3)

The two base cases analyses differ with respect to five inputs:

- **Starting age**: 50 years old in adults, 6 years old in children
- **Time horizon**: 50 years in adults, 94 years in children
- **Paediatric-specific survival**: see B.3.3.4.2
- **Paediatric-specific hospital costs** for specialised visits and line sepsis: see B.3.5.2

Despite these input changes, made to better reflect the paediatric population, the results of the paediatric base case analysis are still likely to underestimate the cost-effectiveness of teduglutide in this population. There are several reasons for this:

- Data from the paediatric clinical trials suggest that children are able to achieve greater reductions in PS when receiving teduglutide than adults (see B.2.6.5), likely because children have an increased potential for intestinal adaptation.

However, the paediatric clinical trial data is limited by small patient numbers and non-continuous treatment in the follow-on studies. Therefore, our paediatric base case analysis conservatively assumes the effectiveness of teduglutide in children is the same as in adults

- Our model assumes that PS-related complications are less frequent when patients reduce PS (following teduglutide treatment), and therefore, that teduglutide generates cost savings from the reduced cost of treating complications (see B.3.3.5). Of the complications modelled, catheter-related infections and liver disease are known to be even more common in children with SBS-IF than adults[35, 40], however, there are little data quantifying the rates of these complications in children. Therefore, our paediatric base case analysis conservatively assumes the same rates of complications in children as in adults
- Children with a body weight less than 20 kg can use the smaller 1.25 mg vial of teduglutide[1], which has a [redacted] lower cost than the 5 mg vial. By assuming all children weigh ≥20 kg[121], our paediatric base case overestimates treatment costs, especially as many children with SBS-IF are born premature and have a lower weight then age-matched 'healthy' counterparts

B.3.2.2 Model structure

The *de novo* economic model was developed using a Markov structure, with health states defined by the number of days per week that patients are required to receive parenteral support (PS), as well as whether patients are alive or dead. This model structure was selected because the number of days per week of PS is the most relevant outcome for patients with SBS-IF. This was confirmed by national leading clinical experts in SBS-IF at an advisory board, who stated that reducing PS by a single day per week is a meaningful endpoint for patients and an important treatment goal. This is supported by the teduglutide EPAR, which states:

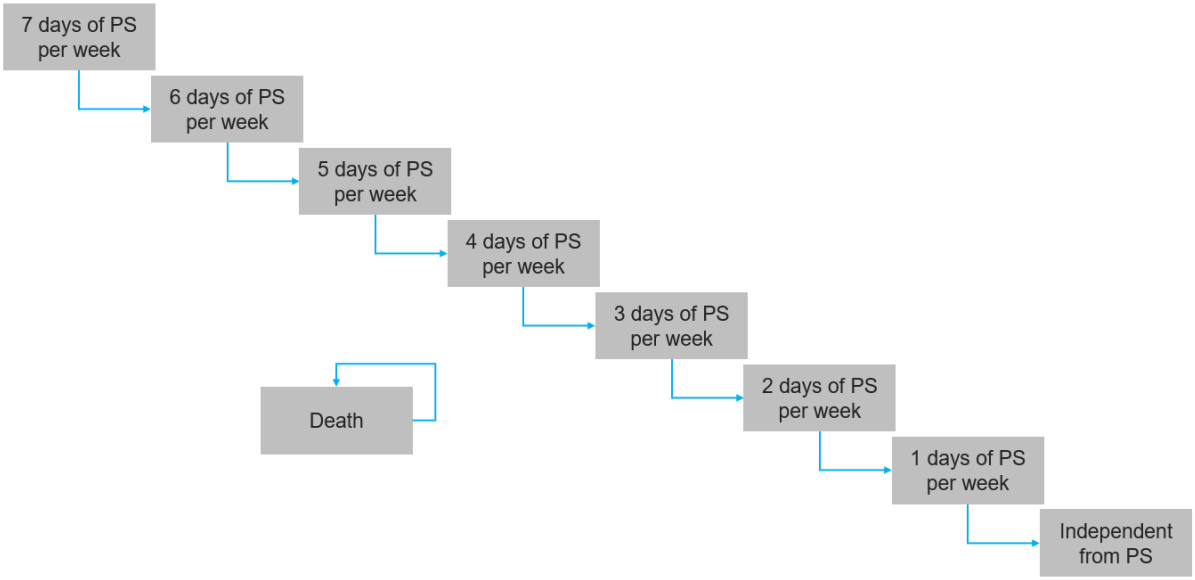
"One or more days without having to be chained to an i.v. line constitutes a real benefit for the patient."[66]

The importance of reducing days per week of PS was also demonstrated using a quality of life instrument designed specifically to capture the effect of PS on everyday life (the PNIQ)[57], reduction in days per week of PS was found to be statistically significantly correlated with improvement in quality of life among patients with type 3 intestinal failure[63]. Similarly, a reduction of a single day of PS per week was associated with a utility gain of 0.04–0.10 in two vignette studies[64, 65].

Clinical trials of teduglutide have typically used a 20% reduction from baseline in volumes of PS as their primary endpoint[72, 76]. This endpoint was agreed with regulators as a 20% PS volume reduction equates to one day off PS per week for most SBS-IF patients, who are typically receiving ≥5 days of PS per week. The relationship between PS volume and patient quality of life is unclear, and none of the studies identified by our quality of life SLR (see B.3.4.2) reported utility values by volume of PS received, hence our model focuses on patients' number of days of PS per week alone.

As each day off PS is meaningful for patients in terms of quality of life improvement, our model has nine health states: one for 0 to 7 days of PS per week and one for death (**Figure 21**).

Figure 21 Economic model structure



Abbreviations: PS, parenteral support

For the teduglutide treatment group in the model, these health-states are separated into on-treatment and off-treatment patient flows to track how many patients are on treatment in each health state over time. This allows the model to accurately account for lost health benefits following treatment discontinuation and to apply treatment costs appropriately.

Patients can start in any of the PS health states; however, this is dependent on the data source and some health states may not be occupied initially. For example, no participants in the STEPS trials started with a PS requirement of less than 3 days per week. From the baseline health states, patients can transition by at most one-step change (reducing only) in each 4-weekly model cycle. We chose this approach to simplify our model, however clinicians in attendance at an advisory board confirmed that allowing patients to reduce PS by at most one day a week in each 4 week cycle was conservative, and that patients may reduce their PS by more than 1 day per week over a 4 week period in the real-world[62].

Key features of the present economic analysis compared to previous appraisals are shown in **Table 23**

Table 23: Key features of the economic analysis compared to previous appraisals

	Previous appraisals	Current appraisal	
Factor	**TA690** (previous appraisal of teduglutide)	**Chosen values**	**Justification**
Starting age	50 years	50 years (adult base case) 6 years (paediatric base case)	Average age of the STEPS trial population,[72] for the adult base case and the C14 trial[79] for the paediatric base case.
Time horizon	40 years	50 years (adult base case) 94 years (Paediatric base case	Assumed to represent a lifetime horizon given an average adult patient age of ~50 years old,[72, 76] and an average age in the paediatric population of ~6 years[79].
Proportion of female patients	53.5%	53.5%	Based on the STEPS trial population.
Treatment waning effect?	No	No	There is no evidence to suggest that the treatment effect of teduglutide wanes over time. As discussed in section B.2.6.2, teduglutide showed continued efficacy with up to 42 months of treatment, underlined by two patients weaning off PS after 126 and 130 weeks of treatment in STEPS-3[75]. No neutralising antibodies to teduglutide were observed in 88 patients treated for up to 30 months of treatment in STEPS-2[73]. Furthermore, as teduglutide allows patients to increase enteral nutrition, and enteral nutrition further promotes intestinal adaptation, there is reason to believe the effectiveness of teduglutide may increase over time.
Source of utilities	Ballinger *et al.* 2018	Ballinger *et al*. 2018	Utilities from Ballinger *et al.* 2018[113] show an improvement in quality of life with reduced days on PS. Clinicians at an advisory board stated that this finding is in-line with their clinical experience. Data from STEPS showed that quality of life peaked at 4 days per week of PS. This is nonsensical, and these data are not appropriate to use unless we believe patients want to increase their PS from 1 day per week to 4 days per week. Furthermore, quality of life data from STEPS was captured using tools that were not sensitive enough to detect quality of life

			improvements in this small heterogenous patient population (discussed more in B.3.4.1 and B.3.4.2).
Source of costs	NHS reference costs	NHS reference costs	As per the NICE methods guide[112]

B.3.2.3 Intervention technology and comparators

B.3.2.3.1 Intervention (teduglutide)

Teduglutide is indicated for the treatment of patients aged 1 year and above with SBS-IF who are stable following a period of intestinal adaptation after surgery.

Teduglutide is the first (and currently only) EMA-licensed pharmacological therapy that has demonstrated an ability to improve the absorptive capacity of the intestine, enhancing intestinal adaptation, increasing nutrient absorption and enabling patients to reduce their reliance on PS.

Teduglutide is administered by subcutaneous injection once daily at alternating sites between 1 of the 4 quadrants of the abdomen. The licensed dose is 0.05 mg/kg/day. Teduglutide is given to patients with SBS-IF in addition to 'standard care', which includes PS, antimotility and antisecretory agents, fluid restriction and dietary optimisation.

B.3.2.3.2 Comparator (standard care)

The comparator for teduglutide in adults and children is standard care, which includes PS, antimotility and antisecretory agents, fluid restriction and dietary optimisation. Standard care in SBS-IF is a critical life-sustaining therapy, that is, patients with SBS-IF would die of dehydration or malnutrition without PS. However the current standard care provides only symptomatic relief and does not treat the underlying disease. PS provides patients with sufficient nutrients and fluids, while the symptom-relieving medication aims to reduce gastric acid secretion (e.g. H2 receptor antagonists, proton pump inhibitors), motility and diarrhoea (e.g. loperamide, diphenoxylate) and bacterial overgrowth (e.g. antibiotics, probiotics). Standard care is an appropriate comparator to teduglutide as there are no other widely-used treatment options for patients with SBS-IF.

Surgical interventions, specifically bowel lengthening surgery and intestinal transplantation, may be considered for a minority of patients with SBS-IF. ESPEN guidelines recommend bowel lengthening procedures are only performed in 'selected' patients[5], however due to the risk of anastomotic breakdown, stricture and vascular injury associated with these procedures, they are rarely performed in practice[16]. Intestinal transplant is only recommended in patients who cannot be managed with PS owing to the lower survival outcomes associated with the procedure[33, 71]. The rarity of intestinal lengthening procedures and different position in the treatment pathway of intestinal transplant means these surgical options are not appropriate comparators for the population of SBS-IF patients considered in this appraisal of teduglutide.

B.3.3 Clinical parameters and variables

B.3.3.1 Parenteral support data

The key measure of effectiveness used to inform the economic model is the number of days of PS required by patients per week.

For the comparator (standard care) our model maintains patients on the same stable level of PS over their lifetime. This is based on the label for teduglutide, which states that patients should be stable following a period of intestinal adaptation[1]. There is no biological reason why patients who are stable on PS should experience a change in their PS needs, and there are no plausible data on which to model any change in PS for standard care.

It could be argued that the standard care arm should include a treatment effect in line with the placebo response seen in the STEPS study. The reasons this is not appropriate are discussed extensively in section B.2.6.1.4, but in summary, we believe that the placebo response is an artefact of the conditions of the STEPS study, likely driven by natural fluctuations in patients' urine volume (which, by the STEPS algorithm, then allowed PS reductions). There is also evidence to suggest that patients in the placebo arm risked dehydration and weight loss due to their PS weaning. [redacted]. In addition, section B.2.6.4/B.2.8 illustrates that the STEPS study is likely to underestimate the benefit of teduglutide relative to that seen in the real-world. As such, a comparison of teduglutide and standard care based on utilising teduglutide vs placebo data from STEPS alone would not be appropriate. To make our model more reflective of real world clinical practice, we have therefore not modelled a treatment effect for standard care. It would also not be appropriate to 'subtract' the placebo response from the teduglutide arm because the PS weaning that occurred in the teduglutide arm was appropriate, associated with healthy weight gain and arguably (based on patients' urine output and the comparison to real-world evidence) could have gone further.

For patients treated with teduglutide, reductions in days per week of PS over time were estimated using a variety of data sources. Given the rarity of the disease, it was considered important to include all available patient-level data that showed strong reliability and generalisability to clinical practice (internal and external validity). Our model therefore includes data from:

- The STEPS clinical programme (STEPS, STEPS-2)
- Takeda's Patient Support Programme (PSP) in Australia

The adult and paediatric base case analyses presented utilise data pooled from STEPS and the PSP. A scenario is provided for each base case that only uses data from the STEPS clinical trial programme.

B.3.3.1.1 Considerations with the STEPS data

The main body of data from the programme of STEPS trials is provided by STEPS and STEPS-2 (STEPS-3, which is not included in the model, provides additional data for a small number of patients in the US only, see B.2.6.2.2). A key consideration in

using the data from these trials to inform the economic model is that STEPS-2 consists of three different groups of patients:

- The TED-TED cohort, who were previously treated with teduglutide in STEPS and continued teduglutide in STEPS-2
- The PBO-TED cohort, who received placebo in STEPS, and initiated teduglutide at the start of the STEPS-2
- The NT-TED cohort, who were screened but not treated in STEPS, and initiated teduglutide at the start of the STEPS-2

As discussed in B.2.6.2.1, the external validity of the data from STEPS-2 is limited by the infrequent PS weaning schedule used (compared to STEPS, where PS weaning was more frequent). Consequently, patients in STEPS-2, particularly in the PBO-TED and NT-TED cohorts (who did not benefit from the more frequent weaning protocol in STEPS when initiating teduglutide) are likely to have required more time to achieve their maximum potential PS reduction. This point was confirmed by clinicians at an advisory board: it was stated that the PS weaning algorithm in STEPS is 'restrictive' relative to real-world practice, and the less frequent weaning in STEPS-2 means that weaning is even slower[62].

The most reliable data from STEPS-2, therefore, come from the TED-TED group. These patients were able to receive the more frequent PS reductions allowed in the STEPS trial at the point of initiating teduglutide; they have the longest period of follow-up on teduglutide (30 months); and the treatment pattern they received (continuous teduglutide) is the most relevant for the present decision problem. Overall, of the clinical trial data, the data from the TED-TED cohort are the most clinically relevant and clinicians at an advisory board confirmed this[62].

B.3.3.1.2 Considerations with additional data sources

In addition to data from the STEPS clinical programme, Takeda has access to patient-level real-world data collected as part of a Patient Support Programme (PSP) in Australia (PSPs are running in other countries but we do not have patients' consent to use their data for reimbursement purposes). Due to similarities in the SBS-IF patient population in Australia and England and comparable care pathways within the respective healthcare systems, real-world data from Australian patients are considered relevant to England. Furthermore, compared with data from STEPS, this PSP data is likely to be more reflective of how teduglutide would impact patient outcomes in UK clinical practice as it is drawn from the real-world. Clinical effectiveness data from the PSP are presented in B.2.6.4.2.

A number of published real-world studies were identified through the clinical SLR

(see B.2.2.2,

Table 7 for a list, and B.2.6.4.1 for their clinical results). We have not used these data in our model as while outcomes based on reductions in PS volume were widely reported, outcomes based on reductions in days per week of PS were not, and we do not have access to the individual patient-level data to calculate the impact on the number of PS days per week manually. [redacted], combining data from the STEPS programme and the PSP therefore strikes an appropriate balance between leveraging rigorous randomised controlled trial data and data with higher external validity.

A description of how data from STEPS and the PSP are incorporated into the economic model is given in B.3.3.2.

B.3.3.2 Estimation of transition probabilities

The base case analysis in the economic model uses data from the STEPS and STEPS-2 trials pooled with data from the PSP. Given the limitations of the STEPS and STEPS-2 trials, specifically the conservative PS weaning algorithm used, the model is likely to provide a conservative estimate of the cost-effectiveness of teduglutide. To reiterate what is described in more detail elsewhere (see B.2.6.1.3), the PS weaning algorithm used in STEPS and STEPS-2 reduced the speed and magnitude at which investigators could reduce patient's PS volumes. In the real-world, clinicians typically wean patients off PS earlier and with greater reductions in volume.

Data from STEPS were captured at week 2, week 4 and then every 4 weeks until week 24. Data from STEPS-2 (where week 0 = week 24 of STEPS) were captured at week 2, month 1, month 2, month 3 and then every three months until month 24. The real-world PSP data is reported at varying intervals and frequency per patient. To estimate reductions in the number of days per week of PS for people receiving teduglutide in the economic model, these data were used to estimate a 4-weekly transition matrix to align with the cycle length of the model. A 4-weekly matrix is appropriate as it is short enough to capture key changes ([redacted]) but not too short as to become computationally burdensome.

Reductions in PS days per week over time in STEPS and STEPS-2 were not linear; larger reductions were seen earlier in treatment (see B.2.6.2.1), so using a fixed set of transition probabilities over time would not result in plausible model outputs. Transition probabilities were therefore estimated separately in 6 month intervals. This aligns well with clinical assessment periods in the real-world and proposed in the SmPC with regard to the evaluation of continuation of treatment *("treatment effect should be evaluated after 6 months…if no overall improvement is achieved after 12 months, the need for continued treatment should be reconsidered"*[1]).

Transition probabilities were estimated using *R* software by initially constructing a square matrix with 7 variable parameters representing the possible single step transitions in each model cycle, with the probability of remaining in the same state

being one minus this probability (see B.3.2.2 for an overview of the model structure). This is depicted in the matrix below, with the probability p_i representing the probability of reducing from i PS days per week to $i-1$ PS days per week.

$$\begin{bmatrix} 1 & - & - & - & - & - & - & - \\ p_1 & 1-p_1 & - & - & - & - & - & - \\ - & p_2 & 1-p_2 & - & - & - & - & - \\ - & - & p_3 & 1-p_3 & - & - & - & - \\ - & - & - & p_4 & 1-p_4 & - & - & - \\ - & - & - & - & p_5 & 1-p_5 & - & - \\ - & - & - & - & - & p_6 & 1-p_6 & - \\ - & - & - & - & - & - & p_7 & 1-p_7 \end{bmatrix}$$

The probabilities in this matrix were estimated using the *Optim* package in *R,* which finds the optimum value of a specified function as inputs are varied across all possible values. In this case, the function specified was 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). The inputs varied are the values p_1 to p_7, with starting values varied between 5%, 10% and 20% to ensure the optimum model fit was achieved.

The optimisation procedure was set to minimisation to estimate the optimum prediction of the outcomes in the model with the least squared error between predictions and outcomes. This procedure was performed separately for each 6 month interval.

Importantly, it should be noted that these transitions only apply to patients in the model while still on teduglutide treatment. For this reason, the initial patient vector used for each 6 month interval is defined by the number of patients in each health state that are still on treatment at that time point. As treatment discontinuation is modelled separately (see B.3.3.3.1), the endpoint vector of each 6 month period is defined using the same denominator as the starting vector. Reducing the denominator in line with the number of patients on treatment at the end of the 6 month interval would introduce a degree of double-counting, as it would over inflate the magnitude of the benefits achieved for those remaining on treatment in the model. For any patients who did discontinue in any of the 6 month intervals, the last health state they received treatment in was carried forward to the end of the 6 month period to ensure that they were appropriately discontinued from the correct health state in the economic model.

To account for the irregular follow-up in the PSP data, the last value recorded was carried forward to estimate the number of people in each state at each 6-month interval. This represents a potentially conservative approach as patients may have been able to achieve further benefits within the 6 month intervals that have not been captured. As teduglutide only recently became available in Australia, there is limited follow-up for a large number of patients in the PSP cohort. We used data to inform the first 12 months of transitions only, [redacted]. STEPS-2 data alone is used afterwards. We believe it is appropriate to continue informing transitions with

STEPS-2 data beyond 12 months as STEPS-2 data showed patients gain continued improvement in days per week of PS beyond 12 months (see B.2.6.2).

In summary, the base case analyses use the pooled STEPS/STEPS-2/PSP data to inform transitions up to 12 months, and STEPS-2 data to inform transition from 12 to 30 months.

Transition probabilities are no longer applied after 30 months of treatment. Beyond 30 months, we have little clinical data with which to inform transitions. The STEPS-3, extension study to STEPS-2, providing up to 42 months of follow-up data, demonstrates that patients may continue to derive benefit from teduglutide (see B.2.6.2.2) but only 5 patients from the TED-TED cohort of STEPS-2 were enrolled. As such, our model is potentially conservative in assuming no further treatment benefit after 30 months.

Transition probabilities are provided in Appendix M.

B.3.3.3 Time on treatment

To model the proportion of patients receiving teduglutide treatment at any given time in the model, a combination of observed discontinuations from the clinical trial/PSP data and a treatment stopping rule were used to ensure that the model reflects treatment usage as expected in real-world clinical practice.

B.3.3.3.1 Treatment discontinuations

The first step in the analysis was to fit survival curves to the time on treatment data using the *flexsurv* package of *R.* For the base case analysis, all discontinuation events in STEPS (patients treated with teduglutide only), STEPS-2 and in the PSP were included in the analysis, with censoring applied at the time patients completed the study/PSP or at their maximum follow-up time for patients still receiving teduglutide in the PSPs. The Kaplan-Meier (KM) plot in **Figure 22**, shows the proportion of patients on treatment in these data sources combined.

Using the data shown in **Figure 22**, standard parametric models (exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma) were fitted, with the best fitting models chosen based on assessment of Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC), as well as the plausibility of the extrapolations. The curves fitted to these data are depicted in **Figure 23**, and the corresponding AIC and BIC statistics are given in **Table 24**.

Figure 22 Kaplan-Meier showing the proportion of patients receiving treatment over time in STEPS, STEPS-2 and the PSP data combined

Figure 23 Parametric survival curves for time on treatment observed in STEPS, STEPS-2 and PSP data combined

[redacted]

Table 24 Goodness-of-fit statistics for time on treatment for STEPS, STEPS-2 and PSP data combined

Parametric model	AIC	BIC
Exponential	162.14	164.39
Weibull	160.68	165.18
Gompertz	162.09	166.59
Log-normal	160.87	165.36
Log-logistic	160.71	165.20
Generalised gamma	162.67	169.42
Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; PSP, patient support programme		

The curve with the best statistical fit based on the AIC statistics, was the Weibull, although this was closely followed by the log-normal and log-logistic curves. The BIC values showed a similar picture with the exception of the exponential curve, which had the lowest BIC despite showing a poor visual fit. This is likely due to the larger penalty that the BIC gives to functions with a greater number of parameters, hence favouring the more simplistic single-parameter exponential model.

The poorest fitting curve statistically was the generalised gamma based on both AIC and BIC. However, upon visual inspection of the curves in **Figure 23**, the exponential curve stands out as the poorest fitting model, clearly not tracking the data well.

In terms of the plausibility of the extrapolations, the Gompertz has a plateau following the trial period, which implies that no further discontinuation events occur. This is not clinically plausible and, therefore, this curve was discounted as an option for the base case analysis. Due to the poor fit of the exponential model, the extrapolation is unlikely to be reliable either and, therefore, this model was also discounted. The remaining curves have some differentiation between the extrapolations; however, given the lack of long term data with teduglutide to inform long-term extrapolations (maximum 42 months in clinical trials[75], and little real-world evidence beyond 36 months[88]), it is difficult to definitively choose between the remaining curves. Therefore, for the base case analysis, the best statistical fitting model, the Weibull, was chosen. The results of the second and third best fitting models (log-normal and log-logistic) are provided in scenario analyses in B.3.8.3.

The best fitting treatment discontinuation curve was used to determine the proportion of patients receiving teduglutide at any time in the model; however, another key aspect of discontinuation for the model concerns the health states from which people discontinue, the health states they move to following discontinuation, and how quickly they move to this health state. This is discussed further in B.3.3.3.3.

B.3.3.3.2 Treatment stopping rule

A limitation of relying partly on the STEPS and STEPS-2 data to inform discontinuation is that some patients who did not benefit from treatment continued to receive teduglutide for long periods, in some cases up to 30 months. This is an artefact of the clinical trial environment and would not occur in real-world clinical practice.

The SmPC suggests that, in adults, outcomes should be evaluated at 6 months and 12 months, and if no treatment benefit is achieved by 12 months, the continuation of treatment should be reconsidered. However, the SmPC does not define the magnitude of treatment benefit that should be considered clinically meaningful at these timepoints[1].

The British Intestinal Failure Alliance (BIFA) 2018 position statement states that the aims of treatment with a peptide growth factor should be *"to stop or achieve more than 2 nights off/week of PS"*, and that treatment should be stopped *"if the treatment goals of reducing PS are not achieved after 24 weeks"*[122].

Three UK clinicians in attendance at an advisory board unanimously agreed that achieving a reduction in PS of one day per week was a clinically meaningful outcome for patients. They acknowledged that if a day off per week had not been achieved after 6 months of treatment, they may not actively encourage patients to continue treatment (depending on whether PS volume reductions had occurred or not), but would leave the decision up to the patient. If a day off per week had not been achieved after 12 months, they would stop treatment[62].

It is worth noting there is evidence that patients continue to benefit from teduglutide beyond 6 months of treatment. Results from STEPS-2 (see B.2.6.2.1) showed that patients continued to reduce days per week of PS throughout 30 months of treatment[73]. The teduglutide SmPC also states, in a discussion about evaluating treatment effect at 6 months, that *"limited data from clinical studies have shown that some patients may take longer to respond to treatment"*[1].

Based on guidance in the SmPC, from BIFA and from our advisory board, we have opted for our base case to include a stopping rule as follows: at 12 months any patients who have not achieved a reduction of at least one day off PS per week compared to baseline is discontinued.

To apply this in the model, the proportion of patients who achieved no reduction in days per week after 12 months were calculated relative to the number of patients remaining on treatment in each health state. The proportion of patients discontinued from each health state by this rule are given in **Table 25**. Note, although the PSP provides data for only 12 months, **Table 25** does consider patients in the PSP programme who did not achieve a day per week reduction within those 12 months.

Table 25 Proportion of patients discontinued from each health state by the stopping rule at 12 months

[redacted]								
[redacted]								
[redacted]								

In our model, at the 12 month timepoint, these proportions were removed from the on-treatment part of the patient flow and moved to the off-treatment part. These patients remain in the same PS health state, as no benefit was achieved in these patients while on treatment, so no benefit needs to be removed following discontinuation.

The rate of discontinuation beyond the 12 month stopping rule is discussed in the next section.

B.3.3.3.3 Distribution of discontinued patients across health states

A key aspect of the treatment discontinuation modelling is ensuring that any treatment benefits achieved prior to discontinuation are appropriately accounted for following the discontinuation of teduglutide treatment. The model conservatively assumes that all patients who discontinue teduglutide revert back to their baseline health state immediately after stopping teduglutide (of note, the SmPC states that *"discontinuation of treatment with teduglutide should be managed carefully to avoid dehydration"*[1]). At a recent advisory board, clinicians stated that after discontinuing teduglutide, they would expect patients to return to their baseline PS needs over a period of 2–8 weeks[62]. Additionally, while there are little data investigating PS needs post-teduglutide, one study reported that only 25% of teduglutide non-responders and 48% of teduglutide responders increased PS within 12 months post-discontinuation of teduglutide (responders were defined as those with a ≥20% reduction in PS from baseline)[123]. Our model is therefore conservative in its assumptions regarding reversion to baseline.

To apply this in the base case analysis of the model, patients who discontinued teduglutide across the STEPS trials and PSP were assessed to estimate the proportion of patients discontinuing from each health state. The baseline health states for this group of patients were also analysed to estimate the proportion of patients expected to be in each health state after discontinuation of treatment.

Before the stopping rule, the model assumes that discontinuations occur from the health states as described in **Table 26** below. After the stopping rule is applied it would be implausible to continue discontinuing patients from these health states. For

example, at 12 months all patients still on 7 days per week of PS are discontinued by the stopping rule, so no further discontinuations can occur from that health state.

Beyond this time point, the data were re-analysed to assess the distribution of patients across health states for those who discontinue treatment after 12 months but who would not be captured by the 12 month stopping rule (i.e., those who achieved a reduction in PS within 12 months but discontinued teduglutide after 12 months). The baseline health states of these patients were also assessed to redistribute these patients across the health states appropriately following discontinuation.

The distribution of patients discontinued from each health state *at the point of discontinuation* pre-12 month stopping rule is given in **Table 26**, and the distribution of patients discontinued from each health state *at the point of discontinuation* post-12 month stopping rule **Table 27**.

Table 26 Distribution of discontinued patients across health states before and after discontinuation of teduglutide before the 12 month stopping rule

[redacted]

Table 27 Distribution of discontinued patients across health states before and after discontinuation of teduglutide after the 12 month stopping rule

[redacted]

[redacted]

This approach introduces some uncertainty given that the distribution of those discontinued post 12 months is informed by data from only 3 patients. However, the alternative would be to assume the distributions do not change post 12 months, implying no further discontinuations occur and this is clinically implausible. For completeness, a scenario that assumes no further discontinuation beyond the 12-month stopping rule is provided in B.3.8.3; however, this should be considered with caution as it does not represent a clinically relevant scenario. It may, however, provide some reassurance as a maximum upper bound of the impact of the uncertainty.

B.3.3.4 Survival

B.3.3.4.1 Adult survival

To assess the cost-effectiveness of a long-term treatment such as teduglutide, it is important to accurately estimate the proportion of patients alive at any time over the life time horizon of the model. Data from the STEPS programme, with a maximum of 42 months of follow-up, provide insufficient data to evaluate life time survival: only 3 deaths occurred during STEPS and STEPS-2. This does not allow us to model long term survival in patients with SBS-IF as a whole, and certainly does not allow any consideration of a potential treatment effect on mortality.

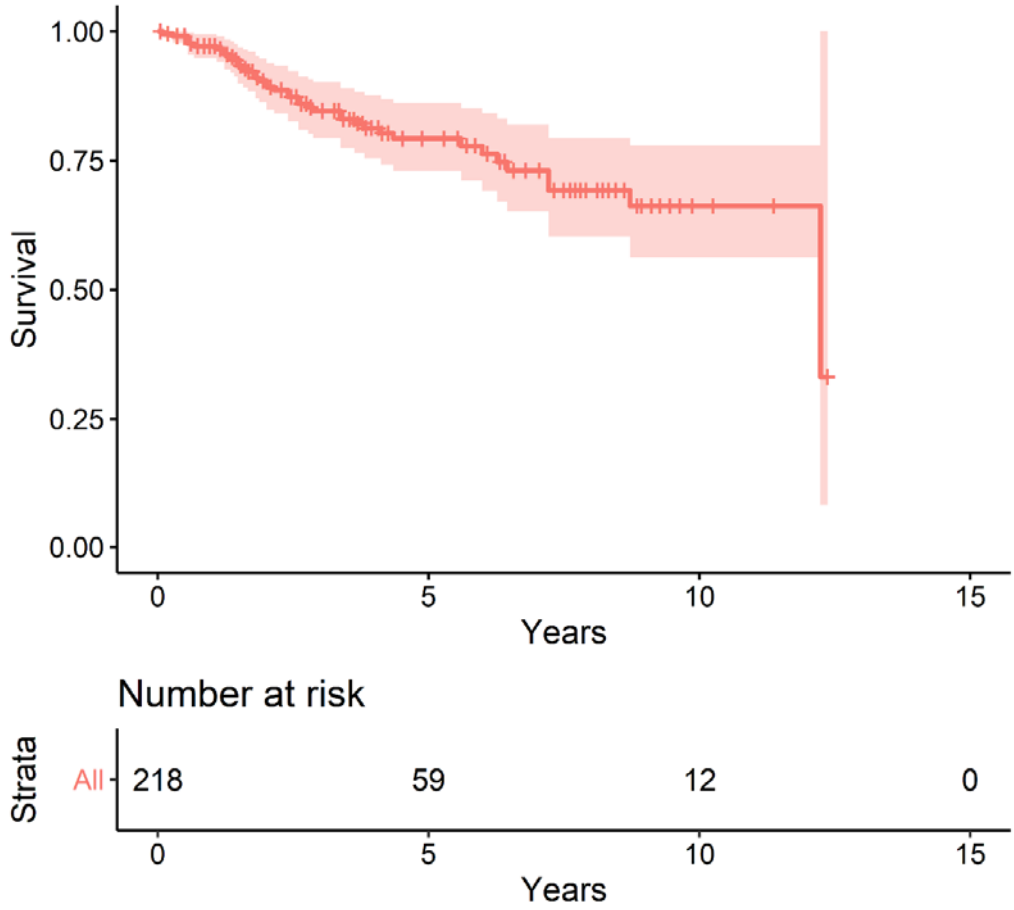
Alongside the lack of data from the trials, there is in general a lack of data examining the survival impact of PS on patients with SBS-IF. The relationship between PS consumption and survival is in general not clear, in part because mortality from the underlying SBS-IF is hard to disentangle. With this in mind, our model assumes that survival is equivalent for those who are PS-dependent and for those who achieve independence from PS.

Clinical expert opinion suggest that mortality rates for people receiving PS are more likely to be related to their underlying SBS-IF than their PS treatment and that mortality has improved in recent years alongside advances in SBS-IF management. As such, it is important to consider the latest data available when estimating the expected survival of the SBS-IF population.

The most relevant study providing the latest data on survival associated with SBS-IF, identified via review of studies obtained through the clinical and economic SLRs, is Salazar 2021. This study provided survival data for 218 patients with SBS-IF who were receiving PS and followed-up for up to 15 years (2003 to 2018) as part of a Canadian PS registry. Importantly, this study presented the KM plot for survival alongside the number of patients at risk in 5 year increments, allowing digitisation and estimation of pseudo individual patient data (IPD)[27].

The KM plot was digitised and pseudo-IPD were estimated using the algorithm developed in Guyot 2012[124]. The resulting KM plot using the pseudo-IPD is presented in **Figure 24**.

Figure 24 Survival of SBS-IF patients from Salazar 2021

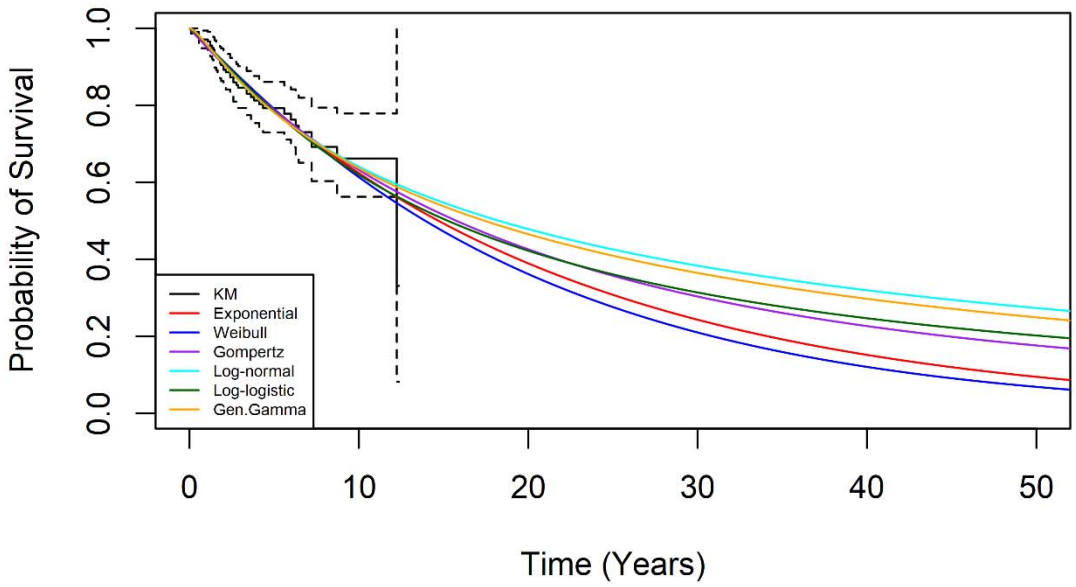


Abbreviations: SBS-IF, short bowel syndrome with type 3 intestinal failure

Source: Salazar 2021[27]

The pseudo-IPD generated from this process was used to fit survival curves using the *flexsurv* package of *R*. Standard parametric models (exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma) were fitted, with the best fitting models chosen based on assessment of the AIC and BIC goodness-of-fit statistics, as well as the plausibility of the extrapolations. The resulting fitted survival curves are shown in **Figure 25** and the corresponding goodness-of-fit statistics are given in **Table 28**.

Figure 25 Survival curves fitted to Salazar *et al.* data



Abbreviations: KM, Kaplan–Meier

Source: Salazar 2021[27]

Table 28 Goodness-of-fit statistics for Salazar *et al.* survival models

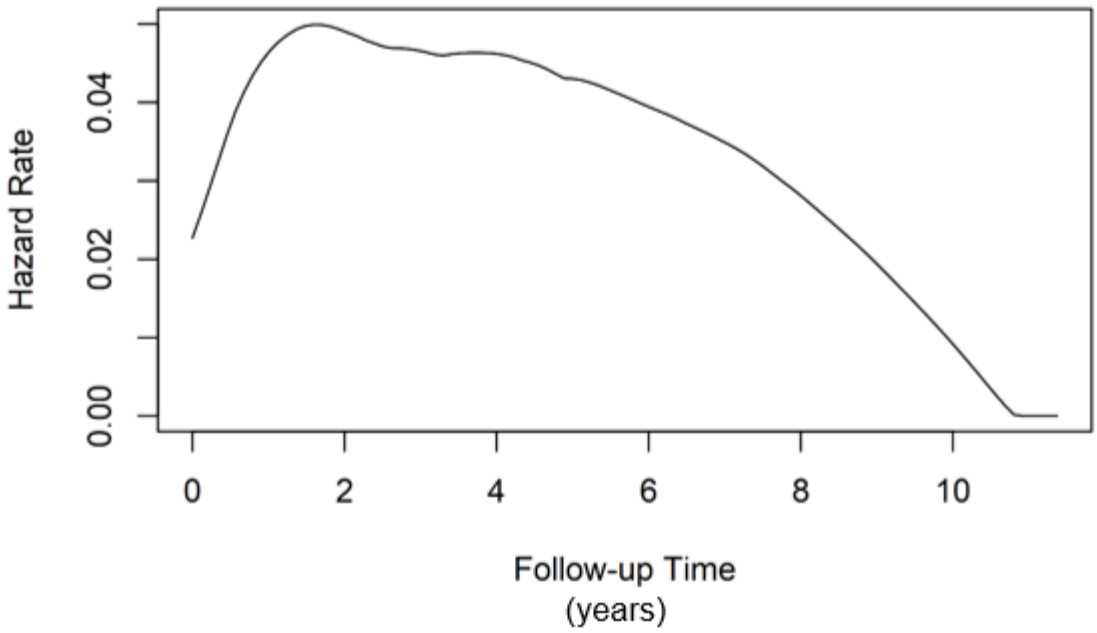
Parametric model	AIC	BIC
Exponential	334.48	337.86
Weibull	336.30	343.07
Gompertz	336.42	343.19
Log-normal	334.62	341.39
Log-logistic	335.47	342.23
Generalised gamma	336.58	346.73
Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion		

The best fitting curve according to AIC and BIC was the exponential. However, the log-normal was a close second, especially when comparing the AIC statistics, which were almost identical.

When visually assessing the plausibility of the extrapolations against the shape of the KM plot, the exponential appears to be too simplistic to capture the diminishing rate of mortality that the KM plot appears to demonstrate. This is also further demonstrated when analysing the hazard function of the Salazar 2021 survival data, which is given in **Figure 26**, estimated using the *muhaz* package of R. This hazard

function shows an initial increase in hazard in the first year or so followed by a gradual reduction in the hazard for the remainder of the time period.

Figure 26 Estimated hazard function of Salazar 2021 survival data



Source: Salazar 2021[27]

This analysis of the hazards demonstrates that the constant hazard rate of an exponential model would provide an implausible extrapolation of the mortality rate as demonstrated by the data. The base case analysis in the economic model therefore, uses the log-normal function, on the basis that it provides a good statistical fit (similar to the best fitting exponential) but with a plausible hazard function that appropriately captures the diminishing rate of death over time.

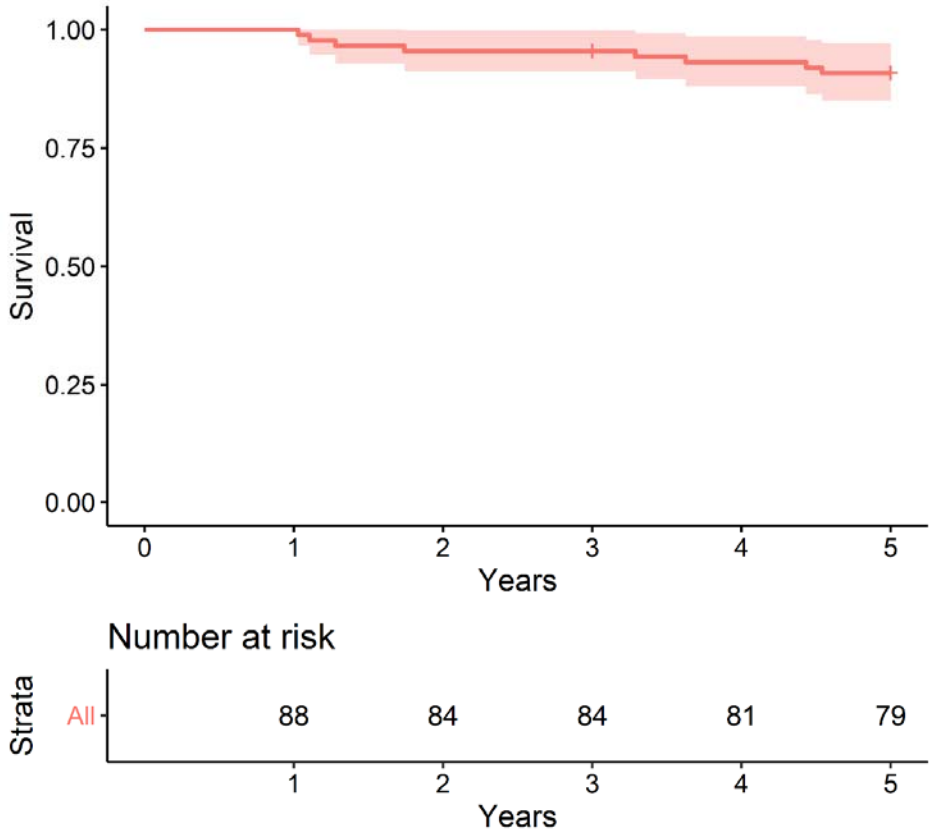
To ensure the extrapolations of the fitted survival model are plausible and do not cause the rate of mortality to reduce below that of the general population, survival probabilities were adjusted using Life Tables for England from the Office for National Statistics (ONS)[125]. To do this, the hazards of death from the ONS Life Tables were used as a minimum hazard. If the hazard rate of the fitted survival model went below the rate of the ONS data, then the ONS mortality rate was applied. This ensures all patients reach the death state by the end of the time horizon of the model, thus resulting in plausible survival estimates.

B.3.3.4.2 Paediatric survival

To model survival for the paediatric base case analysis, the same approach was taken but using a paediatric-specific source of survival data. The largest and most recent source of survival data relating to the paediatric population was identified as Pironi 2011[126], which provides up to 5 years of follow-up data for 88 children. The

plot provided was digitised to estimate pseudo-IPD and the resulting KM plot is given in **Figure 27**.

Figure 27 Survival of SBS-IF patients from Pironi 2011



Abbreviations: SBS-IF, short bowel syndrome with type 3 intestinal failure

Source: Pironi 2011[126]

As per the Salazar *et al.* data for the adult base case, pseudo-IPD generated using the Guyot *et al* 2012[124] algorithm was used to fit survival curves using the *flexsurv* package of *R*. Standard parametric models (exponential, Weibull, Gompertz, log-normal, log-logistic and generalised gamma) were fitted, with the best fitting models chosen based on assessment of the AIC and BIC goodness-of-fit statistics, as well as the plausibility of the extrapolations. The resulting fitted survival curves are shown in **Figure 28** and the corresponding goodness-of-fit statistics are given in **Table 29**.

Figure 28 Survival curves fitted to Pironi *et al*. data

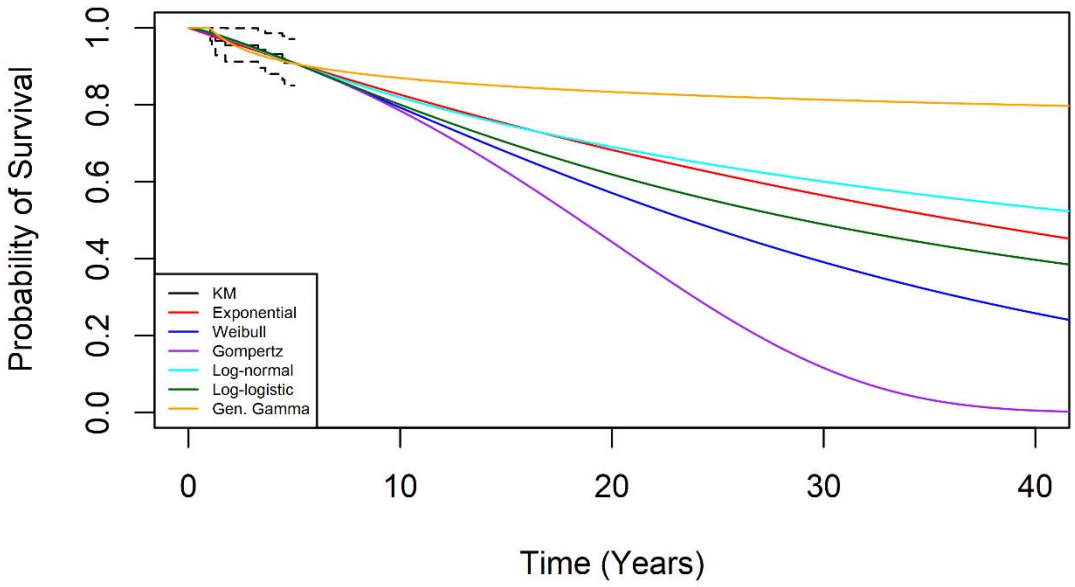


Table 29 Goodness-of-fit statistics for Pironi *et al*. survival models

Parametric model	AIC	BIC
Exponential	81.34	83.81
Weibull	82.89	87.84
Gompertz	83.21	88.17
Log-normal	82.38	87.33
Log-logistic	82.85	87.81
Generalised gamma	79.94	87.73
Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion		

The AIC statistics appear to show that the most complex 3-parameter generalised gamma curve has the best fit to the data, but this is closely followed by the single-parameter exponential curve. Based on the BIC statistics, however, the exponential demonstrates the best fit with no close second place. All the alternatives are in the region of 4 points worse based on the BIC, which is notably different. Based on these results and the limited follow-up to reliably demonstrate changes in hazards over time, the exponential model was chosen for the paediatric base case analysis.

B.3.3.5 Complications

PS is associated with serious, and infrequently fatal, complications. Catheter-related incidents were captured by data in STEPS/STEPS-2, and so are included in the model along with other adverse reactions (see B.3.4.3). Intestinal failure-associated liver disease (IFALD) and chronic kidney disease (CKD) were not, and so are modelled separately.

B.3.3.5.1 Intestinal failure-associated liver disease (IFALD)

A Delphi panel was conducted featuring 9 UK clinical experts. Experts answered questions in an online questionnaire in round 1, and discussed the answers face-to-face in round 2 in order to reach consensus.

It was concluded by this panel that teduglutide would reduce the incidence of IFALD by reducing the requirement for PS. The experts agreed that the prevalence of IFALD at 1 year on PS was 0–1%, at 2 years was 0–2% and at 10 years was 0–3%. To account for the agreement that reduced PS would reduce incidence of IFALD, patients were split into 4 cohorts grouped by days on PS and the rates of IFALD were interpolated using the ranges provided by the experts (Error! Not a valid bookmark self-reference.). The development rates per 28-day cycle are calculated from the prevalence estimates, and are applied to the relevant health-states in each cycle over the horizon of the model.

Table 30. IFALD prevalence estimates from Delphi meeting and calculated development rates per 28 days

	No PS	**PS1–3**	**PS4–5**	**PS6–7**
Prevalence at 1 year on PS	0.00%	0.33%	0.67%	1.00%
Prevalence at 2 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 0-1	0.000%	0.013%	0.026%	0.039%
Development rate years 1-2	0.000%	0.006%	0.013%	0.019%
Development rate years 2+	0.000%	0.006%	0.013%	0.020%
Abbreviations: IFALD, intestinal failure-associated liver disease; PS, parenteral support **Source:** Delphi panel report[127]				

Although clinical experts consider there to be an association between IFALD risk and the number of days PS is required, there is uncertainty around whether a reduction in PS days per week as a result of teduglutide causes a reduction in the risk of IFALD. Given this uncertainty, a scenario using a more conservative approach is provided, where a reduction in the risk of IFALD is only assumed in those who become PS independent. The baseline health states are used to estimate the risk of those who are PS dependent and this is not impacted by changes in PS until independence is achieved, at which point the risk is removed. The results of this scenario are provided in B.3.8.3.

B.3.3.5.2 Chronic kidney disease (CKD)

Alongside IFALD, another complication that is associated with PS dependence in SBS-IF patients is chronic kidney disease (CKD)[32]. Only Stage V CKD (glomerular flow rate <15 ml/min/1.73m^2) impacts resource use in a manner relevant to our economic model. Stages I–IV CKD were therefore not modelled.

As per IFALD, due to a lack of relevant published data, estimates from the Delphi meeting are used to calculate the proportion of patients with Stage V CKD (Error! Not a valid bookmark self-reference.).

Table 31. Stage V CKD prevalence estimates from Delphi meeting and calculated development rates per 28 days

	No PS	PS1–3	PS4–5	PS6–7
Prevalence at 1 year on PS	0.00%	0.33%	0.67%	1.00%
Prevalence at 2 years on PS	0.00%	0.67%	1.33%	2.00%
Prevalence at 10 years on PS	0.00%	1.67%	3.33%	5.00%
Development rate years 0-1	0.000%	0.026%	0.051%	0.077%
Development rate years 1-2	0.000%	0.026%	0.052%	0.078%
Development rate years 2+	0.000%	0.010%	0.020%	0.030%
Abbreviations: CKD, chronic kidney disease; PS, parenteral support. **Source:** Delphi panel report[127]				

An alternative scenario is also provided where the risk of Stage V CKD is only reduced for those who achieve PS independence. This is likely to be a conservative modelling approach. In this scenario, patients' baseline risk of Stage V CKD (as per **Alongside IFALD**, another complication that is associated with PS dependence in SBS-IF patients is chronic kidney disease (CKD)[32]. Only Stage V CKD (glomerular flow rate <15 ml/min/1.73m^2) impacts resource use in a manner relevant to our economic model. Stages I–IV CKD were therefore not modelled.

As per IFALD, due to a lack of relevant published data, estimates from the Delphi meeting are used to calculate the proportion of patients with Stage V CKD (Error! Not a valid bookmark self-reference.).

Table 31) is assumed to remain constant as long as the patient remains PS dependent (the same as the IFALD scenario described above). The results of this scenario are provided in B.3.8.3.

B.3.4 Measurement and valuation of health effects

PS is a highly sophisticated and complex life-saving treatment, for which patients are typically immensely grateful. However it is also incredibly disruptive as patients usually receive PS for 10–14 hours a night, 2–7 nights a week, with more severe cases of SBS-IF requiring more nights per week on treatment. This can seriously inhibit patients' ability to live a normal life. Days per week of PS is therefore a highly relevant outcome for patients, as nights off PS represent nights where a patient can live a more normal social, family or personal life. Clinicians at an advisory board indicated that patients have a strong desire to reduce their number of days of PS per week. This view is also supported by the teduglutide EPAR, which states:

"One or more days without having to be chained to an i.v. line constitutes a real benefit for the patient."[66]

For this reason, we structured our economic model around days per week of PS. Therefore, the key to measuring and valuing health effects in this section relates to the quality of life impact that reducing days per week on PS has on patients with SBS-IF. As discussed in B.2.6.3, quality of life data from clinical trials do not make sense, and so are not appropriate for estimating utilities. In line with other published cost-effectiveness analyses[119, 120], we have used data published by Ballinger *et al*. 2018[113] to estimate utility values; the rationale for this is expanded upon in the sections below.

B.3.4.1 Health-related quality of life data from clinical trials and mapping to utility values

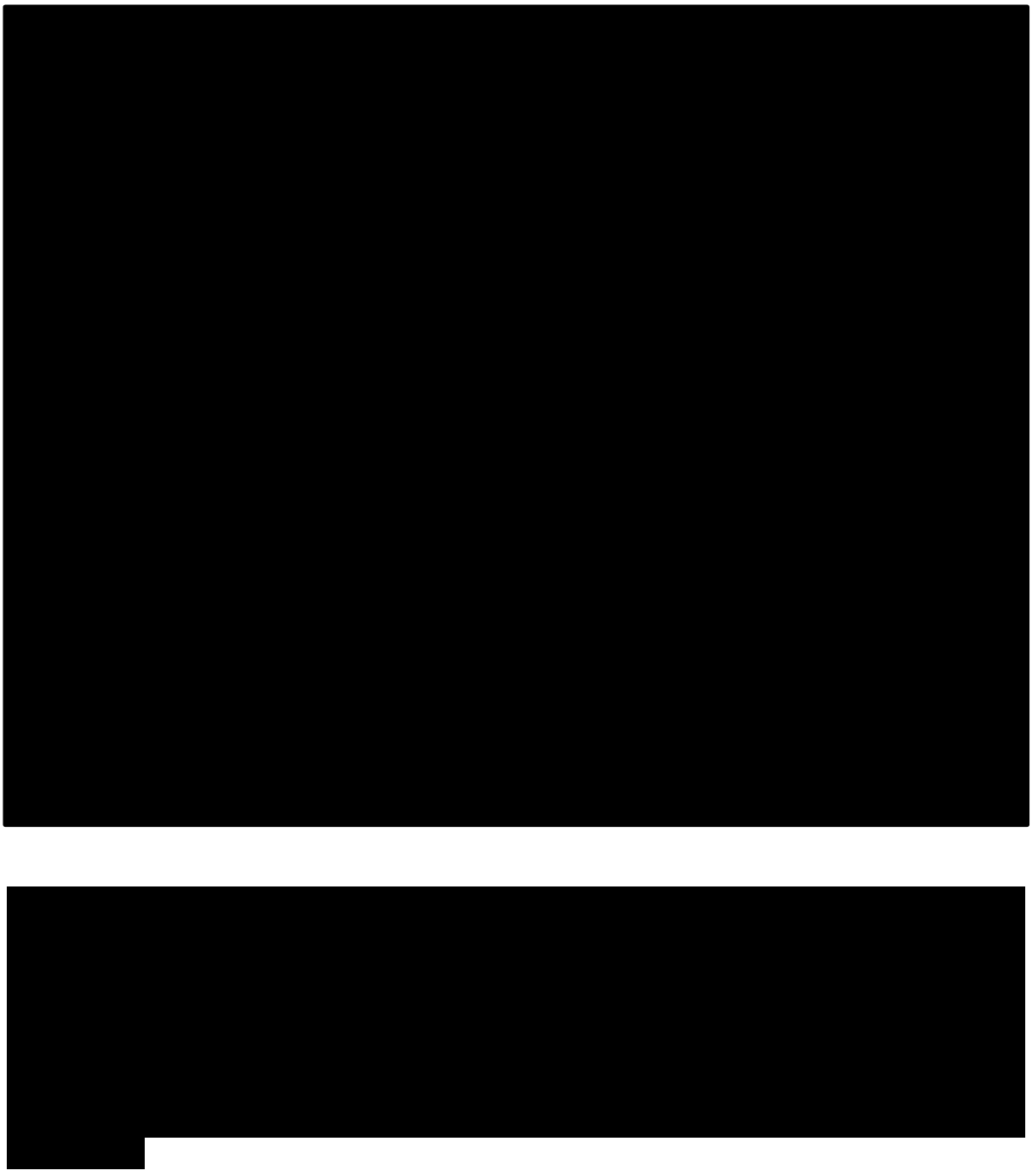
Both STEPS and 004, randomised controlled trials of teduglutide versus placebo, collected data on quality-of-life outcomes. Neither study was powered to detect differences in quality of life, either for comparing baseline versus week 24 within a treatment arm, or for comparing teduglutide versus placebo, and so use of the data are limited.

004 collected quality of life data using the SF-36, EQ-5D and IBDQ instruments. No difference in quality of life was reported for any of these instruments when comparing results for the teduglutide arm versus baseline or versus placebo at week 24. While EQ-5D is preferred by NICE for generating utilities, the teduglutide EPAR noted that the SF-36, EQ-5D and IBDQ instruments had not been developed to assess the quality of life of patients with SBS, and were unlikely to be sensitive enough to detect quality of life changes in this population[66]. We therefore decided that data from 004 were not appropriate to use within our model.

STEPS captured quality of life data using the SBS-QoL instrument. No statistically significant difference in SBS-QoL scores was observed between the teduglutide and placebo arms; potential reasons for this are discussed in section B.2.6.3. As a non-preference-based measure, utilities cannot be derived directly from SBS-QoL outcomes and therefore it cannot be directly used to inform the health state utility values in the model. However, a mapping algorithm[128] provides a link between the SBS-QoL outcomes and utility values derived using a time-trade-off technique in a similar fashion to the EQ-5D.

Outcomes from the SBS-QoL data collected in STEPS were mapped to derive utility values based on days per week of PS. The results from this exercise are presented in **Figure 29**.

Figure 29 Utilities mapped from the SBS-QoL data in STEPS (using the Lloyd algorithm) by number of days per week of PS



B.3.4.2 Health-related quality of life studies

Several systematic literature reviews (SLRs) were performed to identify other relevant health-related quality of life (HRQoL) or health state utility value (HSUV) studies. These were performed in line with NICE guidance in the methods of technology appraisal, using a pre-prepared search strategy and multiple reviewers assessing results (detailed in Appendix H). For the present submission, a HRQoL and HSUV SLR, covering data for adults and children with SBS-IF, was performed on 21st May 2021.

Of the 31 studies identified by the SLRs, six reported utility values for patients with SBS-IF; these are shown in **Table 32**, the remaining quality of life studies are summarised in Appendix H.

Table 32: Summary of published studies reporting health-state utility values

Reference	Population	Intervention & comparators	Method	Outcomes
Culkin *et al.* 2009	Patients with chronic IF (n=48). The definition of chronic IF used in this study is unclear given not all patients receive PS	PS (33 patients out of 48 type 3 IF patients)	Quality of life was calculated using EQ-5D-3L VAS, EQ-5D Index & SF-36	1. Quality of Life EQ-5D Index; all patients (n=48): 0.75 ± 0.19, Patients on PS (n=33): 0.77 ± 0.16 2. Difference in quality of life indices for patients dependent & independent of PS EQ-5D Index (median, IQR); Not on PS (n=15): 0.00, -0.11 - 0.04, On PS (n=32): 0.07, 0.00 - 0.13.
Lachaine *et al.* 2016	SBS patients and the Canadian general population (n=799)	Days and/or hours per day on PS	General population time trade-off survey to elicit health state utility values	PS0 = 0.74 PS1 = 0.70 PS2 = 0.65 PS3 = 0.61 PS4 = 0.57 PS5 = 0.52 PS6 = 0.48 PS7 Low = 0.44 PS7 High = 0.39
Ballinger *et al.* 2018	UK general public (adults; n=100) rating SBS (not specific to type of IF) health states	Days of PS	Health state vignette study involving VAS and time trade-off technique	PS0: 0.82 PS1: 0.78 PS2: 0.72 PS3: 0.65 PS4: 0.58 PS5: 0.51 PS6: 0.41 PS7: 0.36

Carey *et al.* 2019	Australian patients on PS (n=19) rating health states of patients with type 3 IF receiving PS	PS, teduglutide, intestinal transplant	Treatment vignette study involving time trade-off technique	Median values by treatment (note these values are the inverse of utility): Teduglutide: 0.5 Intestinal transplant: 1.0 Reduction in line infections: 0.75 Optimisation of care: 0.5
Raghu *et al.* 2020a	Simulated cohort of adults with SBS-IF	PS, teduglutide	Cost-effectiveness (Markov) model	Utilities obtained from Ballinger et al 2018 and subjected to age adjustment: PS0: 0.84 PS1: 0.77 PS2: 0.70 PS3: 0.63 PS4: 0.56 PS5: 0.49 PS6: 0.42 PS7: 0.35
Raghu *et al.* 2020b	Simulated cohort of children with SBS-IF	PS, teduglutide	Cost-effectiveness (Markov) model	Utilities derived from Ballinger *et al*. 2018 Enteral autonomy/PS0: 0.82 PS7: 0.36

Abbreviations: EQ-5D(-3L), EuroQol five dimensions (3 levels); PS, parenteral support; PSx, x days per week of PS; SBS, short bowel syndrome; SBS-IF, short bowel syndrome with type 3 intestinal failure; SF-36, 36 item short form questionnaire; VAS, visual analogue scale

Source: Studies identified by quality of life SLR [65, 113, 119, 120, 129, 130]

Of the 6 included studies that provide utilities relating to SBS-IF patients, the key studies that can be used to directly inform the economic model are Ballinger 2018[113], Lachaine 2016[65] and Raghu 2020a[119]. These studies all provide utility estimates based on the number of days per week of PS required by patients; however, Raghu 2020a is an economic evaluation that reports age-adjusted values based on the Ballinger 2018 values. Therefore, there are two unique sources of utility values to consider to inform the economic model.

Both Ballinger 2018 and Lachaine 2016 are vignette studies that use a time-trade off technique to elicit utility values, as used for the derivation of the EQ-5D UK valuation tariff. As Ballinger 2018 provides utility estimates derived from a UK general population, this study aligns more closely to the NICE reference case. The utilities reported by Ballinger 2018 are in line with utilities reported in a previous study, where the mean utility value for a patient on PS was 0.52, and reached as low as

0.28 in older patients[131]. Therefore, given the limitations of the utility values derived from STEPS and 004, values from Ballinger 2018 have been used in the base case analyses of the model, and scenarios are provided using values from Lachaine 2016.

B.3.4.3 Adverse reactions

All adverse events (AEs) that occurred in at least 5% of patients in either arm of the STEPS trial were originally considered for the economic model. Based upon clinical assessment, 32 of the total 35 AEs were included as important relevant AEs in the model. The three AEs that were excluded were device dislocation, epistaxis and nasopharyngitis. These were omitted due to their low cost and minimal patient burden, indicating that they would have negligible impact on the cost-effectiveness model. An alternative scenario is also presented in B.3.8.3, in which only severe AEs are included in the model.

AEs were applied as rates per model cycle based on STEPS and STEPS-2 patient-level data (for adverse events, data from all three cohorts of STEPS-2 were used; see B.3.3.1.1). Patients on teduglutide were subject to variable AE rates over time; the rates were informed by STEPS data in the first 6 months, and by STEPS-2 data from beyond 6 months until death. We did not model variability in AE rate by days per week of PS, due to the difficulty in establishing whether AEs are related to SBS-IF or to PS.

The AE rates associated with standard care were obtained from the placebo arm of STEPS. With only 6 months of data, these rates are not time-variable. Patients who discontinued teduglutide became subject to the AE rates associated with standard care. The individual rate per cycle for each included AE is presented in Table 33.

Table 33. Adverse event rates included in the economic model

Adverse event	Teduglutide months 0-6 (rate per month)	Teduglutide after month 6 (rate per month)	Standard care (rate per month)
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]

Adverse event	Teduglutide months 0-6 (rate per month)	Teduglutide after month 6 (rate per month)	Standard care (rate per month)
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]
Source: STEPS and STEPS-2 CSRs[89, 94]; individual patient-level data from STEPS and STEPS-2			

Many AEs and complications of teduglutide and/or PS affect patients' quality of life. For a given AE, the quality of life impact was assumed to be the same regardless of whether the patient received teduglutide or standard care. The impact on quality of life is measured in utility decrements, of which values are informed by the available literature and are combined with the relevant event rate to estimate a decrement per model cycle. Disutilities are applied for the duration of one model cycle (28 days), as there was no information on duration of AEs available from STEPS and it seems reasonable to assume that most AEs evaluated would not last longer than this. Final utility values associated with AEs in our model are presented in B.3.4.5, **Table 36.**

Utility values for intestinal failure-associated liver disease and chronic kidney disease (also presented in **Table 36)** are also included in the model, however these are chronic complications for which the per-cycle utility decrement is applied continuously from the onset of the complication. The average utility decrement for each complication is calculated per model cycle, based on the proportion of patients

in each PS health state (ranging from 0 to 7 days of PS per week, noted as PS0 to PS7).

B.3.4.4 Carer quality of life

SBS-IF and PS requirements are not only a burden to the patient themselves but also to their family and caregivers. Both adults and children with SBS-IF will commonly need an informal caregiver for help with daily living and for emotional support[59]. In a recent global patient and caregiver survey, [redacted]. Caregivers of patients with SBS-IF often suffer a lack of social activities, difficulties with relationships, lost income and employment difficulties and, in some cases, depression[50]. For parents, caring for a child who is receiving PS affects their family and social lives: they report feelings of frustration, annoyance, and stress, as well as problems sleeping[60].

To quantify this impact, two separate studies were conducted, in part due to the inherent uncertainty and difficulty in assessing caregiver quality of life. Firstly, 9 clinical experts recruited for a Delphi panel process were asked to give an estimate of the utility of carers of patients with SBS-IF with low (1–2 days), medium (3–5 days), or high (6–7 days) PS requirements, noting that a utility of 0 is equivalent to death and a utility of 1 represents perfect health. The mean and range of the estimates of the respondents are given in **Table 34**.

Table 34 Carer utilities derived from Delphi panel

Health state	Mean	Range
Carer/family member of a patient receiving 1-3 days of PS per week	0.89	0.85-0.98
Carer/family member of a patient receiving 4-5 days of PS per week	0.77	0.70-0.90
Carer/family member of a patient receiving 6-7 days of PS per week	0.67	0.50-0.80
Abbreviations: PS, parenteral support **Source**: Carer quality of life Delphi panel[127]		

Secondly, a caregiver-specific survey was performed. The survey recruited 47 UK-based carers for patients with SBS-IF and measured the quality of life impact on carers using the EQ-5D. Health state utilities from this study using the EQ-5D are presented in **Error! Not a valid bookmark self-reference.**.

Table 35 EQ-5D utilities from carer quality of life study

Days per week patient spends on PS	Mean utility value for carer	SD
2 days (n=2)	1.00	0.00
3 days (n=10)	0.89	0.11
4 days (n=5)	0.77	0.26
5 days (n=9)	0.97	0.09
6 days (n=11)	0.89	0.11
7 days (n=10)	0.88	0.12
Abbreviations: PS, parenteral support; SD, standard deviation **Source**: Carergiver-specific survey[132]		

By way of validation, the aforementioned global patient and caregiver survey reported a mean carer utility of 0.84 using EQ-5D-5L (n=121 carers surveyed; not stratified by patient PS consumption)[23]. This suggests that the caregiver utility estimates from the Delphi (**Table 34)** may be slightly low, and from the caregiver-specific survey (**Table 35**) slightly high. For these reasons, and recognising the uncertainty in these estimates given the difficulty in measuring carer quality of life, the two sources were combined. Results from the caregiver-specific survey were first grouped as per the Delphi estimates (into 1-3 days, 4-5 days and 6-7 days, weighted by patient numbers) and then midpoints between the Delphi and grouped caregiver-specific estimates were taken.


we have assumed one carer per patient. In the paediatric base case, we have assumed two caregivers per patient on the basis caregivers are likely to be the child's parents.

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

All utility values used in our economic model are shown in **Table 36**.

Table 36 Summary of utility values used in the economic model

State	Utility value: mean (standard error)	Reference in submission (section and page number)	Justification
PS0	0.82	Section B.3.4.2, **Table 32**	Ballinger 2018 UK Vignette study
PS1 disutility	-0.04		
PS2 disutility	-0.10		
PS3 disutility	-0.17		
PS4 disutility	-0.24		
PS5 disutility	-0.31		
PS6 disutility	-0.41		
PS7 disutility	-0.46		
Intestinal failure-associated liver disease (IFALD)	0.596		Sullivan 2011
Chronic kidney disease (CKD)	0.71		Wyld 2012
Abdominal distension	-0.0512	Discussed in section B.3.4.3	Sullivan 2011,'Other gastrointestinal disorders'
Abdominal pain	-0.0512		
Arthralgia	-0.023		Sullivan 2011,'Other bone disease and musculoskeletal disorders'
Bacteraemia	-0.52		NICE TA352, vedolizumab for treating moderate to severely active Crohn's disease after prior therapy, 'serious infection'
Catheter-related infection	-0.52		
Central line infection	-0.52		
Constipation	-0.0512		Sullivan 2011,'Other gastrointestinal disorders'
Diarrhoea	-0.0512		
Injection site haematoma	-0.03		NICE TA352, vedolizumab for treating moderate to severely active Crohn's disease after prior therapy, 'skin site reactions'
Injection site pain	-0.03		
Peripheral oedema	-0.0508		Sullivan 2011,'Aortic, peripheral and visceral artery disorders'
Bacterial overgrowth	-0.52		NICE TA352, vedolizumab for treating moderate to severely active Crohn's disease after prior therapy, 'serious infection'

State	Utility value: mean (standard error)	Reference in submission (section and page number)	Justification
Procedural site reactions	-0.03		NICE TA352, vedolizumab for treating moderate to severely active Crohn's disease after prior therapy, 'skin site reactions'
Small intestinal stenosis	-0.0512		Sullivan 2011,'Other gastrointestinal disorders'
Upper respiratory tract infection	-0.52		NICE TA352, vedolizumab for treating moderate to severely active Crohn's disease after prior therapy, 'serious infection'
Urinary tract infection	-0.09		Bermingham and Ashe 2012, 'Older adults with UTI'
Vomiting	-0.0512		Sullivan 2011,'Other gastrointestinal disorders'
Carer/family member of a patient with PS0	0	Average of values presented in section B.3.4.4 **Table 34** and **Secondly,** a caregiver-specific survey was performed. The survey recruited 47 UK-based carers for patients with SBS-IF and measured the quality of life impact on carers using the EQ-5D. Health state utilities from this study using the EQ-5D are presented in **Error! Not a valid bookmark**	Delphi panel and Carer Utility Study
Carer/family member of a patient with PS1	-0.10		
Carer/family member of a patient with PS2	-0.10		
Carer/family member of a patient with PS3	-0.10		
Carer/family member of a patient with PS4	-0.17		
Carer/family member of a patient with PS5	-0.17		
Carer/family member of a patient with PS6	-0.22		
Carer/family member of a patient with PS7	-0.22		

State	Utility value: mean (standard error)	Reference in submission (section and page number)	Justification
		self-reference.. **Table 35**	

Abbreviations: PS*x*, *x* days per week of parenteral support; SD, standard deviation

Notes: The values provided above are decrements during the AE. All AEs are assumed to have a duration of 1 model cycle (28 days). IFALD and CKD are modelled separately with a disutility applied from onset to death.

Source: UK vignette study[113]; Wyld 2012 [133]; Sullivan 2011[134]; NICE TA352[135]; Bermingham and Ashe 2021[136]; carer survey[137]; carer quality of life Delphi panel[138]

B.3.5 Cost and healthcare resource use identification, measurement and valuation

Search strategies used for the systematic review of the literature for costs and resource use associated with SBS-IF are presented in Appendix I. Five and eight studies reporting data on costs and resource use were included for adult and paediatric SBS-IF populations, respectively. Most studies were conducted outside of the UK, and therefore were not considered suitable for investigating resource use in the UK. Details of the study population, objectives and resource use and/or costs reported in these studies are presented in Appendix I.

B.3.5.1 Intervention and comparators' costs and resource use

The list price is £521.98 per vial containing 5 mg of teduglutide. A smaller vial for patients weighing less than 20kg, containing 1.25 mg of teduglutide, is available at list a price of £260.99. A simple PAS discount of [redacted] on the list price has been agreed with NHS England and this has been applied to all analyses.

Teduglutide dosing in the model matches the recommended posology as per its SmPC. Vials containing a 5 mg and 1.25 mg dose respectively, are used to deliver the recommended daily dose of 0.05 mg/kg body weight (5 mg for patients ≥20 kg, 1.25 mg for patients <20 kg).

The model assumes that one 5 mg vial of teduglutide is sufficient to meet one daily dose in all patients (model assumes all patients, adult and paediatric weigh ≥20 kg). This also assumes no patients weight more than 100 kg; above this weight, a second vial would be needed ([redacted]). The unit cost per 28-day model cycle is therefore [redacted], with the discount applied.

Vial sharing is not included in the model. Its inclusion would imply that a patient could save any unused teduglutide over and above their required daily dose. As the eligible population for teduglutide is small, the potential for vial sharing is somewhat

limited. Nevertheless, assuming no vial sharing at all is likely conservative, which may result in an over-estimate of the ICER.

As per its SmPC, treatment with teduglutide requires a colonoscopy procedure at initiation. Further colonoscopies are required after 1 year and 2 years on treatment, and every 5 years thereafter. The unit cost of these teduglutide-specific colonoscopies is £620 per procedure (

Table 37).

Administration of teduglutide is associated with no other specific costs. No additional travel costs are assumed, as regular community nursing support is already part of receiving PS. A Takeda-sponsored homecare service will be provided alongside teduglutide if it is approved. Yearly costs associated with teduglutide treatment are summarised in **Table 38**.

PS costs are dependent on the health state a patient is in, and are therefore included in the health state costs presented in B.3.5.2.

Table 37 Colonoscopy unit cost calculation

Currency code (NHS reference costs)	Description	Activity	Unit cost
FE31Z	Diagnostic Colonoscopy with Biopsy, 19 years and over	162,820	£690
FE32Z	Diagnostic Colonoscopy, 19 years and over	191,331	£560
		Mean cost weighted by activity	£620
Source: NHS reference costs 2019/2020[139]			

Table 38 Costs per treatment/patient associated with the technology in the cost-effectiveness model

Items	Cost	Source
Price of the technology per patient per year	[redacted]	BNF
Colonoscopy	£620	NHS reference costs, 2019-2020; FE31Z and FE32Z
Abbreviations: PSSRU, Personal Social Services Research Unit **Source**: NHS reference costs 2019/2020[139]; BNF[140]		

B.3.5.2 Health-state unit costs and resource use

Patients with SBS-IF receiving PS require special services. These include the PS itself, additional drugs (such as proton pump inhibitors, antimotility agents, dalteparin and ondansetron), monitoring, as well as services addressing the complications associated with PS. The cost per patient per year on PS was taken from a study performed to inform a previous submission to NICE[141, 142]. The study aimed to capture the cost of managing home PS for SBS-IF patients in the UK, including analysis of the treatment pathway, healthcare provision, and the burden of the disease. This information was used to construct an indication of the costs involved in management of PS in England. The study used data collected from four consultant gastroenterologists, five nurses, one pharmacist and one dietitian from specialised intestinal failure centres in England. Data on key resources driving the cost of home PS management were collected, along with associated costs and estimates of utilisation. From this information, unit costs and resource use could be derived, based on levels of patient PS dependence, additional drug usage and complications other than those simulated directly in the cost-effectiveness model (line sepsis and line fracture). Complications already captured in the model are not considered here to avoid double counting. A summary of the resource use and unit costs used to estimate PS health-state costs is given in **Table 39** and **Table 40**, respectively. The resulting health-state costs used in the economic model for the adult and paediatric base case analyses are given in **Table 41**

Table 41.

Table 39 Resource use for PS by health state

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]									

Table 40 Unit costs for PS

Cost item	Units	Cost per unit	Source
PS bag (≥8 ingredients) band A	day/ week	[redacted]	Estimated from expert discussion.
Delivery	delivery/ month	[redacted]	
Nurse time	hour/ week	[redacted]	
Taurolock	day/ week	[redacted]	
Proton pump inhibitors	day	£10	British National Formulary
Antimotility agents	day	£12	British National Formulary
Fragmin 5 unit (0.2mL syringe)	day	£3	British National Formulary
Ondansetron	day	£24	British National Formulary
Specialist visits (adults)	visit/ year	£179	NHS reference costs, 2019-2020; Service code 301,Gastroenterology; Multiprofessional Non-Admitted Face-to-Face Attendance; WF02A-B (weighted average);
Specialist visits (paediatrics)	visit/ year	£290	NHS reference costs, 2019-2020; Service code 251, Paediatric Gastroenterology; Multiprofessional Non-Admitted Face-to-Face Attendance; WF02A-B (weighted average);

Haematology tests (paediatrics only)	tests/ year	£2.53	NHS reference costs, 2019-2020; DAPS05 Haematology
Inflammatory markers (paediatrics only)	tests/ year	£7.40	NHS reference costs, 2019-2020; DAPS06 Immunology
Clinical biochemistry (paediatrics only)	tests/ year	£1.20	NHS reference costs, 2019-2020; DAPS04 Clinical biochemistry
Line sepsis	episode/ year	£5,715	NHS reference costs, 2019-2020; Sepsis with intervention; WJ06A-F (weighted average)
Line sepsis requiring critical care (adults)	period/ year	£1,666	NHS reference costs, 2019-2020; Adult Critical Care; XC01Z-XC07Z (weighted average)
Line sepsis requiring critical care (paediatrics)	period/ year	£2,391	NHS reference costs, 2019-2020; Paediatric Critical Care; XB01Z-XB07Z (weighted average)
Line fracture occlusion	episode/ year	£575	NHS reference costs, 2019-2020; Attention to Central Venous Catheter; YR43A.
Abbreviations: PS, parenteral support **Sources**: Takeda confidential data; NHS reference costs 2019-2020[143]; British National Formulary[140]			

Table 41 PS health state costs per cycle

Health state	Cost per 28-day cycle (Adult base case)	Cost per 28-day cycle (Paediatric base case)
PS7	[redacted]	[redacted]
PS6	[redacted]	[redacted]
PS5	[redacted]	[redacted]
PS4	[redacted]	[redacted]
PS3	[redacted]	[redacted]
PS2	[redacted]	[redacted]
PS1	[redacted]	[redacted]
PS0	[redacted]	[redacted]

Abbreviations: PS, parenteral support
Note: Values for individual numbers of days per week on PS, aside from those directly estimated in the costing study are linearly interpolated and extrapolated
Source: Takeda confidential data

Intestinal Failure-Associated Liver Disease (IFALD)

The costs of IFALD are taken from Crossan 2015[144] and uplifted to 2019-20 costs using PSSRU 2020[145]. The average time spent in the three liver disease sub-health states (estimated from Cavicchi *et al.* 2000[146]*)* is used to calculate a weighted average of the cost per 28 days; this results in £2,775 per 28 days.

Table 42 Costs associated with IFALD

Health state	Cost per month	Proportion of time spent in state (for patients with IFALD)
Non-progressed liver disease	£17	12%
Fibrosis	£86	8%
Cirrhosis	£3,477	80%
Overall IFALD (weighted average)	£2,775	

Abbreviations: IFALD, intestinal failure-associated liver disease; PSSRU, Personal Social Services Resource Unit
Sources: Crossan 2015[144]; PSSRU[145]; Cavicchi 2000[146]

Chronic Kidney Disease (CKD)

In the model, CKD is included in the base case, and the assumption is made that all patients with Stage V CKD require chronic dialysis; therefore, the monthly costs are

calculated by taking the weighted average of all NHS reference costs for chronic dialysis (LA08G and LA08P)[143], resulting in a cost per 28-day cycle of £2,384.

B.3.5.3 Adverse reaction unit costs and resource use

The rate of each AE was combined with the unit cost of completely resolving that event to estimate the likely total cost of AEs incurred in each model cycle. Each AE was assumed to be resolved within one 28-day model cycle. The unit cost of each AE included in the model is presented in **Table 43**. Some AEs are assumed to have a cost of resolution equal to zero; these AEs were judged by experts in the Delphi panel to be largely transient, such that its management would not directly require healthcare resources.

In some instances, there are several NHS reference spell cost codes that could apply to a particular AE. In these cases, a weighted average of the appropriate costs of resolution based on the recorded levels of activity in the NHS were used. This estimates a cost that would represent the whole range of potential resource usages associated with an AE. Additionally, the NHS does not report the same set of spell costs in each annual iteration. Consequently, some costs of resolving AEs are taken from earlier editions of the NHS reference spell costs. These were inflated to the current price year as the other costs in the model.

There are some AEs for which no exactly corresponding NHS reference spell cost could be found. In these instances, assumptions were made based on similarity of potential resource usage, and these are noted in **Table 43**. For example, the cost of resolution for abdominal pain was a weighted average – based on NHS activity levels – of resolution costs for abdominal pain with and without the requirement for additional treatment. The cost of resolution for abdominal distension was assumed to be the same as the cost for abdominal pain. This assumption was applied due to the similarity of the potential resource usage bundles involved in treating abdominal distension.

Table 43 Adverse event costs of resolution included in the model

Adverse event	NHS reference cost code used	Cost of resolution
Abdominal distension	NHS reference costs, 2019-2020; Non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 0-2; FD10M	£839
Abdominal pain	NHS reference costs, 2019-2020; Non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 0-2; FD10M	£839
Arthralgia	NHS reference costs, 2019-2020; Inflammatory, Spine, Joint or Connective Tissue Disorders, HD23 D-J	£763
Bacteraemia	Cost assumed to be captured by PS line sepsis costs.	£0
Catheter-related infection	Cost assumed to be captured by PS line sepsis costs.	£0

Adverse event	NHS reference cost code used	Cost of resolution
Central line infection	Cost assumed to be captured by PS line sepsis costs.	£0
Constipation	NHS reference costs, 2019-2020; Outpatient gastroenterology (Code 301)	£145
Decreased appetite	No cost assumed	£0
Dehydration	No cost assumed	£0
Diarrhoea	NHS reference costs, 2019-2020; Outpatient gastroenterology (Code 301)	£145
Dizziness	NHS reference costs, 2019-2020; Non-Admitted Face to Face Attendance, Follow-Up (Code 180)	£163
Dyspnoea	NHS reference costs, 2019-2020; Non-Admitted Face to Face Attendance, Follow-Up (Code 180)	£163
Fatigue	No cost assumed	£0
Flatulence	No cost assumed	£0
Gastrointestinal stoma complication	NHS reference costs, 2019-2020; Outpatient gastroenterology (Code 301)	£145
Headache	No cost assumed	£0
Injection site haematoma	NHS reference costs, 2019-2020; Non-Admitted Face to Face Attendance, Follow-Up (Code 180)	£163
Injection site pain	NHS reference costs, 2019-2020; Non-Admitted Face to Face Attendance, Follow-Up (Code 180)	£163
Muscle spasms	NHS reference costs, 2019-2020; Non-Admitted Face to Face Attendance, Follow-Up (Code 180)	£163
Nausea	NHS reference costs, 2019-2020; Outpatient gastroenterology (Code 301)	£145
Peripheral oedema	NHS reference spell costs, 2015-2016; YQ50A-F; uplifted to 2019/2020 costs using PSSRU 2020	£2,135
Bacterial overgrowth	NHS reference spell costs, 2013-2014; WA03A-C; uplifted to 2019/2020 costs using PSSRU 2020	£3,994
Pain	NHS reference spell costs, 2013-2014; AB06Z; uplifted to 2019/2020 costs using PSSRU 2020	£730
Procedural site reactions	NHS reference costs, 2019-2020; Non-Admitted Face to Face Attendance, Follow-Up (Code 180)	£163
Pyrexia	NHS reference costs, 2019-2020; Non-Admitted Face to Face Attendance, Follow-Up (Code 180)	£163
Renal colic	NHS reference costs, 2019-2020; Non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 0-2; FD10M	£839

Adverse event	NHS reference cost code used	Cost of resolution
Small intestinal stenosis	NHS reference costs, 2019-2020; Non-Malignant Gastrointestinal Tract Disorders without Interventions, with CC Score 0-2; FD10M	£839
Upper respiratory tract infection	NHS reference spell costs, 2015-2016; FZ91A-M, weighted average based on costs with and without intervention; uplifted to 2019/2020 costs using PSSRU 2020	£2,215
Urinary tract infection	NHS reference spell costs, 2013-2014; LA04H-S; uplifted to 2019/2020 costs using PSSRU 2020	£3,032
Vomiting	NHS reference costs, 2019-2020; Outpatient gastroenterology (Code 301)	£145
Weight decrease	No cost assumed	£0
Weight increase	No cost assumed	£0
Abbreviations: NHS, National Health Service. **Note:** Where a range of sequential codes is provided (e.g. FZ90A to FZ90B), a weighted average based on recorded activity levels within that whole range (also provided in the NHS reference spell costs) was used **Source**: NHS reference costs 2019-2020[143]; individual patient-level data from STEPS and STEPS-2 (Appendix M)		

B.3.5.4 Miscellaneous unit costs and resource use

No other costs were considered.

B.3.6 Summary of base-case analysis inputs and assumptions

B.3.6.1 Summary of base-case analysis inputs

Two base case analyses are provided to reflect some (albeit far from all) key differences in cost-effectiveness between the adult and paediatric populations. A summary of the inputs in the base case analyses is given in **Table 44**, with specific values noted where they differ between the adult and paediatric base case analyses.

Table 44: Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
Model characteristics			
Start age	50 years (Adult) 6 years (Paediatrics)	Not varied	B.3.2.2
Time horizon	50 years (Adults) 94 years (Paediatrics)	Not varied	B.3.2.2

Cycle length	28 days	Not varied	B.3.2.2
Proportion female	53.5%	Not varied	B.3.2.2
Discount rate (costs and benefits)	3.5%	Not varied	B.3.2
Transition probabilities			
Health-state transition probabilities	See Appendix M	See Appendix M	B.3.2.2 Appendix M
Survival model for adults (Salazar *et al.* [Log-normal])			
Mean	2.91	(2.39, 3.42) [Multivariate normal]	B.3.3.4
SD	0.51	(0.27,0.62) [Multivariate normal]	
Survival model for paediatrics (Pironi *et al.* [Exponential])			
Rate	-3.96	(-4.20,-3.71) [Normal]	B.3.3.4
Time on treatment model (Weibull)			
Shape	-0.48	(-1.03,0.07) [Multivariate normal]	B.3.3.3
Scale	7.31	(6.73,7.89) [Multivariate normal]	
Drug acquisition costs			
Teduglutide acquisition (per cycle) [5 mg vial]	[redacted]	Not varied	B.3.5.1
Health state costs (Adults)			
PS 0	[redacted]	[redacted]	B.3.5.2
PS 1	[redacted]	[redacted]	
PS 2	[redacted]	[redacted]	
PS 3	[redacted]	[redacted]	
PS 4	[redacted]	[redacted]	
PS 5	[redacted]	[redacted]	
PS 6	[redacted]	[redacted]	
PS 7	[redacted]	[redacted]	
Health state costs (Paediatrics)			
PS 0	[redacted]	[redacted]	B.3.5.2

PS 1	[redacted]	[redacted]	
PS 2	[redacted]	[redacted]	
PS 3	[redacted]	[redacted]	
PS 4	[redacted]	[redacted]	
PS 5	[redacted]	[redacted]	
PS 6	[redacted]	[redacted]	
PS 7	[redacted]	[redacted]	
Complication and adverse event treatment costs			
Liver disease	£2,775	(£1,796, £3,964) [Gamma]	B.3.5.2
Renal dialysis	£2,384	(£1,543, £3,406) [Gamma]	
Abdominal distension	£839	(£543, £1,198) [Gamma]	
Abdominal pain	£839	(£543, £1,198) [Gamma]	
Arthralgia	£763	(£494, £1,090) [Gamma]	
Bacteraemia	£0	Not varied	
Catheter related infection	£0	Not varied	
Central line infection	£0	Not varied	
Constipation	£145	(£94, £208) [Gamma]	
Decreased appetite	£0	Not varied	
Dehydration	£0	Not varied	
Diarrhoea	£145	(£94, £208) [Gamma]	
Dizziness	£163	(£105, £233) [Gamma]	
Dyspnoea	£163	(£105, £233) [Gamma]	
Fatigue	£0	Not varied	
Flatulence	£0	Not varied	
Gastrointestinal stoma complication	£145	(£94, £208) [Gamma]	
Headache	£0	Not varied	

Injection site haematoma	£163	(£105, £233) [Gamma]	
Injection site pain	£163	(£105, £233) [Gamma]	
Muscle spasms	£163	(£105, £233) [Gamma]	
Nausea	£145	(£94, £208) [Gamma]	
Peripheral oedema	£2,135	(£1,382, £3,050) [Gamma]	
Bacterial overgrowth	£3,994	(£2,585, £5,705) [Gamma]	
Pain	£730	(£472, £1042) [Gamma]	
Procedural site reactions	£163	(£105, £233) [Gamma]	
Pyrexia	£163	(£105, £233) [Gamma]	
Renal colic	£839	(£543, £1,198) [Gamma]	
Small intestinal stenosis	£839	(£543, £1,198) [Gamma]	
Upper respiratory tract infection	£2,215	(£1,434, £3,164) [Gamma]	
Urinary tract infection	£3,032	(£1,962, £4,331) [Gamma]	
Vomiting	£145	(£94, £208) [Gamma]	
Decreased weight	£0	Not varied	
Increased weight	£0	Not varied	
Other costs			
Colonoscopy	£620	(£401, £886) [Gamma]	B.3.5.1
Adverse event rates per cycle (teduglutide 0-6 months)			
Abdominal distension	[redacted]	[redacted]	B.3.5.3
Abdominal pain	[redacted]	[redacted]	
Arthralgia	[redacted]	[redacted]	
Bacteraemia	[redacted]	[redacted]	
Catheter related infection	[redacted]	[redacted]	
Central line infection	[redacted]	[redacted]	
Constipation	[redacted]	[redacted]	
Decreased appetite	[redacted]	[redacted]	
Dehydration	[redacted]	[redacted]	
Diarrhoea	[redacted]	[redacted]	

Dizziness	[redacted]	[redacted]	
Dyspnoea	[redacted]	[redacted]	
Fatigue	[redacted]	[redacted]	
Flatulence	[redacted]	[redacted]	
Gastrointestinal stoma complication	[redacted]	[redacted]	
Headache	[redacted]	[redacted]	
Injection site haematoma	[redacted]	[redacted]	
Injection site pain	[redacted]	[redacted]	
Muscle spasms	[redacted]	[redacted]	
Nausea	[redacted]	[redacted]	
Peripheral oedema	[redacted]	[redacted]	
Bacterial overgrowth	[redacted]	[redacted]	
Pain	[redacted]	[redacted]	
Procedural site reactions	[redacted]	[redacted]	
Pyrexia	[redacted]	[redacted]	
Renal colic	[redacted]	[redacted]	
Small intestinal stenosis	[redacted]	[redacted]	
Upper respiratory tract infection	[redacted]	[redacted]	
Urinary tract infection	[redacted]	[redacted]	
Vomiting	[redacted]	[redacted]	
Decreased weight	[redacted]	[redacted]	
Increased weight	[redacted]	[redacted]	
Adverse event rates per cycle (teduglutide; after 6 months)			
Abdominal distension	[redacted]	[redacted]	B.3.5.3
Abdominal pain	[redacted]	[redacted]	
Arthralgia	[redacted]	[redacted]	
Bacteraemia	[redacted]	[redacted]	
Catheter related infection	[redacted]	[redacted]	
Central line infection	[redacted]	[redacted]	
Constipation	[redacted]	[redacted]	
Decreased appetite	[redacted]	[redacted]	
Dehydration	[redacted]	[redacted]	
Diarrhoea	[redacted]	[redacted]	

Dizziness	[redacted]	[redacted]	
Dyspnoea	[redacted]	[redacted]	
Fatigue	[redacted]	[redacted]	
Flatulence	[redacted]	[redacted]	
Gastrointestinal stoma complication	[redacted]	[redacted]	
Headache	[redacted]	[redacted]	
Injection site haematoma	[redacted]	[redacted]	
Injection site pain	[redacted]	[redacted]	
Muscle spasms	[redacted]	[redacted]	
Nausea	[redacted]	[redacted]	
Peripheral oedema	[redacted]	[redacted]	
Bacterial overgrowth	[redacted]	[redacted]	
Pain	[redacted]	[redacted]	
Procedural site reactions	[redacted]	[redacted]	
Pyrexia	[redacted]	[redacted]	
Renal colic	[redacted]	[redacted]	
Small intestinal stenosis	[redacted]	[redacted]	
Upper respiratory tract infection	[redacted]	[redacted]	
Urinary tract infection	[redacted]	[redacted]	
Vomiting	[redacted]	[redacted]	
Decreased weight	[redacted]	[redacted]	
Increased weight	[redacted]	[redacted]	
Adverse event rates per cycle (standard care)			
Abdominal distension	[redacted]	[redacted]	B.3.5.3
Abdominal pain	[redacted]	[redacted]	
Arthralgia	[redacted]	[redacted]	
Bacteraemia	[redacted]	[redacted]	
Catheter related infection	[redacted]	[redacted]	
Central line infection	[redacted]	[redacted]	
Constipation	[redacted]	[redacted]	
Decreased appetite	[redacted]	[redacted]	
Dehydration	[redacted]	[redacted]	
Diarrhoea	[redacted]	[redacted]	

Dizziness	[redacted]	[redacted]	
Dyspnoea	[redacted]	[redacted]	
Fatigue	[redacted]	[redacted]	
Flatulence	[redacted]	[redacted]	
Gastrointestinal stoma complication	[redacted]	[redacted]	
Headache	[redacted]	[redacted]	
Injection site haematoma	[redacted]	[redacted]	
Injection site pain	[redacted]	[redacted]	
Muscle spasms	[redacted]	[redacted]	
Nausea	[redacted]	[redacted]	
Peripheral oedema	[redacted]	[redacted]	
Bacterial overgrowth	[redacted]	[redacted]	
Pain	[redacted]	[redacted]	
Procedural site reactions	[redacted]	[redacted]	
Pyrexia	[redacted]	[redacted]	
Renal colic	[redacted]	[redacted]	
Small intestinal stenosis	[redacted]	[redacted]	
Upper respiratory tract infection	[redacted]	[redacted]	
Urinary tract infection	[redacted]	[redacted]	
Vomiting	[redacted]	[redacted]	
Decreased weight	[redacted]	[redacted]	
Increased weight	[redacted]	[redacted]	
Risk of complications			
IFALD rate (0-2 years) [No PS]	0.000%	(0.000%,0.000%) [Beta]	B.3.3.5
IFALD rate (0-2 years) [Low PS]	0.013%	(0.008%,0.018%) [Beta]	
IFALD rate (0-2 years) [Mid PS]	0.026%	(0.017%,0.037%) [Beta]	
IFALD rate (0-2 years) [High PS]	0.039%	(0.025%,0.055%) [Beta]	
IFALD rate (2-6 years) [No PS]	0.000%	(0.000%,0.000%) [Beta]	
IFALD rate (2-6 years) [Low PS]	0.006%	(0.004%,0.009%) [Beta]	
IFALD rate (2-6 years) [Mid PS]	0.013%	(0.008%,0.0018%) [Beta]	

IFALD rate (2-6 years) [High PS]	0.000%	(0.000%,0.000%) [Beta]	
IFALD rate (6+ years) [No PS]	0.019%	(0.013%,0.028%) [Beta]	
IFALD rate (6+ years) [Low PS]	0.000%	(0.000%,0.000%) [Beta]	
IFALD rate (6+ years) [Mid PS]	0.006%	(0.004%,0.009%) [Beta]	
IFALD rate (6+ years) [High PS]	0.013%	(0.008%,0.019%) [Beta]	
Extensive fibrosis rate (0-2 years)	0.020%	(0.013%,0.028%) [Beta]	
Extensive fibrosis rate (2+ years)	2.38%	(1.54%,3.40%) [Beta]	
Cirrhosis rate (0-3 years)	0.98%	(0.63%,1.40%) [Beta]	
Cirrhosis rate (0-3 years)	1.30%	(0.84%,1.86%) [Beta]	
CKD rate (0-1 year) [No PS]	1.20%	(0.78%,1.71%) [Beta]	
CKD rate (0-1 year) [Low PS]	0.00%	(0.00%,0.00%) [Beta]	
CKD rate (0-1 year) [Mid PS]	0.03%	(0.02%,0.04%) [Beta]	
CKD rate (0-1 year) [High PS]	0.05%	(0.03%,0.07%) [Beta]	
CKD rate (1-2 year) [No PS]	0.08%	(0.05%,0.11%) [Beta]	
CKD rate (1-2 year) [Low PS]	0.00%	(0.00%,0.00%) [Beta]	
CKD rate (1-2 year) [Mid PS]	0.03%	(0.02%,0.04%) [Beta]	
CKD rate (1-2 year) [High PS]	0.05%	(0.03%,0.07%) [Beta]	
CKD rate (2+ year) [No PS]	0.08%	(0.05%,0.11%) [Beta]	
CKD rate (2+ year) [Low PS]	0.00%	(0.00%,0.00%) [Beta]	
CKD rate (2+ year) [Mid PS]	0.01%	(0.01%,0.01%) [Beta]	
CKD rate (2+ year) [High PS]	0.02%	(0.01%,0.03%) [Beta]	
Utilities			
No PS	0.820	(0.44,0.99) [Beta]	B.3.4.5
Disutility PS 1 day per week	-0.040	(-0.03,-0.06) [Beta]	

Disutility PS 2 days per week	-0.100	(-0.06,-0.14) [Beta]	
Disutility PS 3 days per week	-0.170	(-0.11,-0.24) [Beta]	
Disutility PS 4 days per week	-0.240	(-0.15,-0.34) [Beta]	
Disutility PS 5 days per week	-0.310	(-0.2,-0.44) [Beta]	
Disutility PS 6 days per week	-0.410	(-0.26,-0.57) [Beta]	
Disutility PS 7 days per week	-0.460	(-0.29,-0.64) [Beta]	
Carer utility PS0	0	Not varied	
Carer utility decrement PS1	-0.10	(-0.13,-0.29) [Beta]	
Carer utility decrement PS2	-0.10	(-0.13,-0.29) [Beta]	
Carer utility decrement PS3	-0.10	(-0.13,-0.29) [Beta]	
Carer utility decrement PS4	-0.17	(-0.21,-0.47) [Beta]	
Carer utility decrement PS5	-0.17	(-0.21,-0.47) [Beta]	
Carer utility decrement PS6	-0.22	(-0.28,-0.62) [Beta]	
Carer utility decrement PS7	-0.22	(-0.28,-0.62) [Beta]	
Liver disease (Overall) utility value	0.596	(0.53,0.66) [Beta]	
Non-progressed Liver disease Utility value	0.770	(0.43,0.97) [Beta]	
Extensive fibrosis Utility value	0.660	(0.39,0.88) [Beta]	
Cirrhosis Utility value	0.570	(0.35,0.78) [Beta]	
CKD V Utility value	0.710	(0.41,0.93) [Beta]	
Abdominal distension	-0.0512	(-0.03,-0.07) [Beta]	
Abdominal pain	-0.0512	(-0.03,-0.07) [Beta]	
Arthralgia	-0.023	(-0.01,-0.03) [Beta]	
Bacteraemia	-0.52	(-0.32,-0.72) [Beta]	
Catheter related infection	-0.52	(-0.32,-0.72) [Beta]	
Central line infection	-0.52	(-0.32,-0.72) [Beta]	

Constipation	-0.0512	(-0.03,-0.07) [Beta]	
Decreased appetite	0	Not varied	
Dehydration	0	Not varied	
Diarrhoea	-0.0512	(-0.03,-0.07) [Beta]	
Dizziness	0	Not varied	
Dyspnoea	0	Not varied	
Fatigue	0	Not varied	
Flatulence	0	Not varied	
Gastrointestinal stoma complication	0	Not varied	
Headache	0	Not varied	
Injection site haematoma	-0.03	(-0.02,-0.04) [Beta]	
Injection site pain	-0.03	(-0.02,-0.04) [Beta]	
Muscle spasms	0	Not varied	
Nausea	0	Not varied	
Peripheral oedema	-0.0508	(-0.03,-0.07) [Beta]	
Bacterial overgrowth	-0.52	(-0.32,-0.72) [Beta]	
Pain	0	Not varied	
Procedural site reactions	-0.03	(-0.02,-0.04) [Beta]	
Pyrexia	0	Not varied	
Renal colic	0	Not varied	
Small intestinal stenosis	-0.0512	(-0.03,-0.07) [Beta]	
Upper respiratory tract infection	-0.09	(-0.06,-0.13)	
Urinary tract infection	-0.09	(-0.06,-0.13)	
Vomiting	-0.0512	(-0.03,-0.07)	
Decreased weight	0	Not varied	
Increased weight	0	Not varied	
Abbreviations: CI, confidence interval; CKD, chronic kidney disease; IFALD, intestinal failure-associated liver disease; PS, parenteral support			

B.3.6.2 Assumptions

An outline of the key assumptions applied in the economic model is given in

Table *45*, along with a justification for each. A list of alternative assumptions explored as scenario analyses is also shown alongside. The results of these scenario analyses are given in section B.3.8.3.

Table 45. Base case analysis assumptions

Input/Parameter	Source/Assumption	Justification	Alternative scenarios
Discount rate	3.5% annual discounting applied for both costs and QALYs.	As per the NICE reference case.	Discount rate of 1.5% for costs and QALYs as per NICE methods guide Section 6.2.19[147]. Teduglutide gives the opportunity for patients to be restored to near full health from an otherwise severely impaired life. This impact is also expected to be life-long and therefore a 1.5% discount rate should be considered by the Appraisal Committee.
Health-state transition probabilities for the teduglutide group.	Estimated from pooled STEPS/STEPS-2 and PSP data. The STEPS/STEPS-2 data provides a cohort of 42 patients who received teduglutide for up to 30 months. The PSP cohort provides data for up to 12 months of treatment. To account for patients with <12 months of data, a last-value-carried-forward approach was taken to impute values up to 12 months. This is likely to be a very conservative assumption, as the patients who have only been on teduglutide for a shorter time will not have had chance to experience the full benefits.	Includes the data that is most reflective of clinical practice (PSP) and the clinical trial data that most closely aligns with this to ensure the sample size is sufficient to give robust results.	Using only STEPS/STEPS-2 data. This applies to all parameters informed by these data, i.e., starting population distributions, health-state transitions, and treatment discontinuation modelling.

Health-state transition probabilities for the standard care group.	Patients remain in their stable PS health-state.	As patients are required to achieve a stable PS level while receiving standard care before commencing teduglutide, these patients are assumed to remain stable.	No clinically plausible alternatives to explore.
Survival	Survival of adult patients based on survival modelling in Salazar 2021[27]; survival of paediatric patients based on Pironi 2011[126]. No treatment-related mortality benefit is assumed in either base case.	Salazar 2021[27] and Pironi 2011[126] provides the most recently published survival data identified relevant to the adult/paeditraic SBS-IF population. Clinical experts suggested that SBS-IF management and therefore survival has improved in recent years and it is therefore important to capture the most up-to-date evidence. No suitable data exist that can disentangle PS-related vs SBS-IF-related mortality. Assuming no survival benefit is likely to be conservative, as a mortality benefit from reduced PS-associated complications is plausible.	Amiot 2013[24] (adult base case only)
Time on treatment	Estimated using survival models extrapolated from pooled STEPS/STEPS-2 and PSP data to align with health-state transitions. The best fitting Weibull model was used.	Most reliable source of discontinuation data available and it aligns with the treatment effectiveness data. The Weibull model provided the best fit to the data.	Alternative models: • Log-logistic • Lognormal No further discontinuation after stopping rule.

Health-state distribution of those who discontinue teduglutide.	Estimated using the pooled STEPS/STEPS-2 and PSP data for those who discontinued treatment at any time. Assumed constant until stopping rule is applied. After the stopping is applied, the distribution is recalculated from the same datasets but using only the patients who discontinued but would not be captured by the stopping rule i.e. those that achieved a benefit before the (12 month) stopping rule but discontinued thereafter.	Source of data aligns with the data used to inform the health-state transition probabilities as well as the rates of discontinuation. A time-varying distribution was not appropriate due to the diminishing number of discontinuation events occurring with time. Assuming no discontinuations post-12 months is not clinically plausible	None.
Health-state distribution after discontinuation. (Reversion to baseline)	Estimated using the baseline PS requirements from the pooled STEPS/STEPS-2 and PSP data for those who discontinued treatment at any time and assumed to occur immediately post-discontinuation of treatment.	Clinical expert opinion suggests that patients would not be able to sustain benefits achieved while on teduglutide treatment unless they continued to use it. Reversion to baseline (or close to baseline) is likely to occur within a matter of weeks after discontinuation. Clinicians did note however that patients may be able to sustain a small amount of the benefit achieved and that (to ensure a healthy nutritional balance) reversion would be managed over 2-8 weeks, and therefore this is likely to be a conservative assumption.	None
Treatment stopping rule	Patients who have not achieved a reduction in days of PS per week are assumed to stop teduglutide at 12 months.	Aligns with the SmPC and anticipated clinical management.	No clinically relevant alternatives.
Health-state utility values	Based on the health-state utility values reported in Ballinger 2018[113]	Ballinger 2018[113] is the only reliable source of data providing plausible health-state utility values from a UK perspective.	Lachaine 2016[65] provides an alternative set of plausible utility values by PS days per week but from a Canadian perspective.

Complications	Complication rates for intestinal-failure-related liver disease and chronic kidney disease are included based on estimates elicited from a Delphi panel[127]. These rates are stratified by PS requirements, with maximum rates for the highest PS consumption Patients' baseline PS requirements are used to estimate risks of complications for PS dependence in the alternative scenario in which a reduction in risk is only assumed for those who achieve independence.	Published data informing the rates of complications related to PS is limited. However, as these complications have been linked to PS, it seems reasonable that reducing PS with teduglutide treatment will reduce incidence.	An alternative scenario where a benefit is only achieved if PS independence is achieved.
Adverse events	Based on STEPS trial data for teduglutide and standard care.	Most reliable source of data available to inform safety.	Limit to severe adverse events only.
Paediatric base case analysis (see B.3.2.1)	All inputs are the same as for adults, except for: • Starting age 6 years (vs 50 in adults) • Time horizon 94 years (vs 50 in adults) • Survival data modelled using Pironi 2011 (vs Salazar 2021 in adults) • Paediatric-specific hospital costs for specialised visits and line sepsis	Different starting age, time horizon and survival modelling reflect children's younger age and longer expected lifetime. Clinical feedback suggests children have longer hospital stays and more frequent hospitalisation, reflected in the higher hospital costs. Even with these assumptions, our paediatric base case is still likely to be conservative (see B.3.2.1).	No additional paediatric-specific alternative scenarios.
Abbreviations: PS, parenteral support ; SmPC, Summary of Product Characteristics; PSP, patient support programme; SBS-IF, short bowel syndrome with type 3 intestinal failure; QALYs, quality-adjusted life years			

B.3.7 Base-case results

B.3.7.1 Base-case incremental cost-effectiveness analysis results

The base case results for teduglutide compared to standard care in the adult population are given in **Table 46**, and the results for the paediatric base case analysis are given in **Table 47**. Both sets of results incorporate the current PAS discount for teduglutide of [redacted].

Table 46: Base-case results (adults)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Standard Care	[redacted]	[redacted]	[redacted]	-	-	-	-
Teduglutide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,652
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table 47: Base-case results (paediatrics)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER versus baseline (£/QALY)
Standard Care	[redacted]	[redacted]	[redacted]	-	-	-	-
Teduglutide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£4,811
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

To capture the uncertainty of all parameters within the economic model, a probabilistic sensitivity analysis (PSA) was performed to assess the impact of this uncertainty on the results of the base case analyses. All parameters were randomly sampled simultaneously based on the distribution and parameter information given in **Table 44** (see B.3.6.1)

The PSA was performed using 10,000 parameter samples for both the adult and paediatric base case analyses. The mean probabilistic results for the adult and paediatric base cases are given in **Table 48** and **Table 49**, respectively.

Table 48: Probabilistic sensitivity analysis results (adults)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Standard Care	[redacted]	[redacted]			
Teduglutide	[redacted]	[redacted]	[redacted]	[redacted]	£18,962
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years					

Table 49: Probabilistic sensitivity analysis results (paediatric)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER versus baseline (£/QALY)
Standard Care	[redacted]	[redacted]			
Teduglutide	[redacted]	[redacted]	[redacted]	[redacted]	£5,404
Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years					

A scatterplot showing the spread of the PSA sampled results for each base case is given in **Figure 30**, showing the majority of PSA samples fall under the upper NICE-preferred willingness-to-pay threshold of £30,000 per QALY.

Figure 30. Cost-effectiveness plane with 10,000 PSA samples for A) adult base case and B) paediatric base case

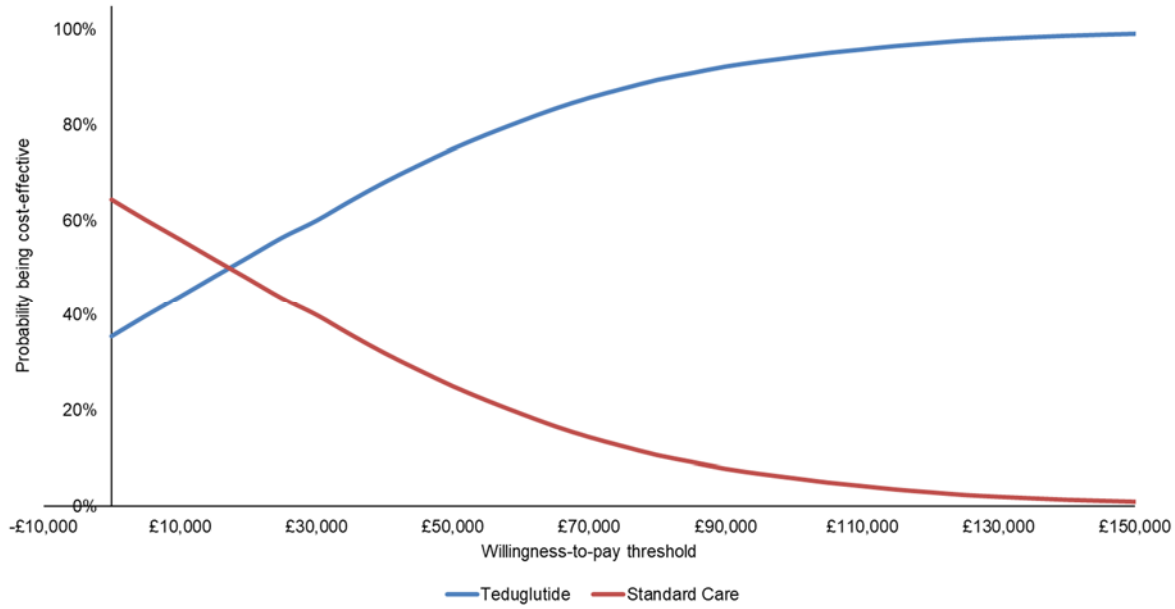
A)

B)

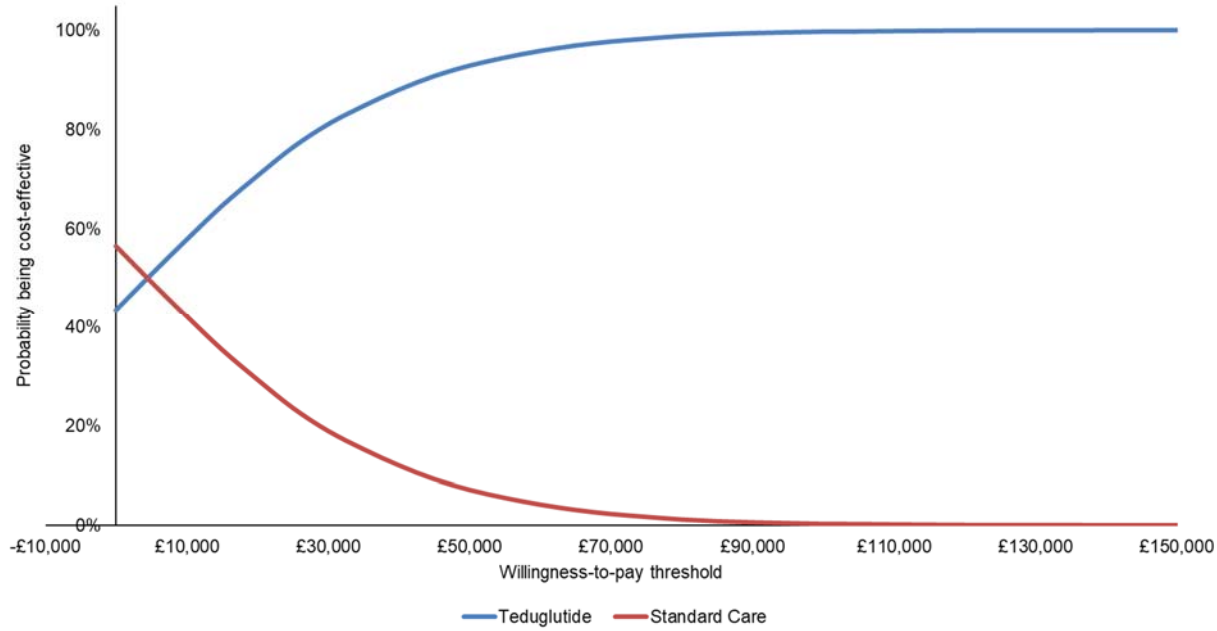
A cost-effectiveness acceptability curve for each of the two base case analyses is also given in **Figure 31**, demonstrating the likelihood of cost-effectiveness at varying willingness-to-pay thresholds.

Figure 31. Cost-effectiveness acceptability curve for A) adult base case and B) paediatric base case

A)



B)



B.3.8.2 Deterministic sensitivity analysis

One-way sensitivity analyses were performed to assess the impact of each individual parameter while others were kept constant. Each parameter was varied using the

upper and lower bounds of the confidence intervals for each parameter, given in **Table 44**.

The results of the ten most sensitive parameters for the adult and paediatric base case analyses are depicted in **Figure 32** and **Figure 33**, respectively.

Figure 32. One-way sensitivity analysis results for ten most sensitive parameters (adult base case)

Figure 33. One-way sensitivity analysis results for ten most sensitive parameters (paediatric base case)

B.3.8.3 Scenario analysis

The results of the scenario analyses described alongside the base case inputs and assumptions in

Table *45* are given in **Table 50** and **Table 51**, relative to the adult base case and paediatric base case, respectively.

Table 50 Summary of scenario analyses (adults)

Model component	Base case	Scenario	Relevant section of submission	ICER (£/QALY)
Base case				£16,652
Discount rate	3.5% for both costs and QALYs	1.5% for both costs and QALYs.	B.3.2	£9,339
Data source	STEPS/STEPS-2 and PSP data pooled	STEPS/STEPS-2 only	B.3.3.1	£20,413
Survival modelling	Salazar 2021 (Log-normal)	Salazar 2021 (Exponential)	B.3.3.4	£19,836
		Salazar 2021 (Log-logistic)		£18,545
		Amiot 2013 (Gen.gamma)		£21,573
		Amiot 2013 (Log-normal)		£23,543
		Amiot 2013 (Log-logistic)		£24,083
Treatment discontinuation model	Weibull	Log-normal	B.3.3.3	£18,645
		Log-logistic		£17,089
Treatment discontinuation assumptions after stopping rule.	Rate based on extrapolated survival model	No further discontinuation after stopping rule	B.3.3.3.2	£37,459
Heath-state utility data source	Ballinger 2018	Lachaine 2016	B.3.4.5	£20,846
Complications	Based on Delphi panel rates	Assumes benefit only achieved for PS 0 (based on Delphi panel rates applied to baseline PS for all others)	B.3.3.5	£17,609
		No complications		£20,949
Adverse events	All adverse events	Serious adverse events only	B.3.4.3	£20,247
Carer quality of life		Delphi panel	B.3.4.4	£14,533

	Mid-point of Delphi panel and survey	Survey		£19,494
Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; PS, parenteral support; PSP, patient support programme				

Table 51 Summary of scenario analyses (paediatrics)

Model component	Base case	Scenario	Relevant section of submission	ICER (£/QALY)
Base case				£4,811
Discount rate	3.5% for both costs and QALYs	1.5% for both costs and QALYs.	B.3.2	Dominates
Data source	STEPS/STEPS-2 and PSP data pooled	STEPS/STEPS-2 only	B.3.3.1	£8,400
Treatment discontinuation model	Weibull	Log-normal	B.3.3.3	£6,394
		Log-logistic		£5,149
Treatment discontinuation assumptions after stopping rule	Rate based on extrapolated survival model	No further discontinuation after stopping rule	B.3.3.3.2	£25,381
Heath-state utility data source	Ballinger 2018	Lachaine 2016	B.3.4.5	£5,835
Complications	Based on Delphi panel rates	Assumes benefit only achieved for PS 0 (based on Delphi panel rates applied to baseline PS for all others)	B.3.3.5	£5,844
		No complications		£9,728
Adverse events	All adverse events	Severe adverse events only	B.3.4.3	£7,827
Carer quality of life	Mid-point of Delphi panel and survey	Delphi panel	B.3.4.4	£4,049
		Survey		£5,928
Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; PS, parenteral support; PSP, patient support programme				

B.3.8.4 Summary of sensitivity analyses results

The scenarios performed demonstrate that the base case analysis is robust to plausible alternative assumptions and data sources. For the adult scenario analyses, all but one resulted in an ICER below the £30k per QALY willingness-to-pay threshold. The scenario that assumes that no further treatment discontinuation occurs after the stopping rule raised the ICER above the £30k per QALY willingness-

to-pay threshold; however, this scenario is not clinically plausible and merely acts as a maximum upper bound when considering the uncertainty around the benefits lost by those who discontinue.

For the paediatric scenario analyses, all but one were consistent with the base case analysis in demonstrating ICERs well below NICE's lower willingness-to-pay threshold of £20k. Again, the scenario that assumes no further treatment discontinuation occurs after the stopping rule was the outlier. However, the ICER for this scenario was still under the £30k per QALY willingness-to-pay threshold, thus, providing strong support that teduglutide represents a very cost-effective treatment.

B.3.9 Subgroup analysis

No subgroup analyses were performed.

B.3.10 Validation

B.3.10.1 Validation of the cost-effectiveness analysis

To ensure the economic model is fit for purpose and provides reliable results suitable for decision making, the use of data sources and key assumptions applied in the model were validated at an advisory board consisting of three clinicians experienced in the treatment of SBS-IF, covering both adults and paediatrics. There was consensus that the data sources used were appropriate and the assumptions made were clinically plausible[62].

Advice from expert health economists was also obtained to discuss how the evidence was incorporated into the model and the justifications for key assumptions applied in the model. While acknowledging some uncertainties in the evidence base, the experts considered the approach taken for the economic analyses to be appropriate and justifications for the evidence used and the assumptions applied to be sound.

The model was also quality assured by a health economist not involved in the development of the model, to ensure that the inputs applied in the model were accurate and the functionality of the model reliable. The model was considered fit for purpose with no major issues identified. All minor issues were amended before submission of the model.

The validity of the outputs of the economic model were assessed by comparing the predicted clinical outcomes against those observed in the STEPS trials and, more importantly, the more clinically generalisable real-world outcomes. For the base case analysis, the model predicts that 22% of people receiving teduglutide achieve PS independence, compared to a total of [redacted] who actually achieved independence across the STEPS, STEPS-2 and PSP study populations combined. [redacted]. As our model leans heavily on STEPS and STEPS-2 data, it is likely that more than [redacted] of patients would actually be able to achieve independence from PS in the real-world.

The model, therefore, is underestimating the benefits of teduglutide, and although the difference may seem slight, the proportion of patients who achieve PS independence is a key driver of the model results. This is because it not only provides additional QALY gains, but also a larger cost saving by removing not just an additional PS bag, but also the need for any of the expensive fixed costs of PS treatment incurred by all PS dependent patients.

Published cost-effectiveness analyses (Raghu 2020[119]) do not provide a reliable source to validate outputs of the economic model, as their analyses were based on a US costs perspective and were based on the list price of teduglutide. Their modelling approach was also much more simplistic as it assumed all patients started on 7 days of PS per week, and probabilities of transitioning were based on achieving either a one day reduction or achieving a reduction of greater than two days. Their model also used outdated mortality data and did not consider the impact on carers. However, their model followed the same general structure and used health-state utility values from the same source as our model, as was also accepted by the committee in NICE appraisal TA690.

B.3.11 Interpretation and conclusions of economic evidence

The results of the economic analyses presented demonstrate that treatment with teduglutide for patients with short bowel syndrome and type 3 intestinal failure (SBS-IF) represents a cost-effective use of NHS resources. Teduglutide provides large quality-of-life benefits to patients whose lives are heavily restricted by their dependence on parenteral support (PS): [redacted].

Given the nature of SBS-IF as an ultra-rare disease and teduglutide as a life-long treatment, there is inherent uncertainty within the data and therefore the economic analyses also. Every effort has been made to obtain as much relevant evidence as possible to mitigate the uncertainties in the analysis. This includes extensive use of real-world data both as a model input and to validate model assumptions. This extent of real-world data is not normally available for use in NICE submissions. Where it was not possible to resolve uncertainties within the data, we opted to take a conservative approach. Examples of this include:

- Our model assumes no further reduction in PS after 30 months (end of STEPS-2), whereas some clinical data show continued improvement is possible beyond this time(see B.2.6.2.2)
- Patient support programme (PSP) data (which represent the model input most reflective of teduglutide's real-world effectiveness) only contributes towards the first 12 months of transition probabilities in our model. [redacted] (see B.3.3.2). Additionally, to account for the irregular follow-up in the PSP data, the last value recorded was carried forward to estimate the number of people in each state at each 6-month interval. This represents a potentially

conservative approach as patients may have been able to achieve further benefits within the 6 month intervals that have not been captured

- Upon discontinuing teduglutide, our model assumes all patients immediately revert to their baseline PS needs, whereas clinical data and expert opinion suggest reversion may not be complete and takes longer (see B.3.3.3.3)

Furthermore, all relevant clinically plausible scenario analyses and sensitivity analyses have been performed to demonstrate the impact of these uncertainties. A majority of probabilistic sensitivity analysis samples fall within NICE's willingness-to-pay threshold (a vast majority for the paediatric analysis). Our model estimates that teduglutide has a ~60% probability of being cost effective for adults (~80% for children) at a willingness-to-pay threshold of £30,000 per QALY. This demonstrates that despite the uncertainty, and including conservative assumptions, teduglutide is likely to be a cost-effective use of NHS resources.

Despite the ultra-rare nature of SBS-IF (an estimated 350 patients are eligible to receive teduglutide in England[14, 15]); the chronic and disabling nature of treatment with PS; and the likelihood of life-long requirements for the treatment, teduglutide was not considered suitable to be appraised via NICE's highly specialised technology (HST) appraisal route. As such, teduglutide is being assessed via the single technology appraisal (STA) route, with a willingness-to-pay threshold ten-fold lower. This puts SBS-IF patients at risk of being restricted access to a potentially life-changing treatment because the willingness-to-pay is on par with that of highly prevalent and less severe diseases. In this light, our base case analyses, with ICERs <£20,000 per QALY gained, represent a *very* cost-effective treatment in an ultra-rare setting. It should be noted that these considerations were taken into account by other HTA bodies meaning that teduglutide is already available in many other parts of the world, including in Scotland[2, 3].

Further to this, there are wider societal benefits that treatment with teduglutide and reducing the need for PS dependence can bring that cannot be explicitly captured within the economic analysis. [redacted]. There is, therefore, a wider societal benefit that treatment with teduglutide brings beyond that captured in the economic analysis.

The current standard care, PS combined with best supportive care, represents essential life preserving treatment with high costs, complication risks, and severe impacts on the quality-of-life of patients' and their caregivers. The innovation of teduglutide, however, provides patients with this ultra-rare disease the opportunity to live a life less restricted by PS. A positive NICE recommendation for teduglutide would provide patients with a chance to reduce their dependence on PS, an opportunity that does not otherwise exist. This represents a huge improvement in patients' ability to socialise, travel, work and sleep; better mental wellbeing; reduced burden on intimate relationships; and freedom from medical issues and stress resulting from serious PS-associated complications.

Representatives of patient advocacy groups talk of how gaining independence from PS, *"must feel like freedom has come at last"*.

B.4 References

1. Shire Pharmaceuticals Limited. Revestive 1.25 and 5 mg powder and solvent for solution for injection. Summary of Product Characteristics2020.
2. Scottish Medicines Consortium. Advice for teduglutide: paediatric patients (1139/16) 2018 [Available from: https://www.scottishmedicines.org.uk/medicines-advice/teduglutide-revestive-fullsubmission-113916/.
3. Scottish Medicines Consortium. Advice for teduglutide: adult patients (SMC2225) 2020 [Available from: https://www.scottishmedicines.org.uk/medicines-advice/teduglutide-revestive-resub-smc2225/.
4. Buchman AL. Etiology and initial management of short bowel syndrome. Gastroenterology. 2006;130(2 Suppl 1):S5-S15.
5. Pironi L, Arends J, Bozzetti F, Cuerda C, Gillanders L, Jeppesen PB, et al. ESPEN guidelines on chronic intestinal failure in adults. Clin Nutr. 2016;35(2):247-307.
6. Huisman-de Waal G, Schoonhoven L, Jansen J, Wanten G, van Achterberg T. The impact of home parenteral nutrition on daily life-a review. Clin Nutr. 2007;26(3):275-88.
7. Persoon A, Huisman-de Waal G, Naber TA, Schoonhoven L, Tas T, Sauerwein H, et al. Impact of long-term HPN on daily life in adults. Clin Nutr. 2005;24(2):304-13.
8. Heaney A, McKenna SP, Wilburn J, Rouse M, Taylor M, Burden S, et al. The impact of Home Parenteral Nutrition on the lives of adults with Type 3 Intestinal Failure. Clin Nutr ESPEN. 2018;24:35-40.
9. Duro D, Kamin D, Duggan C. Overview of pediatric short bowel syndrome. J Pediatr Gastroenterol Nutr. 2008;47 Suppl 1:S33-6.
10. Buchman AL, Scolapio J, Fryer J. AGA technical review on short bowel syndrome and intestinal transplantation. Gastroenterology. 2003;124(4):1111-34.
11. Seetharam P, Rodrigues G. Short bowel syndrome: A review of management options. Saudi J Gastroenterol. 2011;17(4):229-35.
12. Tappenden KA. Pathophysiology of Short Bowel Syndrome. Journal of Parenteral and Enteral Nutrition. 2014;38(1_suppl):14S-22S.
13. Tappenden KA. Intestinal adaptation following resection. JPEN J Parenter Enteral Nutr. 2014;38(1 Suppl):23s-31s.
14. Pironi L, Corcos O, Forbes A, Holst M, Joly F, Jonkers C, et al. Intestinal failure in adults: Recommendations from the ESPEN expert groups. Clin Nutr. 2018;37(6 Pt A):1798-809.
15. Smith TN, M. BANS Report 2016: Artificial Nutrition Support in the UK 2005-2015. 2016.
16. Massironi S, Cavalcoli F, Rausa E, Invernizzi P, Braga M, Vecchi M. Understanding short bowel syndrome: Current status and future perspectives. Dig Liver Dis. 2020;52(3):253-61.
17. Howard L. Home parenteral nutrition: survival, cost, and quality of life. Gastroenterology. 2006;130(2 Suppl 1):S52-9.

18. Pironi L, Hébuterne X, Van Gossum A, Messing B, Lyszkowska M, Colomb V, et al. Candidates for intestinal transplantation: a multicenter survey in Europe. The American journal of gastroenterology. 2006;101(7):1633-43.
19. Höllwarth ME. Surgical strategies in short bowel syndrome. Pediatr Surg Int. 2017;33(4):413-9.
20. Dibb M, Teubner A, Theis V, Shaffer J, Lal S. Review article: the management of long-term parenteral nutrition. Aliment Pharmacol Ther. 2013;37(6):587-603.
21. Winkler MF, Hagan E, Wetle T, Smith C, Maillet JO, Touger-Decker R. An exploration of quality of life and the experience of living with home parenteral nutrition. J Parenter Enteral Nutr. 2010;34(4):395-407.
22. Jeppesen P, Shahraz SH, T, Genestin E, editors. Symptoms, Comorbidities and Treatment Satisfaction in Adult Patients Receiving Parenteral Support for Intestinal Failure Associated with Short Bowel Syndrome. Digestive Disease Week; 2021; Virtual.
23. ICON. Short Bowel Syndrome (SBS) Multi-national Survey Not published - Takeda confidential data; 2020.
24. Amiot A, Messing B, Corcos O, Panis Y, Joly F. Determinants of home parenteral nutrition dependence and survival of 268 patients with non-malignant short bowel syndrome. Clin Nutr. 2013;32(3):368-74.
25. Hallum NS, Tan LB, Baxter JP, McKee RF. Home parenteral nutrition: Outcome and seven year prospective follow up in a nationwide adult population. e-SPEN Journal. 2012;7(1):e30-e4.
26. Noelting J, Gramlich L, Whittaker S, Armstrong D, Marliss E, Jurewitsch B, et al. Survival of Patients With Short-Bowel Syndrome on Home Parenteral Nutrition: A Prospective Cohort Study. JPEN J Parenter Enteral Nutr. 2020.
27. Salazar E, Clermont-Dejean NM, Schwenger KJP, Noelting J, Lu Z, Lou W, et al. Patients With Severe Gastrointestinal Dysmotility Disorders Receiving Home Parenteral Nutrition Have Similar Survival As Those With Short-Bowel Syndrome: A Prospective Cohort Study. JPEN J Parenter Enteral Nutr. 2021;45(3):530-7.
28. Persoon A, Huisman-de Waal G, Naber TA, Schoonhoven L, Tas T, Sauerwein H, et al. Impact of long-term HPN on daily life in adults. Clinical nutrition. 2005;24(2):304-13.
29. Bond A, Chadwick P, Smith TR, Nightingale JMD, Lal S. Diagnosis and management of catheter-related bloodstream infections in patients on home parenteral nutrition. Frontline Gastroenterol. 2020;11(1):48-54.
30. Wu G, Jiang Y, Zhu X, Jin D, Han Y, Han J, et al. Prevalence and risk factors for complications in adult patients with short bowel syndrome receiving long-term home parenteral nutrition. Asia Pac J Clin Nutr. 2017;26(4):591-7.
31. Macdougall L, Hanley J, Mountford C, Thompson NP. UK practice in the prevention of central venous catheter-associated thrombosis in adults on home parenteral nutrition. Frontline Gastroenterol. 2017;8(3):163-6.
32. Agostini F, Sasdelli AS, Guidetti M, Comai G, La Manna G, Pironi L. Outcome of kidney function in adults on long-term home parenteral nutrition for chronic intestinal failure. Nutrition. 2019;60:212-6.
33. Messing B, Crenn P, Beau P, Boutron-Ruault MC, Rambaud J-C, Matuchansky C. Long-term survival and parenteral nutrition dependence in adult patients with the short bowel syndrome. Gastroenterology. 1999;117(5):1043-50.

34. Carroll RE, Benedetti E, Schowalter JP, Buchman AL. Management and Complications of Short Bowel Syndrome: an Updated Review. Curr Gastroenterol Rep. 2016;18(7):40.
35. Kelly DA. Intestinal failure-associated liver disease: what do we know today? Gastroenterology. 2006;130(2 Suppl 1):S70-7.
36. Cohen-Solal M, Baudoin C, Joly F, Vahedi K, D'Aoust L, De Vernejoul MC, et al. Osteoporosis in patients on long-term home parenteral nutrition: a longitudinal study. J Bone Miner Res. 2003;18(11):1989-94.
37. Hwa YL, Rashtak S, Kelly DG, Murray JA. Iron Deficiency in Long-Term Parenteral Nutrition Therapy. JPEN J Parenter Enteral Nutr. 2016;40(6):869-76.
38. Santos D, Batoreu C, Mateus L, Marreilha dos Santos AP, Aschner M. Manganese in human parenteral nutrition: Considerations for toxicity and biomonitoring. NeuroToxicology. 2014;43:36-45.
39. Citla Sridhar D, Abou-Ismail MY, Ahuja SP. Central venous catheter-related thrombosis in children and adults. Thromb Res. 2020;187:103-12.
40. Hodge D, Puntis JWL. Diagnosis, prevention, and management of catheter related bloodstream infection during long term parenteral nutrition. Archives of Disease in Childhood - Fetal and Neonatal Edition. 2002;87(1):F21.
41. Appleman SS, Kalkwarf HJ, Dwivedi A, Heubi JE. Bone Deficits in Parenteral Nutrition–Dependent Infants and Children With Intestinal Failure Are Attenuated When Accounting for Slower Growth. Journal of Pediatric Gastroenterology and Nutrition. 2013;57(1).
42. Pichler J, Chomtho S, Fewtrell M, Macdonald S, Hill S. Body composition in paediatric intestinal failure patients receiving long-term parenteral nutrition. Arch Dis Child. 2014;99(2):147-53.
43. Mutanen A, Mäkitie O, Pakarinen MP. Risk of metabolic bone disease is increased both during and after weaning off parenteral nutrition in pediatric intestinal failure. Horm Res Paediatr. 2013;79(4):227-35.
44. Joly F, Baxter J, Staun M, Kelly DG, Hwa YL, Corcos O, et al. Five-year survival and causes of death in patients on home parenteral nutrition for severe chronic and benign intestinal failure. Clin Nutr. 2018;37(4):1415-22.
45. Sowerbutts AM, Burden S, Griffiths J, Abraham A, Farrer K, Leahy G, et al. Glucagon-like peptide 2 analogues in the treatment of intestinal failure: A qualitative exploration of the views of patients and their families in decision making. Clin Nutr ESPEN. 2021;44:263-9.
46. Sowerbutts AM, Panter C, Dickie G, Bennett B, Ablett J, Burden S, et al. Short bowel syndrome and the impact on patients and their families: a qualitative study. Journal of Human Nutrition and Dietetics. 2020;33(6):767-74.
47. PROMIS. A brief guide to the PROMIS® Fatigue instruments 2019 [Available from: http://www.healthmeasures.net/images/PROMIS/manuals/PROMIS_Fatigue_Scoring_Manual.pdf.
48. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics. 1993;4(5):353-65.
49. Price BS, Levine EL. Permanent total parenteral nutrition: psychological and social responses of the early stages. JPEN J Parenter Enteral Nutr. 1979;3(2):48-52.

50. Winkler MF, Smith CE. Clinical, social, and economic impacts of home parenteral nutrition dependence in short bowel syndrome. JPEN J Parenter Enteral Nutr. 2014;38(1 Suppl):32s-7s.
51. Engstrom I, Bjornestam B, Finkel Y. Psychological distress associated with home parenteral nutrition in Swedish children, adolescents, and their parents: preliminary results. J Pediatr Gastroenterol Nutr. 2003;37(3):246-50.
52. Johnson T, Sexton E. Managing children and adolescents on parenteral nutrition: Challenges for the nutritional support team. Proc Nutr Soc. 2006;65(3):217-21.
53. Brand PL, de Haan WS, Affourtit MJ, Tibboel D, Verhulst FC, Molenaar JC. [Psychosocial aspects of the so-called short-bowel syndrome in children]. Ned Tijdschr Geneeskd. 1989;133(42):2078-81.
54. Baxter JP, Fayers PM, McKinlay AW. A review of the quality of life of adult patients treated with long-term parenteral nutrition. Clin Nutr. 2006;25(4):543-53.
55. Baxter JP, Fayers PM, McKinlay AW. The development and translation of a treatment-specific quality of life questionnaire for adult patients on home parenteral nutrition. e-SPEN, the European e-Journal of Clinical Nutrition and Metabolism. 2008;3(1):e22-e8.
56. Berghöfer P, Fragkos KC, Baxter JP, Forbes A, Joly F, Heinze H, et al. Development and validation of the disease-specific Short Bowel Syndrome-Quality of Life (SBS-QoL) scale. Clin Nutr. 2013;32(5):789-96.
57. Wilburn J, McKenna SP, Heaney A, Rouse M, Taylor M, Culkin A, et al. Development and validation of the Parenteral Nutrition Impact Questionnaire (PNIQ), a patient-centric outcome measure for Home Parenteral Nutrition. Clin Nutr. 2018;37(3):978-83.
58. Eiser C, Morse R. A review of measures of quality of life for children with chronic illness. Archives of Disease in Childhood. 2001;84(3):205.
59. Jeppesen P, Chen K, Murphy R, Shahraz S, Goodwin B, editors. Impact on Caregivers of Adult Patients Receiving Parenteral Support for Intestinal Failure Associated with Short Bowel Syndrome: A Multinational, Non-interventional, Cross-Sectional Survey. Digestive Disease Week; 2021; Virtual.
60. Wong C, Akobeng AK, Miller V, Thomas AG. Quality of life of parents of children on home parenteral nutrition. Gut. 2000;46(2):294-5.
61. Mutanen A, Kosola S, Merras-Salmio L, Kolho K-L, Pakarinen MP. Long-term health-related quality of life of patients with pediatric onset intestinal failure. Journal of Pediatric Surgery. 2015;50(11):1854-8.
62. Takeda UK Ltd. Confidential: Teduglutide NICE submission advisory board 2021 21st June 2021.
63. Burden ST, Jones DJ, Gittins M, Ablett J, Taylor M, Mountford C, et al. Needs-based quality of life in adults dependent on home parenteral nutrition. Clin Nutr. 2019;38(3):1433-8.
64. Ballinger R, Macey J, Kosmas C, Lloyd A. Measurement of utilities in short bowel syndrome: Vignette study in support of teduglutide. 2016.
65. Lachaine J, Laliberté AG, Miron A, Xenopoulos A. Time Trade Off Study for Parenteral Support in Short Bowel Syndrome in Canada. Value Health. 2016;19(3):A251.
66. European Medicines A. Revestive EPAR summary for the public 2012 [Available from:

http://www.ema.europa.eu/ema/?curl=pages/medicines/human/medicines/002345/human_med_001583.jsp&mid=WC0b01ac058001d124.
67. Olieman J, Kastelijn W. Nutritional Feeding Strategies in Pediatric Intestinal Failure. Nutrients. 2020;12(1).
68. Sulkowski JP, Minneci PC. Management of short bowel syndrome. Pathophysiology. 2014;21(1):111-8.
69. Matarese LE. Nutrition and fluid optimization for patients with short bowel syndrome. JPEN J Parenter Enteral Nutr. 2013;37(2):161-70.
70. Kelly DG, Tappenden KA, Winkler MF. Short Bowel Syndrome. Journal of Parenteral and Enteral Nutrition. 2014;38(4):427-37.
71. Joly F, Baxter J, Staun M, Kelly DG, Hwa YL, Corcos O, et al. Five-year survival and causes of death in patients on home parenteral nutrition for severe chronic and benign intestinal failure. Clinical nutrition. 2018;37(4):1415-22.
72. Jeppesen P, Pertkiewicz M, Messing B, Iyer K, Seidner D, O'Keefe S, et al. Teduglutide reduces need for parenteral support among patients with short bowel syndrome with intestinal failure. Gastroenterology. 2012;143(6):1473-81.
73. Schwartz LK, O'Keefe SJ, Fujioka K, Gabe SM, Lamprecht G, Pape UF, et al. Long-term teduglutide for the treatment of patients with intestinal failure associated with short bowel syndrome. Clin Transl Gastroenterol. 2016;7:e142.
74. Takeda UK Ltd. Revestive atHOME Patient Support Program Blueprint. Not pubilished - Takeda confidential data; 2019.
75. Seidner DL, Fujioka K, Boullata JI, Iyer K, Lee HM, Ziegler TR. Reduction of Parenteral Nutrition and Hydration Support and Safety With Long-Term Teduglutide Treatment in Patients With Short Bowel Syndrome-Associated Intestinal Failure: STEPS-3 Study. Nutr Clin Pract. 2018;33(4):520-7.
76. Jeppesen PB, Gilroy R, Pertkiewicz M, Allard JP, Messing B, O'Keefe SJ. Randomised placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome. Gut. 2011;60(7):902-14.
77. O'Keefe SJ, Jeppesen PB, Gilroy R, Pertkiewicz M, Allard JP, Messing B. Safety and efficacy of teduglutide after 52 weeks of treatment in patients with short bowel intestinal failure. Clin Gastroenterol Hepatol. 2013;11(7):815-23.e1-3.
78. (Shire) T. Safety, Efficacy and Pharmacokinetic Study of Teduglutide in Infants 4 to 12 Months of Age With Short Bowel Syndrome ClinicalTrials.gov [Available from: https://clinicaltrials.gov/ct2/show/NCT03571516.
79. Kocoshis SA, Merritt RJ, Hill S, Protheroe S, Carter BA, Horslen S, et al. Safety and Efficacy of Teduglutide in Pediatric Patients With Intestinal Failure due to Short Bowel Syndrome: A 24-Week, Phase III Study. Journal of Parenteral and Enteral Nutrition. 2020;44(4):621-31.
80. Mercer D, Carter B, Hill S, Horslen S, Kaufman S, Kocoshis S, et al. A PROSPECTIVE, OPEN-LABEL, LONG-TERM SAFETY AND EFFICACY STUDY OF TEDUGLUTIDE IN PEDIATRIC PATIENTS WITH SHORT BOWEL SYNDROME–ASSOCIATED INTESTINAL FAILURE: 6-MONTH INTERIM ANALYSIS (SHP633-304). In: North American Society for Pediatric Gastronenterology HaN, editor. Chicago2019.
81. Carter BA, Cohran VC, Cole CR, Corkins MR, Dimmitt RA, Duggan C, et al. Outcomes from a 12-week, open-label, multicenter clinical trial of teduglutide in pediatric short bowel syndrome. J Pediatr. 2017;181:102-11 e5.

82. Carter B, Hill S, Horslen S, Kocoshis S, Yoon M, Grimm A. LONG-TERM RETROSPECTIVE FOLLOW-UP OF PEDIATRIC PATIENTS WITH SHORT BOWEL SYNDROME–ASSOCIATED INTESTINAL FAILURE (SBS–IF) WHO COMPLETED 12 WEEKS OF TREATMENT IN TED-C13-003 (SHP633-303). In: North American Society for Pediatric Gastronenterology HaN, editor. Chicago2019.
83. (Shire) T. Study in Japanese Pediatric Subjects With Short Bowel Syndrome (SBS) Who Are Dependent on Parenteral Support ClinicalTrials.gov [Available from: https://clinicaltrials.gov/ct2/show/NCT02980666.
84. Wada M, Mizushima T, Sugita A, Tazuke Y, Udagawa E, Yoon M, et al. A PHASE III STUDY OF TEDUGLUTIDE IN ADULT JAPANESE PATIENTS WITH SHORT BOWEL SYNDROME–ASSOCIATED INTESTINAL FAILURE. Gastreoenterology. 2020;158:S-742.
85. Lambe C, Talbotec C, Kapel N, Piketty M, Goulet O. 300.6: The REVE study, preliminary results. A Monocentric Single-arm study to characterize the long-term safety, efficacy, and pharmacodynamic of GLP-2 analog (Revestive®) in the management of short bowel syndrome pediatric patients on home-parenteral nutrition (HPN). Transplantation. 2019;103(7S2).
86. Iturrino J, Camilleri M, Acosta A, O'Neill J, Burton D, Edakkanambeth Varayil J, et al. Acute Effects of a Glucagon-Like Peptide 2 Analogue, Teduglutide, on Gastrointestinal Motor Function and Permeability in Adult Patients With Short Bowel Syndrome on Home Parenteral Nutrition. J Parenter Enteral Nutr. 2016;40(8):1089-95.
87. Joly F, Seguy D, Nuzzo A, Chambrier C, Beau P, Poullenot F, et al. Six-month outcomes of teduglutide treatment in adult patients with short bowel syndrome with chronic intestinal failure: A real-world French observational cohort study. Clin Nutr. 2020;39(9):2856-62.
88. Puello F, Wall E, Herlitz J, Lozano ES, Semrad C, Micic D. Long-Term Outcomes With Teduglutide From a Single Center. JPEN J Parenter Enteral Nutr. 2020;45(2):318-22.
89. NPS Pharmaceuticals Inc. STEPS CSR. Clinical Study Report. Not published - Takeda confidential
2011.
90. NPS Pharmaceuticals Inc. 004 CSR. Clinical Study Report. Not published - Takeda confidential
2013.
91. Shire. C14 CSR. Not published - Takeda confidential2018.
92. NPS Pharmaceuticals Inc. C13 CSR. Clinical Study Report TED-C13-003: version 10. Not published - Takeda confidential
2015.
93. Jeppesen P. CONFIDENTIAL: Expert testimony on the unexpectedly high placebo rate in the pivotal 020/STEPS Study in relation to intestinal adaptation and baseline demographics of placebo/SOC arm. In: Ltd T, editor. 2018.
94. NPS Pharmaceuticals Inc. STEPS-2 CSR. Clinical Study Report. Not published - Takeda confidential data2013.
95. Chen K, Mu F, Xie J, Kelkar SS, Olivier C, Signorovitch J, et al. Impact of Teduglutide on Quality of Life Among Patients With Short Bowel Syndrome and Intestinal Failure. JPEN J Parenter Enteral Nutr. 2020;44(1):119-28.

96. Lam K, Schwartz L, Batisti J, Iyer KR. Single-Center Experience with the Use of Teduglutide in Adult Patients with Short Bowel Syndrome. JPEN J Parenter Enteral Nutr. 2018;42(1):225-30.
97. Martin A, Boehm V, Zappa M, Billiauws L, Bonvalet F, Nuzzo A, et al. Imaging as predictor of clinical response to teduglutide in adult patients with short bowel syndrome with chronic intestinal failure. The American journal of clinical nutrition. 2021;113(5):1343-50.
98. Pevny S, Maasberg S, Rieger A, Karber M, Blüthner E, Knappe-Drzikova B, et al. Experience with teduglutide treatment for short bowel syndrome in clinical practice. Clin Nutr. 2019;38(4):1745-55.
99. Schoeler M, Klag T, Wendler J, Bernhard S, Adolph M, Kirschniak A, et al. GLP-2 analog teduglutide significantly reduces need for parenteral nutrition and stool frequency in a real-life setting. Therap Adv Gastroenterol. 2018;11:1756284818793343.
100. Tamara PR, Alicia HA. Teduglutide in adult patients with short bowel syndrome. Eur J Clin Pharm. 2020;22(3):166-70.
101. Ukleja A, To C, Alvarez A, Lara LF. Long-Term Therapy With Teduglutide in Parenteral Support-Dependent Patients With Short Bowel Syndrome: A Case Series. JPEN J Parenter Enteral Nutr. 2018;42(4):821-5.
102. Seidner DL, Gabe SM, Lee HM, Olivier C, Jeppesen PB. Enteral Autonomy and Days Off Parenteral Support With Teduglutide Treatment for Short Bowel Syndrome in the STEPS Trials. JPEN J Parenter Enteral Nutr. 2020;44(4):697-702.
103. Takeda UK Ltd. Revestive atHOME_PS reduction report. Not published - Takeda confidential data [DPD]; 2021.
104. Ramos Boluda E, Redecillas Ferreiro S, Manrique Moral O, García Romero R, Irastorza Terradillos I, Nuñez Ramos R, et al. Experience With Teduglutide in Pediatric Short Bowel Syndrome: First Real-life Data. J Pediatr Gastroenterol Nutr. 2020;71(6):734-9.
105. National Institute for Health and Care Excellence (NICE). Response to consultee and commentator comments on the draft remit and draft scope (pre-referral) for Single Technology Appraisal of teduglutide (ID3937) NICE website; Teduglutide for treating short bowel syndrome [ID3937]2021 [Available from: https://www.nice.org.uk/guidance/gid-ta10842/documents/draft-scope-and-provisional-matrix-comments-table-post-referral.
106. Jeppesen PB, Gabe SM, Seidner DL, Lee HM, Olivier C. Factors Associated With Response to Teduglutide in Patients With Short-Bowel Syndrome and Intestinal Failure. Gastroenterology. 2018;154(4):874-85.
107. Iyer KR, Kunecki M, Boullata JI, Fujioka K, Joly F, Gabe S, et al. Independence From Parenteral Nutrition and Intravenous Fluid Support During Treatment With Teduglutide Among Patients With Intestinal Failure Associated With Short Bowel Syndrome. JPEN J Parenter Enteral Nutr. 2017;41(6):946-51.
108. Harvey B. Confidential: REVESTIVE® (TEDUGLUTIDE) FOR TREATMENT OF SHORT BOWEL SYNDROME (SBS): META-ANALYSIS RESULTS. Not published - Takeda confidential data; 2021 5th August 2021.
109. Pape U-F, Iyer KR, Jeppesen PB, Kunecki M, Pironi L, Schneider SM, et al. Teduglutide for the treatment of adults with intestinal failure associated with short bowel syndrome: pooled safety data from four clinical trials. Therap Adv Gastroenterol. 2020;13:1756284820905766-.

110. Hill S, Carter BA, Cohran V, Horslen S, Kaufman SS, Kocoshis SA, et al. Safety Findings in Pediatric Patients During Long-Term Treatment With Teduglutide for Short-Bowel Syndrome-Associated Intestinal Failure: Pooled Analysis of 4 Clinical Studies. JPEN J Parenter Enteral Nutr. 2020.
111. Turner RB. Epidemiology, pathogenesis, and treatment of the common cold. Ann Allergy Asthma Immunol. 1997;78(6):531-9; quiz 9-40.
112. National Institute for H, Care E. Guide to the methods of technology appraisal 2013 [Available from: http://www.nice.org.uk/article/pmg9/chapter/1-introduction.
113. Ballinger R, Macey J, Lloyd A, Brazier J, Ablett J, Burden S, et al. Measurement of Utilities Associated with Parenteral Support Requirement in Patients with Short Bowel Syndrome and Intestinal Failure. Clin Ther. 2018;40(11):1878-93.e1.
114. Ukleja A. Weaning from Parenteral Nutrition. Gastroenterol Clin North Am. 2019;48(4):525-50.
115. European Medicines A. CHMP extension of indication variation assessment report 2016 [updated 26 May 2016. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/002345/WC500211148.pdf.
116. Roskott AM, Groen H, Rings EH, Haveman JW, Ploeg RJ, Serlie MJ, et al. Cost-effectiveness of intestinal transplantation for adult patients with intestinal failure: a simulation study. Am J Clin Nutr. 2015;101(1):79-86.
117. Migliaccio-Walle K, Caro JJ, Moller J. Economic implications of growth hormone use in patients with short bowel syndrome. Curr Med Res Opin. 2006;22(10):2055-63.
118. CADTH Common Drug Review. Teduglutide 2016 [updated 30 October 2015. Available from: https://www.cadth.ca/teduglutide.
119. Raghu VK, Binion DG, Smith KJ. Cost-effectiveness of teduglutide in adult patients with short bowel syndrome: Markov modeling using traditional cost-effectiveness criteria. The American journal of clinical nutrition. 2020;111(1):141-8.
120. Raghu VK, Rudolph JA, Smith KJ. Cost-effectiveness of teduglutide in pediatric patients with short bowel syndrome: Markov modeling using traditional cost-effectiveness criteria. The American journal of clinical nutrition. 2020.
121. Royal College of Paediatrics and Child Health. UK-WHO growth chart 2-18 years [Available from: https://www.rcpch.ac.uk/resources/uk-who-growth-charts-2-18-years.
122. Oke S, Nightingale J, Jeppesen P, committee B. British Intestinal Failure Alliance (BIFA) Position Statement: Use of peptie growth factors for adult patients with intestinal failure. 2018.
123. Compher C, Gilroy R, Pertkiewicz M, Ziegler TR, Ratcliffe SJ, Joly F, et al. Maintenance of parenteral nutrition volume reduction, without weight loss, after stopping teduglutide in a subset of patients with short bowel syndrome. JPEN J Parenter Enteral Nutr. 2011;35(5):603-9.
124. Guyot P, Ades AE, Ouwens MJNM, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Medical Research Methodology. 2012;12(1):9.
125. Office for National Statistics. National life tables 2017-19 2019 [Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables.

126. Pironi L, Joly F, Forbes A, Colomb V, Lyszkowska M, Baxter J, et al. Long-term follow-up of patients on home parenteral nutrition in Europe: Implications for intestinal transplantation. Gut. 2011;60(1):17-25.
127. BresMed. P15133 Teduglutide – Modified Delphi Panel Report. Not published - confidential Takeda data; 2016.
128. Lloyd A, Kerr C, Breheny K, Brazier J, Ortiz A, Borg E. Economic evaluation in short bowel syndrome (SBS): an algorithm to estimate utility scores for a patient-reported SBS-specific quality of life scale (SBS-QoL). Qual Life Res. 2014;23(2):449-58.
129. Culkin A, Gabe SM, Madden AM. Improving clinical outcome in patients with intestinal failure using individualised nutritional advice. J Hum Nutr Diet. 2009;22(4):290-8; quiz 300-1.
130. Carey S, Tu W, Hyde-Jones L, Koh C. Assessing Patient Preferences for Intestinal Failure Management Using the Time Trade-Off Methodology. JPEN J Parenter Enteral Nutr. 2019;43(7):912-7.
131. Richards DM, Irving MH. Cost-utility analysis of home parenteral nutrition. Br J Surg. 1996;83(9):1226-9.
132. ICON. Impacts on Carers of Patients with Short Bowel Syndrome-associated Intestinal Failure Receiving Parenteral Support - Study Report. Not published - Takeda confidential data; 2017.
133. Wyld M, Morton RL, Hayen A, Howard K, Webster AC. A systematic review and meta-analysis of utility-based quality of life in chronic kidney disease treatments. PLoS Med. 2012;9(9):e1001307.
134. Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. Catalogue of EQ-5D scores for the United Kingdom. Med Decis Making. 2011;31(6):800-4.
135. National institute for Health and Care Excellence (NICE). TA352: Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy 2015 [Available from: http://www.nice.org.uk/guidance/TA352.
136. Bermingham SL, Ashe JF. Systematic review of the impact of urinary tract infections on health-related quality of life. BJU Int. 2012;110(11 Pt C):E830-6.
137. Shire. Impacts on carers of patients with short bowel syndrome-associated intestinal failure receiving parenteral support. Study report. 2017.
138. Shire. Outcomes Round 2 Delphi Questionnaire. 2016.
139. National Health S. 2019/20 National Cost Collection data 2020 [Available from: https://www.england.nhs.uk/national-cost-collection/.
140. NICE. BNF 2021 [Available from: https://bnf.nice.org.uk/.
141. Parexel Access C. Parexel SBS costing study for paediatrics: final report. 2017.
142. Parexel Access C. Parexel SBS costing study for adults: final report. 2017.
143. National Health Service (NHS). Department of Health Reference Costs 2019-2020 2020 [Available from: https://www.england.nhs.uk/national-cost-collection/.
144. Crossan C, Tsochatzis EA, Longworth L, Gurusamy K, Davidson B, Rodriguez-Peralvarez M, et al. Cost-effectiveness of non-invasive methods for assessment and monitoring of liver fibrosis and cirrhosis in patients with chronic liver disease: systematic review and economic evaluation. Health Technol Assess. 2015;19(9):1-409, v-vi.
145. PSSRU. Unit Costs of Health and Social Care 2020 2020 [Available from: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2020/.

146. Cavicchi M, Beau P, Crenn P, Degott C, Messing B. Prevalence of liver disease and contributing factors in patients receiving home parenteral nutrition for permanent intestinal failure. Ann Intern Med. 2000;132(7):525-32.
147. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013 [Available from: http://www.nice.org.uk/article/pmg9/chapter/1-introduction.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Teduglutide for treating short bowel syndrome [ID3937]

Responses to clarification questions

September 2021

File name	Version	Contains confidential information	Date
Teduglutide NICE submission_ID3937_Responses to clarification questions_[redacted]	**1.0**	**Yes**	**24th September 2021**

Section A: Clarification on effectiveness data

Methods used to assess the clinical effectiveness evidence

A1. Appendix D, Section D.1.8 Please clarify how many reviewers conducted risk of bias assessment of the studies identified by the systematic reviews (and their updates) and whether reviewers worked independently.

We can confirm that quality assessments were performed by one reviewer and then checked and validated by a second independent reviewer.

A2. Appendix D (SLR report). Please provide a complete version of Appendix D. The ERG notes that the page numbers suggest there may be missing pages (e.g., the document starts at page 5 and there is missing text on pages 9 and 16).

We have amended the pagination and made sure there is no missing wording in the version of the clinical systematic literature review report provided below:

Clinical SLR_2021.docx

A3. Document B, Section B.2.2.1, Table 6. The reason for excluding studies SHP633-303 and TED-C14-004 is given as "*Japanese population deemed less applicable to the UK*". Please clarify the rationale for this statement.

We would first like to clarify that this question should refer to SHP633-302 (a study of teduglutide in Japanese paediatric patients) rather than SHP633-303 (a study of teduglutide in paediatric patients that was an extension to C13).

In summary, we considered that these two studies had weak internal and external validity. Given the stronger internal and external validity of the data we present in Document B, Section B.2, we felt on balance that these two studies did not contribute significantly to an understanding of the clinical and cost effectiveness of teduglutide in the UK.

An overview of the design for both studies in Japanese patients can be seen in **Table 1**. Both studies were small in size, open-label and feature no comparator arm, all aspects that limit the internal validity and hence conclusions that can be drawn from the study. In addition, data from the 2011 census show that at most 2.2% of the UK population are of East Asian descent (Chinese + Asian Other[1]). This underlines that the two studies in exclusively Japanese patients lack external validity in terms of relevance to the UK. This is to be expected given that SHP633-302 and TED-C14-004 were designed as 'bridging' studies to confirm the efficacy and safety of teduglutide in a different ethnic group than the core clinical studies.

Table 1: Overview of the study design of the two clinical studies in Japanese patients

Study	**SHP633-302**[2]	**TED-C14-004**[3]
Population	Japanese patients with SBS-IF aged 4 months to 15 years	Japanese adults (≥16 years) with SBS-IF
Duration of study	24 weeks	24 weeks
Intervention	Teduglutide 0.05 mg/kg/day	Teduglutide 0.05 mg/kg/day
Comparator	None – single arm	None – single arm
Number of patients	10 (2 patient <1 year old)	11

Sources: Data from ClinicalTrials.gov[2, 3]

Abbreviations: SBS-IF, short bowel syndrome with type 3 intestinal failure

In addition to the weak internal and external validity, the populations of these two studies do not align with our present decision problem. Twenty percent of patients recruited to study SHP633-302 were <1 year old, a cohort for which teduglutide is not licensed in Europe or the UK[4], and which are not in the scope of this decision problem. Additionally, the definition of 'adult' used in TED-C14-004 was ≥16 years, notably not aligned with the definition used in STEPS (≥18 years).

Our economic model is built on data from three sources: STEPS (randomised controlled trial in North American and European patients, including patients from the UK), STEPS-2 (long-term extension study in North American and European patients, again including UK patients) and a Patient Support Programme (PSP; real-world data from Australian patients). In addition, our dossier makes reference to two clinical trials conducted in a paediatric population (C14 and C13), both of which recruited patients from the UK, had a control arm (albeit without randomisation), and are suitable for confirming the efficacy of teduglutide in children. We felt that the addition of two small, uncontrolled studies in a substantially different population was of little value.

A4. Document B Sections B.2.3.5, Table 10, B.2.6.4, Table 15, and B.2.6.4.2, Table 16. The number of patients with colon in-continuity is quite high in some of the trials and real world evidence studies (>50%). This may explain some of the benefit seen in terms of reduction of days on PS as the colon absorbs liquid. Please provide comparable data for end stomas if this is available.

The number of patients with an end-stoma (and with colon-in-continuity) across clinical and real world studies of teduglutide is provided in **Table 2**.

Table 2: Number of patients with colon-in-continuity and end-stoma across STEPS, the PSP and real-world studies

Study	Number of patients	Patients with colon-in-continuity, n (%)	Patients with end-stoma, n (%)
STEPS TED arm	43	26 (61%)	21 (49%)
STEPS PBO arm	43	23 (54%)	17 (40%)
PSP	[redacted]	[redacted]	[redacted]
Joly 2020	54	35 (65%)	NR
Lam 2018	18	15 (83%)	3 (17%)
Martin 2021	31	16 (52%)	15 (48%)
Pevny 2019	27	21 (78%)	6 (22%)
Puello 2020	18	9 (50%)	10 (56%)
Schoeler 2018	14	9 (64%)	NR
Tamara 2020	4	1 (25%)	3 (75%)
Ukleja 2018	6	3 (50%)	3 (50%)

Abbreviations: PBO, placebo; PSP, patient support programme; TED, teduglutide

Source: STEPS primary publication[5]; STEPS CSR[6]; STEPS-2 primary publication[7]; STEPS-2 CSR[8]; real-world study publications[9-16]

We recognise that there is variability across sources of data with respect to the proportion of patients with colon-in-continuity and end-stoma. However, we would like to highlight three points with respect to these data.

Firstly, following randomisation, the teduglutide and placebo arms in STEPS were well-balanced with respect to both characteristics (the differences between study arms are not statistically significant). The conclusions of the STEPS study, that teduglutide is more efficacious than placebo in allowing patients with short bowel syndrome and type 3 intestinal failure (SBS-IF) to reduce parenteral support (PS), are robust[5].

Secondly, the percentage of patients with colon-in-continuity and end-stoma in the studies that are 'core' to our economic model (STEPS teduglutide arm and the PSP) sit comfortably within the ranges across all studies in Table 2 (61% and 48%, respectively within a range for colon-in-continuity of 25%–83%; 49% and 48%, respectively within a range for end-stoma of 17%–75%). This suggests that patients within STEPS and the PSP are representative of this small and heterogenous patient group. The results of STEPS and the PSP therefore have high external validity with regards the wider SBS-IF population.

Thirdly, because the patient cohort in STEPS was representative of the wider patient population, our conclusion that the weaning algorithm in STEPS inhibited patients gaining independence from PS is robust. As shown in Figure 15 of Document B (B.2.6.4.1, p 63), at every time point the percentage of patients who gained independence from PS lags behind all real-world studies. [redacted]

Taken together, we can conclude that 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. Therefore our conclusion that in the real-world, patients are more capable of achieving PS independence (compared to in STEPS) remains robust. We remain of firm belief that it is the weaning protocol of STEPS (which restricts the ability of patients to gain independence from PS, and is not applied in real-world treatment) that has driven the difference in treatment outcomes we see across these studies.

Placebo response in STEPS

A5. Section B.2.6.1.4. Arguments are provided to support the assertion that the placebo response in STEPS is an artefact of the weaning algorithm applied. Please comment on the types of interventions the subjects underwent during follow up reviews? For example, were medications reviewed (including Dyoralite or St Mark's solutions, Loperamide or Codeine), were subjects provided with re-education on oral fluid intake? Could the above have contributed to the reduction of PN days in both groups, placebo and teduglutide?

The schedule of evaluations and procedures during the dosing period of STEPS is provided in **Table 3** below, which is taken from the study protocol. None of the interventions would be expected to affect patients days per week of parenteral support (PS).

Table 3: Schedule of evaluations and procedures during dosing period[17]

Procedures	Stage 2								
	Base-line	Dosing Week 1[a]	Dosing Week 2	Dosing Week 4	Dosing Week 8	Dosing Week 12[a]	Dosing Week 16	Dosing Week 20	Dosing Week 24 (or early term[b])
Visit Number:	V2	V3	V4	V5	V6	V7	V8	V9	V10
Study Day	0	7	14	28	56	84	112	140	168
Visit Window (days)		±2	±3	±3	±5	±5	±5	±7	±7
Eligibility	X								
Crohn's disease assessment	X								
Colonoscopy[c]	X								
Physical examination[d]	X		X	X	X		X	X	X
Evaluation of PN/I.V.	X[e]		X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X
Vital signs	X		X	X	X		X	X	X
Body weight	X[f]		X	X	X		X	X	X
12-lead ECG	X			X					X
Safety laboratory tests	X		X	X	X	X	X	X	X
Citrulline	X			X	X		X		X
Antibodies to teduglutide, ECP	X					X			X
Urine pregnancy test	X		X	X	X	X	X	X	X
Drug dispensing	X		X	X	X		X	X	
Interim safety evaluations[g]			[X][h]	[X]	[X]	[X]	[X]	[X]	
e-diary 48-hour oral fluid intake[i]	X		X	X	X	X	X	X	X
e-diary 48-hour urine output[i]	X		X	X	X	X	X	X	X
SBS-specific QoL questionnaire	X			X	X	X	X	X	X
e-diary	X	X	X	X	X	X	X	X	X
PN usage	X								

PN/I.V.=parenteral nutrition/intravenous; ECG=electrocardiogram; ECP=*E.coli* protein; e-diary=electronic diary; QoL=quality of life; SBS=short bowel syndrome; V=visit.

[a] Subject did not have to visit the clinic for study visit. Assessments were completed over the phone.

[b] Subjects with an early termination visit had to have all applicable Visit 10 assessments. The sponsor was to be contacted for guidance.

[c] Colonoscopy was completed toward the end of the stabilization period, if required.

[d] Full physical examination was performed at baseline and Visit 10, a brief examination at all other dosing weeks with a clinic visit.

[e] PN/I.V. evaluation confirmed weekly volume for Inclusion Criteria 6 (PN/I.V. frequency) and 7 (stable PN/I.V.).

[f] This was the second of 2 body weight measurements that was used to determine drug volume.

[g] Interim safety evaluations were to be performed 5-7 days after any scheduled visit when a reduction was made to the subject's PN/I.V. These measures included 48-hour oral fluid intake, 48-hour urine output, Hct, serum BUN and creatinine, and urine sodium.

[h] At the Visit 4/Week 2 interim safety visit, laboratory test results, and 48-hour I/O were not required. A phone call was made to assess if the PN/I.V. adjustment was tolerated.

[i] All subjects measured 48-hour oral fluid intake and urine output at home immediately prior to the scheduled visit. The measurements included 1 day on and 1 day off PN/I.V., unless PN/I.V. was infused daily.

As per the STEPS study protocol, the usage of concomitant medications were assessed at each study visit (weeks 1, 2, 4, 8, 12, 16, 20 and 24) but the changes to these medications were not deemed relevant to report in the clinical study report. No new medications were started during the treatment period unless medically

necessary. Specific re-education from clinicians to patients on oral fluid intake was not protocolised or recorded.

There are several reasons to believe that use of concomitant medications would not have influenced patients' ability to reduce PS.

Firstly, prior to treatment in STEPS, all patients underwent 8–16 weeks of PS optimisation and stabilisation. The aim of this period was to find the patient's 'minimally tolerated stable volume of PS'[6]. During this period, concomitant medications were also optimised, as these medications form part of existing standard care. Therefore, if any impact of concomitant medications on patients' PS consumption were to occur, it would have occurred prior to study treatment.

Secondly, expert clinical feedback sought by Takeda confirms that the concomitant medications received by patients do not enable patients to reduce their days of PS. Clinicians emphasise that these medications (in the real-world, as in STEPS) are only *"supportive"* and used to optimise standard care, minimising disease-related symptoms (e.g. thirst, pain, diarrhoea, stoma leakage, dehydration) and thereby improving patients' quality of life. One expert summarised the role of concomitant medications as being to *"help patients achieve stability and manage with PS"*. In sum, clinicians felt strongly that the use of these medications would be reviewed *in response* to changes in PS consumption and it was implausible that PS consumption would be reviewed in response to adjustments in co-medications.

A6. Section B.2.6.1.4. The company states: [redacted]. Could the company comment on the intestinal losses and strategies to reduce the stoma/ gut output via hypertonic solutions, codeine or loperamide? By reducing gut losses using the above strategies, PN could be reduced due to less electrolytes being lost thought the gut.

Our response to question A5 is also relevant here: namely that standard care (which includes concomitant medications) was optimised prior to entry in STEPS and so would not have contributed to parenteral support (PS) reduction; and that clinicians optimise concomitant medications in response to PS changes (optimising PS around concomitant medication changes is implausible).

With regards hypertonic solutions specifically, the British Intestinal Failure Alliance (BIFA)[18] and the British Society of Gastroenterology (BSG)[19] do not recommend the use of hypertonic solutions to treat high output stomas, instead recommending that oral fluids are restricted and glucose-saline replacement solutions (such as St Mark's solution) are used to correct sodium and water depletion. Again, clinicians emphasise that such solutions are merely supportive of optimisation and do not help patients to wean off PS.

With regards loperamide and codeine, one of the expert UK clinicians we spoke to summarised their effect as follows:

"Loperamide and codeine are 'cosmetic' interventions: they improve fluid retention in the gut but do not improve intestinal absorption. Teduglutide is in a different league because it actually improves intestinal adaptation."

A7. Section B.2.6.1.4. The company states: [redacted] However, it is stressed in the document that decisions based solely on the weaning protocol may have underestimated the reduction in PN in patients on Teduglutide. Please further clarify how in the placebo group the weaning protocol would have caused an over-reduction while in the teduglutide group an under-reduction?

A detailed argument is provided below, but in summary, the condition required for a parenteral support (PS) reduction in STEPS (urine volumes ≥10% above baseline in the previous 48 hours) could be met without improved intestinal absorption, thereby causing an over-reduction of PS in the placebo group. The limitation of only being able to reduce PS by at maximum 30% of baseline volume every 4 weeks caused an under-reduction of PS in the teduglutide group.

We do indeed argue in our dossier that the STEPS study overestimates the magnitude of PS reduction in the placebo arm and underestimates it in the teduglutide arm. We are aware that this is an unusual position to take. In all other aspects STEPS is well-designed (it meets all the criteria provided by Centre for Reviews and Dissemination guidance for undertaking reviews in health care), it is internationally supported and recognised, and it provides clinically meaningful results. However, the weaning algorithm used in STEPS has significant implications, causing both the overestimated effect of placebo and the underestimated effect of teduglutide.

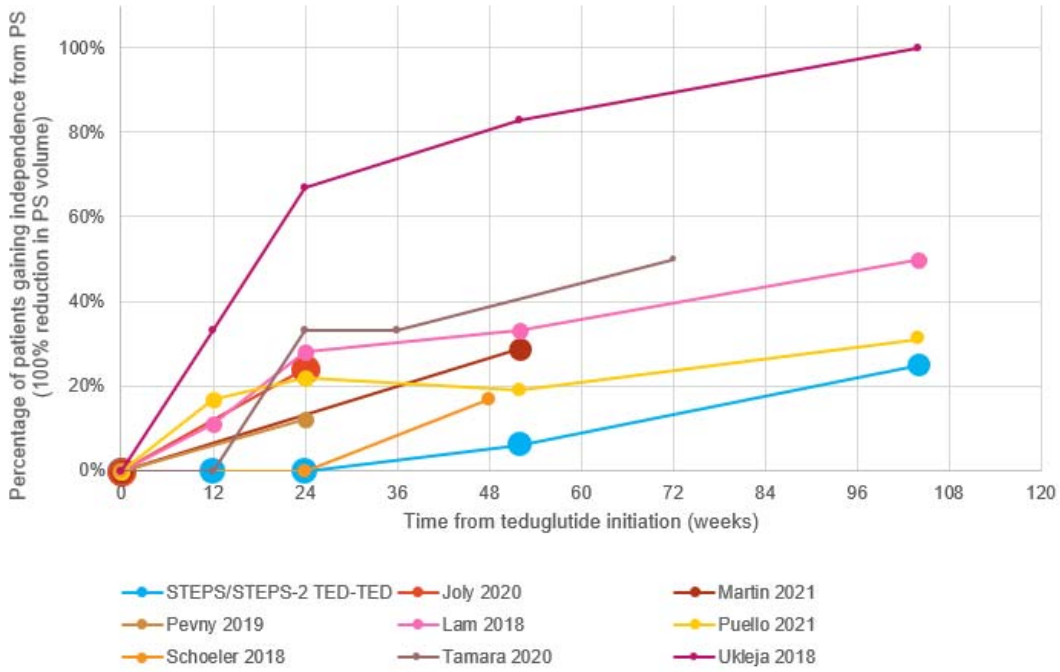
The protocol for allowing patients to reduce PS used in STEPS was as follows[5]:

- **Condition**: if urine volumes during the preceding 48 hours were ≥10% above baseline, PS volume could be reduced
- **Magnitude**: PS volume could be reduced by between 10–30% of baseline PS volume at each visit (every ~4 weeks in STEPS)

The first bullet explains the overestimated efficacy in the placebo arm. [redacted]. These fluctuations are likely to have triggered PS reductions in the placebo arm, despite no underlying change in the absorptive capacity of the intestine and therefore no change in need for PS. That patients receiving placebo had to increase their oral fluid intake over the STEPS study highlights that their reduced PS was not meeting their hydration needs; that they also lost weight highlights that their reduced PS was not meeting their nutritional needs (patients in the teduglutide arm did not increase their oral fluid intake and managed to gain weight while their PS was reduced). [redacted] In real-world practice, clinical feedback suggests that the decision to reduce PS would be made considering a number of factors, rather than just urine volume. Together, these points underline that the urine volume condition was likely to have been the driver of PS weaning in patients receiving placebo.

The second bullet of the weaning protocol explains the underestimated efficacy in the teduglutide arm. At each study visit in STEPS, clinicians could only reduce a patient's PS by at most 30% of their baseline volume. In the real-world, clinicians can reduce patients PS more flexibly, which results in greater and more rapid PS reductions. This point is best illustrated by comparing the proportion of patients gaining independence from PS in STEPS/STEPS-2 with other real world data. These data can be found in Document B, B.2.6.4.1, p 63 but are also shown in **Figure 1** below for reference.

Figure 1: Percentage of patients gaining independence from PS over time in real-world studies and STEPS/STEPS-2



Abbreviations: PS, parenteral support; TED-TED, the subgroup of patients from STEPS-2 who were previously treated with teduglutide in STEPS (see Document B, B.2.3.2, p 34)

Notes:

Size of marker is proportional to number of patients on teduglutide at given timepoint

% indicates (number gaining independence from PS) / (number receiving teduglutide at the time) for all studies. An exception here is Lam 2018, which does not provide patient numbers at each timepoint of assessment; we have therefore assumed all 18 patients remained on teduglutide throughout follow-up as this gives the most conservative estimate of complete response rate

Results from Ukleja 2018 and Martin 2021 should be considered an outliers due to low PS consumption at baseline

Source: STEPS primary publication[5]; STEPS CSR[6]; STEPS-2 primary publication[7]; STEPS-2 CSR[8]; real-world study publications[9-16]

It is notable that despite the variety of study locations and variability in patients' baseline characteristics across these real-world studies (see Document B, B.2.6.4.1, p 60), the percentage of patients gaining independence from PS in STEPS/STEPS-2 lagged behind all of them. When we meta-analysed the real-world data (Document B, B.2.8, p 71-74), it showed that the percentage of patients gaining independence in

the real-world was statistically significantly higher at month 6 and month 12 of treatment compared to in STEPS/STEPS-2.

This point about the weaning algorithm of STEPS/STEPS-2 restricting the degree of patients' PS reductions relative to what can be achieved in the real-world was, in fact, originally posited by the authors of the above studies:

"In our "real-life" experience of the weaning process, fluid intake and urine output monitoring could be less strict than in the published trials, allowing more freedom in PS reduction" [9]

"When compared with the STEPS study series, in which enteral independence required >6 months of teduglutide therapy, we have demonstrated more rapid gains in PS reduction and achievement of enteral independence likely as a result of the less strict optimization protocols when compared with the clinical trials."[13]

A8. Section B.2.13.1, placebo results in STEPS. In Section B.1.3.1, it is stated that "the majority of intestinal adaptation occurs in the first two years following resection", but the eligibility criteria for STEPS appears to have allowed inclusion of patients who had been on PS for less than 2 years (≥12 months). Please provide a breakdown of the number of participants in each arm of STEPS who had been on PS for less than two years, and provide details of the outcome (reduction in PS days per week) in these patients compared to those who had been on PS for more than 2 years at baseline.

Firstly, we would not expect any patients in STEPS to have ongoing intestinal adaptation, and so baseline time on PS in STEPS should not affect results with teduglutide. Published literature supports that intestinal adaptation is usually complete within one to two years[21, 22]. To enter STEPS patients had to be receiving PS for at least one year, and be stable on their minimal tolerated volume of PS[5, 6]. Taken together, the inclusion criteria in STEPS should have prohibited any patient with ongoing intestinal adaptation from entering the study.

The requested analysis is provided in **Table 4** below. We have included sample sizes and mean reduction in days per week of parenteral support (PS), split by whether patients had <2 years of PS or ≥2 years of PS at baseline from STEPS/STEPS-2, the patient support programme (PSP) and pooled data from STEPS/STEPS-2 and the PSP (as used in our base case).

Table 4*:* Reduction in days per week of PS in STEPS/STEPS-2, the PSP and STEPS/STEPS-2 and the PSP combined split by time on PS at baseline

Decrease in PS days from baseline, mean (SD) [n]	**Teduglutide**		**Placebo**	
	<2 years on PS	**≥2 years on PS**	**<2 years on PS**	**≥2 years on PS**
STEPS				
6 months	[redacted]	[redacted]	[redacted]	[redacted]
STEPS-2				
12 months	[redacted]	[redacted]	N/A	
18 months	[redacted]	[redacted]		
24 months	[redacted]	[redacted]		
30 months	[redacted]	[redacted]		
PSP				
6 months	[redacted]	[redacted]	N/A	
12 months	[redacted]	[redacted]		
Pooled data (STEPS/STEPS-2 & PSP)				
6 months	[redacted]	[redacted]	N/A	
12 months	[redacted]	[redacted]		
Abbreviations: N/A, not applicable PS, parenteral support; PSP, patient support programme; SD, standard deviation				

[redacted]. It should be noted, however, that across all these descriptive analyses patient sample sizes are small and the standard deviations relatively large, so there is a large degree of uncertainty.

The different trends in outcomes that we see in **Table 4** are attributable to the different baseline characteristics of patients by subgroup within each dataset; these are acting as confounders. A descriptive comparison as presented in **Table 4** is therefore not appropriate, as the baseline characteristics are not well balanced; this can be seen in **Table 5**.

Table 5: Patients' baseline characteristics in the STEPS teduglutide arm, STEPS placebo arm and in the PSP split by time on PS at baseline

		STEPS teduglutide arm		STEPS placebo arm		PSP	
Parameter		**<2 years on PS** [redacted]	**≥2 years on PS** [redacted]	**<2 years on PS** [redacted]	**≥2 years on PS** [redacted]	**<2 years on PS** [redacted]	**≥2 years on PS** [redacted]
Sex (male:female)		36:64	52:48	46:54	43:57	[redacted]	[redacted]
Age (years)		50.0	51.8	46.6	51.2	[redacted]	[redacted]
Baseline PS (days/wk)		6.00	5.44	6.08	6.05	[redacted]	[redacted]
Baseline PS (volume, L/wk)		12.7	12.4	12.3	13.9	[redacted]	[redacted]
Colon in continuity (%)		78%	64%	73%	56%	[redacted]	[redacted]
Estimated length of small intestine (cm)		96.9	82.0	68.2	68.8	[redacted]	[redacted]
Stoma (%)		45%	52%	18%	47%	[redacted]	[redacted]
Illeocecal valve present (%)		9%	6%	18%	25%	[redacted]	[redacted]
Reason for resection (%)	Crohn's	9%	29%	9%	22%	[redacted]	[redacted]
	Cancer	9%	0%	0%	6%	[redacted]	[redacted]
	Vascular	27%	32%	27%	41%	[redacted]	[redacted]
	Volvulus	9%	6%	27%	9%	[redacted]	[redacted]
	Injury	9%	10%	9%	9%	[redacted]	[redacted]
	Other	36%	23%	27%	12%	[redacted]	[redacted]
Abbreviations: PS, parenteral support; PSP, patient support programme; wk, week							

There are large discrepancies in some characteristics between subgroups, of particular note: patients' baseline PS volume in the PSP ([redacted] L/wk); patients' baseline number of days per week of PS in the PSP ([redacted] days/wk); the percentage of patients with colon-in-continuity (STEPS teduglutide arm 78% vs 64%; STEPS placebo arm 73% vs 56%; PSP [redacted]), and the reasons for resection (most notably the percentage of patients with Crohn's disease) in the STEPS teduglutide and placebo arms. These imbalances in patients' baseline characteristic are relevant as previously published literature have suggested that baseline PS consumption, vascular vs inflammatory bowel disease aetiology, and colon-in-continuity (among other characteristics) affect the degree to which patients can reduce PS[9, 23-25].

Furthermore, while the subgroups appear well balanced in STEPS with respect to mean number of days of PS per week at baseline (STEPS teduglutide arm: 6.00 days vs 5.44 days; placebo arm: 6.08 vs 6.05 days), the spread of patients' baseline number of days of PS per week is not even, as demonstrated in **Table 6**.

Table 6: Days per week of PS at baseline in STEPS

	Teduglutide arm		Placebo arm	
Baseline number of PS days/wk, n (%)	**<2 years on PS**	**≥2 years on PS**	**<2 years on PS**	**≥2 years on PS**
3 days	[redacted]	[redacted]	[redacted]	[redacted]
3.5 days	[redacted]	[redacted]	[redacted]	[redacted]
4 days	[redacted]	[redacted]	[redacted]	[redacted]
4.5 days	[redacted]	[redacted]	[redacted]	[redacted]
5 days	[redacted]	[redacted]	[redacted]	[redacted]
5.5 days	[redacted]	[redacted]	[redacted]	[redacted]
6 days	[redacted]	[redacted]	[redacted]	[redacted]
6.5 days	[redacted]	[redacted]	[redacted]	[redacted]
7 days	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: PS, parenteral support; wk, week

Notes: Days per week of PS is defined as the number of days on PS from the previous 14 days divided by two. As a result, some patients' PS is counted as 'half days'

Of particular note, patients on between 3 and 4 days of PS at baseline are overrepresented in the ≥2 years of PS at baseline subgroup for the teduglutide arm (9% of patients in the <2 years PS subgroup were on 3 or 4 days per week of PS at baseline vs 35% of patients in the ≥2 years PS subgroup). Patients on fewer days of PS at baseline need a greater percentage reduction of PS volume to reduce a further day. Furthermore, the nature of reducing days of PS changes once a patient reaches 7 days per fortnight (equivalent to 3.5 days per week) of PS. If patients receive more than 3.5 days a week of PS, going a day without PS means lasting ~36 hours from the end of one feed to the beginning of the next. After reaching 3.5 days per week, going a further day without PS means lasting ~60 hours from the end of one feed to the beginning of the next, as the patient is required to have two consecutive nights off. Clinical feedback suggests this can be challenging. These points further highlight the way in which the imbalance in the baseline characteristics of STEPS for the <2 years of PS and ≥2 years of PS subgroups will influence the results seen in **Table 4**.

To explore this issue further we analysed the pooled STEPS/STEPS-2 and PSP data using a mixed effects regression model (using the lme4 package of R). We explored whether, after adjusting for imbalanced baseline characteristics, the time on PS prior to commencing teduglutide had an impact on patients' days per week of PS over 30 months of follow-up (with the PSP data contributing for only 12 months).

As the key outcome of days per week of PS is measured repeatedly over various time points, a repeated-measures model was specified. This was done by including random intercepts for each individual to account for the correlation between baseline values and subsequent measures. All other selected covariates were then included as fixed effects.

For the specification of the model, fixed effects for baseline number of PS days, time on teduglutide treatment and a categorical variable for prior time on PS (<2 years vs ≥2 years) were included as a minimum. Additional variables for small bowel length, colon-in-continuity, presence of a stoma, presence of the ileocecal valve, and the reason for bowel resection were also considered for inclusion.

An initial analysis including all variables demonstrated only baseline number of PS days and time on teduglutide reached the threshold for statistical significance. Time

on PS prior to commencing teduglutide was in fact the least significant variable with a *p*-value of [redacted]. The full set of results are given in **Table 7**.

Table 7. Output of mixed effects model (all covariates)

Variable	Estimate	Standard Error	*P* value
(Intercept)	[redacted]	[redacted]	[redacted]
Baseline number of PS days	[redacted]	[redacted]	[redacted]
Time on teduglutide (weeks)	[redacted]	[redacted]	[redacted]
Time on PS: ≥2 years	[redacted]	[redacted]	[redacted]
Small bowel length (cm)	[redacted]	[redacted]	[redacted]
Colon-in-continuity: Yes	[redacted]	[redacted]	[redacted]
Stoma: Yes	[redacted]	[redacted]	[redacted]
Ileocecal valve: Yes	[redacted]	[redacted]	[redacted]
Reason for resection†: Crohn's	[redacted]	[redacted]	[redacted]
Reason for resection†: Injury	[redacted]	[redacted]	[redacted]
Reason for resection†: Other	[redacted]	[redacted]	[redacted]
Reason for resection†: Vascular disease	[redacted]	[redacted]	[redacted]
Reason for resection†: Volvulus	[redacted]	[redacted]	[redacted]
Abbreviations: PS, parenteral support **Notes:** †calculated relative to rates for gastric cancer			

Given the limited number of patients who have been on PS for less than 2 years prior to starting teduglutide, there is a large degree of uncertainty in any regression analysis performed to assess the impact of this variable. The inclusion of a large number of variables may add further uncertainty and the estimates are potentially not robust. To assess the impact of these variables on the regression results, an additional analysis was performed including only the time on PS prior to teduglutide, time on teduglutide and baseline number of days of PS as covariates. This analysis further supported the case that time on PS prior to teduglutide was not statistically significantly associated with days of PS (estimate [redacted]; *p*=[redacted]). Despite removing covariates that are known clinically to have an impact on patients' requirements for PS and that were imbalanced between the subgroups based on previous time on PS, time on PS prior to teduglutide treatment was still shown to have a relatively small and non-significant impact.

These results show that time on PS at baseline is not a relevant factor for explaining teduglutide's effectiveness. These analyses demonstrate that the differences in descriptive outcomes reported in **Table 4** by prior time on PS are likely to be driven by variation in the patient populations and the unrobust estimation driven by small patient numbers. The subgroup analysis in **Table 4** should therefore be considered unrobust and unreliable; to reliably assess the effectiveness of teduglutide on patients' PS requirements, the data should be considered as a whole.

To summarise the above, no patient in STEPS should have had ongoing intestinal adaptation at study entry based on the study's inclusion criteria. The relationship between time on PS at baseline and reductions in days per week of PS is not clear. [redacted]. Differences in baseline characteristics between the subgroups, particularly in characteristics that affect PS weaning, confound this analysis, and small patient numbers make it hard to control for these factors. A regression analysis showed no relationship between time on PS at baseline and reductions in days per week of PS with teduglutide. All in all, we believe that the results in **Table 4** are spurious.

Aligned with our conclusions, we would also like to draw attention to the European Public Assessment Report for teduglutide, which concluded with regards subgroups:

"Considering the rarity and heterogeneity of the disease it was not considered useful to define subgroups of patients."[26]

Patient Support Programme data

A9. Section B.2.6.4.2, results from the PSP programme. The company argue that the greater reduction in PS observed for patients enrolled in the Patients Support Programme in Australia are due to the application of less restrictive weaning criteria in routine practice. Please provide further reassurance that the patients receiving teduglutide in the PSP are comparable with those recruited to STEPS in terms of the distribution of time on PS at baseline and not just with respect to the mean; e.g. less than 12 months, 12-24 months, and > 24 months.

We have provided additional baseline characteristics as requested in **Table 8**. This table is the same as Table 16 in Document B (B.2.6.4.2, p 64), with the additional data provided in italics.

Table 8: Baseline characteristics in PSP and STEPS

Characteristic	**PSP data** [redacted]	**STEPS TED arm (n=43)**
Time receiving PS at baseline, n (%)		
<1 year, n (%)	[redacted]	*0 (0)*
≥1 year to <2 years, n (%)	[redacted]	*11 (26)*
≥2 years, n (%)	[redacted]	*32 (74)*
Average percentage of colon remaining (SD)	[redacted]	*55.6 (20.8; data for n=24)*
Proportion of patients with end stoma, %	[redacted]	*50.0 (data for n=42)*
Cause of disease, n (%)		
Crohn's disease	[redacted]	10 (23.3)
Ischaemia/vascular disease	[redacted]	13 (30.2)
Small bowel atresia	[redacted]	0
Radiation enteritis	[redacted]	0
Gastroschisis	[redacted]	0
Gastric cancer	[redacted]	1 (2.3)

Other	[redacted]	19 (44.2)
Average remnant small bowel length, cm (SD)	[redacted]	84.4 (64.6; data for n=39)
Colon in continuity, n (%)	[redacted]	26 (61)
Average time on PS, years (SD)	[redacted]	6.8 (6.3)
Weekly PS volume at baseline, L (SD)	[redacted]	12.6 (7.4)
Days per week of PS at baseline (SD)	[redacted]	5.6 (1.6)
Abbreviations: PS, parenteral support; PSP, patient support programme; SD, standard deviation; TED, teduglutide **Source**: STEPS pivotal publication[5]; STEPS CSR[6]; Revestive atHOME PS reduction report[27]		

As can be seen, the baseline characteristics of patients within the patient support programme (PSP) are in-line with the baseline characteristics of teduglutide patients in the STEPS study. This suggests that our comparison of parenteral support (PS) reduction between the two sources of evidence is appropriate given the data are generated from comparable populations. Our conclusion that the greater reductions in PS achieved by patients in the PSP are due to there being no restrictive weaning criteria applied in the real-world is therefore robust.

Section B: Clarification on cost-effectiveness data

Model structure

B1. Section B.3.2.2, Figure 21. The structure of the economic model only allows patients to remain stable, reduce the number of days per week of PS or die. Please provide further justification for this structure with respect to the any potential for PS requirements to increase over time for some patients.

As a point of clarification, while the transition matrices applied in the economic model do not include backward transitions, the model does allow patients to increase their parenteral support (PS). This can occur when patients discontinue teduglutide (if they have received a treatment benefit from teduglutide) because in our model, at the point of discontinuation of teduglutide, patients' PS consumption immediately reverts back to their baseline PS requirements.

We believe that our model transitions are appropriate in only allowing patients to remain stable or decrease their PS while on treatment. While we acknowledge that patients PS needs can fluctuate and lead to short-lived increases, we have modelled a cohort of patients with a) stable PS requirements at baseline and b) where the overwhelming trend is for stable or reducing PS requirements over time. We therefore considered it an unnecessary overcomplication to model individual fluctuations in PS requirements. Our approach was confirmed with clinical and health economic experts as an appropriate reflection of the disease pathway and a suitable way of modelling the key impacts of teduglutide on the cohort of patients as a whole.

Furthermore, as can be seen in our answer to question B5 (specifically **Table 10** and **Table 11**), our model accurately reflects STEPS/STEPS-2/PSP data with regards to the proportion of patients in each health state from baseline to month 30. This validates that our model structure is appropriate.

Due to the demands of growth, it is conceivable that paediatric patients may see their PS needs increase for longer-term periods. While our model does not account for this, we do not believe it is necessary. Such increases would occur equally in both the teduglutide and the standard care arm of the model. As such, the increases

would cancel each other out, and so there was no benefit to including them in the model.

B2. Section B.3.2.2. In Table 23 of document B it is stated that "…teduglutide allows patients to increase enteral nutrition, and enteral nutrition further promotes intestinal adaption, there is reason to believe the effectiveness of teduglutide may increase over time". Please discuss whether there is potential for teduglutide to provide patients with ongoing long-term benefits in terms of reduction in days of PS upon discontinuation of treatment.

With an *in vivo* half-life of 2 hours and a complex intestinotrophic mechanism of action[4], it is not immediately clear how long we would expect the benefits of teduglutide to last once treatment stops. Further to this, there is very limited clinical evidence that indicates how a patient's PS consumption changes after they stop teduglutide.

Neither of the randomised controlled trials conducted in adults with short bowel syndrome and type 3 intestinal failure (SBS-IF; STEPS[6] and 004[28]), nor any of their extension studies (STEPS-2[8], STEPS-3[29], 005[30]) followed-up patients after they discontinued teduglutide. Both of the paediatric clinical trials (C13 and C14) had a 4-week follow-up period at the study end during which patient's PS consumption was monitored after they had stopped teduglutide. In both cases, average PS volume increased slightly in the 4 weeks following the end of the teduglutide treatment[31, 32]. However, given children's increased capacity for intestinal adaptation[33], these data have limited applicability to the adult SBS-IF population.

Although the data were not collected as part of the 004/005 clinical programme, one published study investigated how patients PS consumption changed following the end of teduglutide treatment in 004/005. Of 37 patients, 15 (41%) had their PS increased in the 12 months after stopping teduglutide and 22 (59%) had no change or their PS decreased. Among patients who had responded to teduglutide treatment, 12 (of 25, 48%) had their PS increased and 13 (52%) had no change or a decrease[34]. A second study looking at 10 patients treated with teduglutide in clinical

trials also showed that on average, patients' PS consumption 4 years after stopping teduglutide (10.0 L/wk) was lower than their PS consumption before starting teduglutide (12.5 L/wk). This suggests that some benefit of teduglutide may last longer-term after treatment is stopped[35].

It is worth noting our model is conservative in its assumptions for when patients stop teduglutide treatment: it assumes patients immediately revert back to their baseline PS. This is conservative on two counts: firstly, data from the studies described above suggest that not all patients will revert back to their baseline PS consumption following discontinuation[34]. Secondly, clinical feedback sought by Takeda suggests that where PS use does return to baseline, the process would take 2 to 8 weeks[36]. The non-immediate return to baseline is echoed in the teduglutide summary of product characteristics, which states "*due to the risk of dehydration, discontinuation of treatment with teduglutide should be managed carefully*"[4]. However, in taking this conservative approach, we are recognising feedback from the previous appraisal of teduglutide (where the approach to modelling a continued treatment effect for teduglutide post-discontinuation was deemed not clinically plausible).

Clinical parameters and variables

B3. Section B.3.3.2, Estimation of transition probabilities. The company state that the PSP data contributed to informing the transition probabilities for the first 12 months only, because [redacted]. Please provide further justification why this longer-term data for PSP patients should be ignored and provide a scenario analysis that includes it.

In summary, we do not believe that using longer term follow-up data from the patient support programme (PSP) provides a realistic estimate of the cost effectiveness of teduglutide; this is due to the small sample sizes available, which means that we have to rely on implausible assumptions. However, in the interest of transparency, we have provided these scenarios in **Table 9**. These scenarios use a conservative 'last value carried forward' assumption that is described further below, along with our rationale for why this unreasonably 'dilutes' the treatment effect of teduglutide.

Table 9: Scenario analysis using longer-term follow up data from the PSP

Scenario	**Number (%) of patients with follow-up within 6 months prior to the specified timepoint (of [redacted] in the PSP)**	**ICER**
Base case (PSP data up to 12 months)	[redacted]	£16,652
PSP data up to 18 months	[redacted]	£14,891
PSP data up to 24 months	[redacted]	£14,129
PSP data up to 30 months	[redacted]	£22,138
Abbreviations: ICER, incremental cost-effectiveness ratio; PSP, patient support programme		

As a source of real-world evidence, the PSP data has no regular follow-up timepoints of assessment and patients have varying lengths of follow-up. As a result, in using the PSP data, we need to strike a balance between informing transitions for as long as possible, but avoiding implausible assumptions that result from irregular follow-up timepoints, limited patient follow-up and small patient numbers.

Our approach to using data from the PSP to inform transitions for up to 12 months is a conservative one. We adopted a last value carried forward approach which assumes no further parenteral support (PS) reduction ('zero further effect') beyond the 6 month interval in which their last assessment was taken (a 6 month interval is used as transition probabilities were estimated separately in 6 month intervals, see Document B, B.3.3.2 p 99 for further detail). By way of example, if a patient's last assessment was at month 4 we assumed zero further effect (their parenteral support requirements remain stable) for the next interval between month 6 and month 12, although in reality they may well have experienced continued treatment benefit.

If we used this last value carried forward approach but allowed data from the PSP to inform model transitions beyond 12 months, this would mean that an ever increasing proportion of patients would be assumed to have 'zero further effect' for an ever increasing period of time. This does not reflect clinical and real-world evidence, which shows treatment benefits can occur for at least 30 months. Beyond 12 months, when [redacted] of patients have follow-up data, the transitions would be based on a [redacted] of patients with an assumed 'zero further effect' from their last timepoint, and a [redacted] of patients providing actual observed data. The later the timepoint, the greater still the contribution of 'zero further effect' versus actual data (see **Table 9** for patient numbers and proportions). The increasing contribution of 'zero further effect' would inappropriately dilute the treatment effects actually observed in STEPS/STEPS-2 and produce an underestimated treatment effect of teduglutide. Given our approach of assuming zero further effect from last follow-up is conservative to begin with, allowing the PSP data to 'inform' (predominantly via assumptions) transitions beyond 12 months would grossly underestimate the treatment benefit of teduglutide.

B4. Section B.3.3.2. Estimation of transition probabilities. While the explanation for removing the response observed in the placebo arm of STEPS may be plausible for the base case analysis, it remains uncertain. Can the company please explore the upward uncertainty in the ICER associated with:

a. Including health state transitions for SoC as observed in the placebo arm of STEPS.
b. Removing the placebo response from the transitions applied in the teduglutide arm of the model.

As stated in Document B (B.3.3.1, p 97), we consider it inappropriate to apply transition probabilities to standard care based on the placebo group of STEPS due to the placebo outcomes being driven by weaning algorithm used. [redacted]

Although the ERG acknowledges the plausibility of this approach we appreciate that the NICE committee may want to explore the uncertainty further. Therefore, we have added a scenario analysis to the economic model as per part A of this question. The scenario includes the protocol-derived parenteral support (PS) reduction achieved by patients receiving placebo during STEPS. The incremental cost effectiveness ratio (ICER) for this scenario increased to £17,616 per quality-adjusted life year (QALY) for the adult population (base case £16,652 per QALY), and £5,365 per QALY for the paediatric population (base case £4,811 per QALY).

As discussed and aligned upon with the ERG at the clarification meeting (14th September 2021), we consider there to be no benefit in removing the placebo effect from the teduglutide arm (as per part B of this question) for two reasons. Firstly, the impact is expected to be almost exactly the same as the request outlined in part A. This is because both scenarios are essentially applying the same relative effect observed in the trial: A) adds this effect to standard care, B) subtracts this effect from teduglutide. Furthermore, any uncertainty with regards the placebo effect lies in the standard care arm, and not in the teduglutide arm. We have demonstrated in our meta-analysis of real-world evidence (Document B, B.2.8, p 71-74) that the STEPS data underestimate the treatment effect of teduglutide relative to the real-world. As

our model relies heavily on STEPS data, it also underestimates the treatment effect of teduglutide. Therefore, reducing the treatment effect of teduglutide further (as requested in part B of this question) does not address any uncertainty; it potentially adds more uncertainty. As it would provide no further value (beyond our scenario analysis for part A of this question), we have not presented a scenario for part B of this question.

B5. Section B.3.10.1, Validation. A validation of the model-based percentage achieving PS independence is provided by comparing this to the observed percentage in STEPS, STEPS2 and PSP data. Can the company please provide a similar validation of the overall health state distribution predicted by the model at 6, 12, 18, 24 and 30 months.

Table 10 and **Table 11** below show a comparison of the health state distributions over time in the model and in the combined study data (STEPS, STEPS-2 and the patient support programme [PSP]). In general, the health state distributions produced by the model align well with the STEPS, STEPS-2 and PSP data at all time points, validating the output of our model.

Table 10. Health state distributions produced by the model (base case)

Health state distributions (model)	**PS0**	**PS1**	**PS2**	**PS3**	**PS4**	**PS5**	**PS6**	**PS7**
Baseline	0%	0%	0%	11%	14%	10%	13%	52%
6 months	3%	2%	8%	11%	20%	13%	16%	29%
12 months	7%	5%	9%	12%	17%	13%	9%	28%
18 months	9%	8%	10%	5%	18%	13%	10%	28%
24 months	20%	1%	8%	5%	20%	9%	9%	28%
30 months	22%	4%	5%	10%	17%	8%	7%	28%
Abbreviations: PS*x, x* days per week on parenteral support								

Table 11. Health state distributions as per STEPS, STEPS-2 and the PSP

Health state distributions (model)	PS0	PS1	PS2	PS3	PS4	PS5	PS6	PS7
Baseline	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
12 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
18 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
24 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
30 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abbreviations: PS*x, x* days per week on parenteral support; PSP, patient support programme								

For consistency, in **Table 10** and **Table 11**, patients who discontinue teduglutide are included at their baseline health state after the point of discontinuation (to align with the assumption that patients revert back to baseline, as applied in the model). Also to align with the model, the observed study data for those with short follow up in the PSP are carried forward in their last observed health state: they remain on treatment so are assumed to maintain their effects.

Complications

B6. Section B.1.3.2. It is stated that “Chronic kidney disease and liver failure are both potentially fatal.” With respect to the inclusion of chronic kidney disease and liver failure in the economic model, please:

a. Provide details on how the excess mortality risk associated with liver disease was determined and the source of data used.
b. Provide justification for the assumption that stage 5 CKD does not carry any additional mortality risk in the model.

As a point of clarification for part A, our model assumes no mortality risk for either intestinal failure-associated liver disease (IFALD) or chronic kidney disease (CKD).

There are a number of reasons why this approach is justified, despite IFALD and CKD being potentially fatal. Firstly, following a National Service Review, patients with short bowel syndrome with type 3 intestinal failure (SBS-IF) are managed in specialist centres by expert multi-disciplinary teams per the NHS England Service Specification[37]. Clinical feedback sought by Takeda suggests that due to the high standard of care patients receive, deaths due to IFALD or CKD are extremely rare.

Secondly, our model already accounts for the reduced survival of patients with SBS-IF using data from Salazar et al. 2021[38] for adults and Pironi et al. 2011[39] for children. As deaths from complications were captured in these real-world data, separately modelling deaths from IFALD or CKD would introduce double counting. It is worth noting that this approach makes our model conservative in estimating the treatment benefit of teduglutide: as patients who reduce their dependence on parenteral support are likely to have lower rates of complications, we would expect to see a survival gain with teduglutide.

B7. Section B.3.3.5. Please clarify whether adjustments to parenteral support or teduglutide administration would be made if a patient was diagnosed with IFALD or CKD.

The Summary of Product Characteristics (SmPC) for teduglutide specifies that the *"recommended dose is 0.05 mg/kg body weight, once daily"* and *"in adults and children with moderate and severe renal impairment (creatinine clearance less than 50 ml/min), and end-stage renal disease, the daily dose should be reduced by 50%"*. No other dose adjustments are specified in the SmPC[4].

We have not applied a dose adjustment of teduglutide for these patients within our economic model because we have assumed that every patient (including children) requires one 5 mg vial per dose and that no vial sharing occurs. In clinical practice, patients ≤20 kg, or ≤40 kg with moderate or severe renal impairment (per the definition above) or end-stage renal disease, can use the smaller 1.25 mg vial of teduglutide which is 50% cheaper. As such, our approach is conservative and over-estimates teduglutide drug costs.

Clinical experts in the treatment of short bowel syndrome with type 3 intestinal failure (SBS-IF) confirm that although the composition of patients' parenteral support (PS) is often adjusted in patients diagnosed with intestinal failure-associated liver disease (IFALD) or chronic kidney disease (CKD), no adjustment is typically made to their number of days per week of PS. Patients diagnosed with liver disease often have the lipid content of their PS reduced, and those with end-stage liver disease may also reduce their PS volume. However this reduction in volume would usually be a reduction in their hours per night of PS, rather than their number of days of PS.

In patients diagnosed with CKD, their electrolytes and PS volume would likely be adjusted. However, it is very important that CKD patients maintain a daily fluid equilibrium so it would be highly unlikely that their number of days per week of PS would be adjusted. Based on this clinical feedback, our economic model does not assume any adjustment in the number of days per week of PS in patients diagnosed with CKD or IFALD.

B8. Section B.3.3.5. Please provide full details of the Delphi panel exercise used to determine the risks of IFALD and CKD applied in the model (e.g. a separate study report if one exists).

We have attached the Delphi panel report that was used to generate the rates. An overview of the process is provided below.

BresMed [AIC] 2016_Delphi panel r

In a two-stage process, nine healthcare professionals with expertise in the management of short bowel syndrome with type 3 intestinal failure (SBS-IF) were asked first to complete an online questionnaire. Among the questions asked were two relating to the prevalence of intestinal failure-associated liver disease (IFALD) and chronic kidney disease (CKD), the results of these are shown in **Table 12** below.

Table 12. Prevalence of IFALD and CKD derived from the first stage of the Delphi process

Category	Prevalence at 2 years, mean (range)	Prevalence at 6 years, mean (range)	Prevalence at 10 years, mean (range)
No PS	1.38% (0-5%)	1.88% (0-5%)	2.25% (0-5%)
Low volume user	3.25% (0-10%)	5.5% (0-15%)	9% (0-20%)
Mid volume user	7% (1-15%)	13.13% (2-25%)	16.38% (2-30%)
High volume user	11% (2-26%)	20.25% (5-50%)	24.38% (5-50%)

Category	Prevalence at 1 year, mean (range)		Prevalence at 2 year, mean (range)		Prevalence at 10 years, mean (range)	
	CKD Stage IV and V	CKD Stage V only	CKD Stage IV and V	CKD Stage V only	CKD Stage IV and V	CKD Stage V only
No PS	1.75% (0-5%)	1.22% (0-5%)	2.5% (0-6%)	1.44% (0-10%)	5.13% (0-10%)	3.11% (0-10%)
Low volume user	3.13% (0-6%)	2.56% (0-7.5%)	4.88% (0-10%)	2.89% (0-10%)	9.25% (0-20%)	6.67% (2-35%)
Mid volume user	5.38% (0-10%)	4.39% (0-10%)	9% (2-20%)	6.22% (0-15%)	16.25% (3-35%)	12.56% (2-35%)
High volume user	8.25% (2-20%)	7.89% (1-15%)	12.63% (4-30%)	10.61% (2-20%)	20.75% (6-50%)	20% (10-50%)

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

At the second stage, a face-to-face meeting was held where the results of the online questionnaire were discussed and it was decided that these initial estimates for the

prevalence of IFALD and CKD were too high. In the meeting, the experts agreed that the prevalence of IFALD after 2 years would be 0–1%; after 6 years it would be 0–2% and after 10 years it would be 0–3%. It was also agreed that the prevalence of CKD would be higher than IFALD.

From the ranges given for IFALD, these were interpolated to give prevalence estimates by days per week of PS that were used in the model (**Table 13**). The ranges for CKD were estimated based on the IFALD rates, taking into account the consensus that rates of CKD would be higher than IFALD. These were also interpolated to give the prevalence estimates by days per week of PS used in our model (**Table 13**).

Table 13. Prevalence of IFALD and CKD used in our economic model

IFALD	**No PS**	**PS1–3**	**PS4–5**	**PS6–7**
Prevalence at 2 years 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%
CKD	**No PS**	**PS1–3**	**PS4–5**	**PS6–7**
Prevalence at 1 year on PS	0.00%	0.33%	0.67%	1.00%
Prevalence at 2 years on PS	0.00%	0.67%	1.33%	2.00%
Prevalence at 10 years on PS	0.00%	1.67%	3.33%	5.00%

Abbreviations: CKD, chronic kidney disease; IFALD, intestinal failure-associated liver disease; PS, parenteral support; PS*x*, *x* days of PS per week
Source: Delphi panel report[40]

Although interpolation was used to assign prevalence of IFALD and CKD to PS health states, recent publications using real-world data confirm that increasing days of PS per week is associated with greater risk of IFALD[41], and that increasing PS volume is associated with decreased renal function[42]. We were not able to validate the prevalence of CKD in patients with SBS-IF with reference to published literature however for IFALD, Pironi et al. 2020 report 31 new cases in 2,194 patients receiving

PS for one year; a 1-year prevalence of 1.4%. This suggests our Delphi panel estimate is conservative, as we assume a 1-year prevalence of 1.0% for patients with the highest PS requirements[41].

Utilities

B9. Section B.3.4.1. Health related quality of life data from clinical trials, Figure 29. The ERG assumes that the summary data presented data in Figure 29 are descriptive and have not been adjusted for baseline utility. The data could have been analysed more usefully using a regression framework to provide baseline adjusted estimates of PS health state utility or utility increments associated with reductions in PS requirements. Please explore this further and provide further justification as to why these mapped data should not be considered relevant.

We strongly believe that re-analysis of the SBS-QoL data will produce results of no value. This is because the SBS-QoL as a tool is deeply flawed: it completely fails to capture the experience of patients receiving PS and is scored and calculated in a way that does not produce meaningful results. Clinicians, patients and patient-reported outcome (PRO) experts alike, highlight that to make use of the SBS-QoL data for the purposes of our submission would be doing patients a great disservice.

From a clinical standpoint, there is universal agreement in the community that the SBS-QoL tool has been a disappointment. Nurses, patients, psychologists and clinicians will all emphatically state that reducing a night of parenteral support (PS) improves patient quality of life, and at a minimum a quality of life tool should be able to detect this. That the mapped utility data from STEPS do not show this (as per figure 29, Document B, B.3.4.1, p 116) is a critical flaw. [redacted]

[redacted]

[redacted]

[redacted]

[redacted] This is acknowledged by the developers of the SBS-QoL themselves[47]: the authors note that patients suffer from, among other things, a fear of incontinence, an inability to act spontaneously, diminished self-esteem, problems with clothing, concerns with their sexual life, reduced fitness and restriction of time for personal and private activities. These important, patient-relevant, aspects are either not captured by the 17 items of the SBS-QoL, or are captured under vague terminology such as ‘emotional life’ and ‘everyday activities’. Representatives of patient advocacy groups reiterate that these aspects of living with SBS-IF missed by the SBS-QoL are all highly important and relevant to patients’ quality of life. Whilst the SBS-QoL might ignore fear of incontinence, representatives of patient advocacy groups share accounts of patients who do not have this luxury; patients who have been trapped in toilets with burst stoma bags, unable to clean themselves up or leave the cubicle and for whom the fear of this happening again lives with them daily and inhibits them from leaving the house, let alone acting spontaneously.

From a technical perspective, the development, design and scoring of the SBS-QoL are also flawed. [redacted]

[redacted]

Published literature reporting results using the SBS-QoL also highlight the flaws inherent in its design. Jeppesen et al. 2013, discussing the SBS-QoL results in STEPS, note that

"When calculating SBS-QoL scores, no weighting of item scores was included. This was the first confirmatory study using the SBS-QoL scale, and therefore data were not available for such an adjustment. Consequently, all 17 items of the scale contributed to the sum score to the same extent, (i.e. 10 score points), although they could be assumed to be of variable relevance for the patients"[44]

Chen et al. 2020, discussing the same data, note that:

"No clinical consensus has been reached on what the MCID [minimum clinically important difference] *is, and the benchmark is developing as more research is conducted on the QoL* [quality of life] *of patients with SBS."*[50]

Furthermore, Nordsten et al. 2020 describe that:

"The clinical use of the SBS-QoL score has revealed that it still does not sufficiently address the heterogeneity within the SBS-IF population."[51]

In summary, the SBS-QoL has underperformed from a clinical perspective, likely due to its numerous technical flaws, and it is unfit and unable to produce meaningful patient utilities. This will be the case regardless of how the data are analysed, including per the request in question B9. For this reason, we opted in our submission to use utility data from Ballinger et al. 2018, as this represented the utility values of greater relevance to patients[52].

From a patient perspective, the difference between being on PS every night in a week and being independent from PS is enormous. A representative from a patient group described that patients on PS every day of the week are *"like prisoners in their own home. They can never have a night out".* In contrast, being independent from PS is *"an opportunity to be free. Children can meet their friends, parents can meet people"*. The range in the utilities presented in Ballinger et al. 2018, which we have used in our model, are therefore reasonable given this breadth of patient experience. A representative of a patient group also confirmed the health state descriptions used to generate utilities in Ballinger et al. reflect life on PS; patients from their organisation contributed to the development of those health states. Furthermore, the utilities that are derived are supported by other published literature: in Richards et al. 1997, the mean utility value for a patient on PS was 0.52, reaching as low as 0.28 in older patients. Over the time horizon of our base case model, the weighted average utility is between 0.44 to 0.58. This is in-line with the average reported by Richards et al., and the lowest utility value we apply (of 0.36) is higher than the lowest utility reported by Richards et al[53].

To conclude, we believe that Ballinger et al. 2018 represents a source of utilities that best reflect the lived experience of patients receiving PS, and are therefore most appropriate source of utilities for our submission.

B10. Section B.3.4.1. Health related quality of life data from clinical trials. The company state that trial 004 collected health related quality of life data using the EQ-5D. Can the company please report these data, provide adjusted estimates by PS health state or reductions in PS requirements (days per week), and provide further evidence/justification that the data are unsuitable for application in the model.

The results of the EQ-5D in this patient population are of no value and are universally considered irrelevant. This point is clearly made in the European Public Assessment Report (EPAR) published by the European Medicines Agency. They state with regards to the EQ-5D results from study 004:

"it is conceded that these tools [the EQ-5D, and also the SF-36 and Inflammatory Bowel Disease Questionnaire] *may not have been appropriately sensitive to catch any potential difference."*[54]

Similarly, the developers of the SBS-QoL emphasised with reference to the EQ-5D:

"non-disease-specific QoL scales are limited in their ability to detect small but clinically important, treatment-induced changes over time"[47]

Investigators of the Teduglutide 004 Study Group dismissed the relevance of the results and they were not reported in the clinical study report[55], nor has any analysis of this data ever been performed.

Given the highly specific needs of patients with short bowel syndrome and type 3 intestinal failure (SBS-IF), the small patient population, the heterogeneity within said population and the unusual nature of parenteral support as a treatment, it is unsurprising that this measure has no relevance for measuring SBS-IF patients' quality of life. We are firm in believing analysis of these data to be unnecessary and unhelpful.

Resource use and costs

B11. Section B.3.5.2. Table 39 (Resource use of PS health states). Please address the following:

- Nurse time is costed as [redacted] per hour. Please clarify the nature of the time required and the source of the unit cost.

Parenteral support (PS) is provided to patients via the confidential Home Parenteral Nutrition (HPN) framework contract agreed with NHS England[56]. This framework provides an agreement between the NHS and commercial companies who provide PS to patients to a) source, combine and deliver the necessary bags of PS; b) provide and maintain of the equipment needed to administer PS; and c) provide nursing support required by patients on an ongoing basis. The HPN suppliers which are contracted through the framework are commercial entities providing highly qualified specialist nurses working independently in the community to provide a specific HPN service. The hourly rate for nurses provided within the framework includes travel time and additional administrative work required outside of the patient-facing time.

With regards the amount of nurse time estimated per day of PS, we took onboard feedback from the previous submission process and assumed 0.8 hours of nurse time per day of PS (based on an estimate of 2 hours nursing time per day from a resource use study[57] weighted by the 40% of the cohort that require nurse time).

- Please provide the source reference for the resource use requirements detailed Table 39. The reference pack contained duplicates of the costing report for the paediatric population.

Please find the adult resource use study in the file below.

Parexcel 2017_
Adult resource use.p

- Please clarify the source and details of the unit prices for the PN bag and the delivery costs.

As stated above, parenteral support (PS) costs are outlined within the confidential Home Parenteral Nutrition (HPN) framework contract which came into force from 1st April 2020 between the NHS and HPN companies[56].

As per average nurse time costs, the average costs of PS (a parenteral nutrition bag, TauroLock, and delivery) are specified within that contract as confidential and thereby not accessible to us.

This challenge was discussed with NICE during the Company checkpoint meeting on 14th July 2021. We explained that we would not be able to access the latest average costs of PS, and nor were NICE or the ERG able to provide these to us because the costs are confidential. For this reason, we estimated PS costs based on expert opinion sought by Takeda; an approach that was agreed to be acceptable at the checkpoint meeting.

- Patients who are PS independent do not require any resource use. Please justify the assumption that these patients would not require any ongoing visits to a specialist or further support with enteral nutrition.

Table 39 within Section B.3.5.2 of Document B (p 127–129) provides "Resource use for parenteral support (PS) by health state", rather than resource use for short bowel syndrome and type 3 intestinal failure (SBS-IF). As such, patients who are PS independent do not use any PS are assumed to have no costs. Costs associated with patients' underlying SBS-IF are assumed to be equal between teduglutide and standard care treated patients and are not included within our cost-effectiveness model.

That said, we acknowledge there is uncertainty as to whether patients with SBS-IF who achieve PS independence with teduglutide will require specialist visits to monitor their nutritional balance and provide enteral nutrition support, separate from their routine SBS-IF appointments. This uncertainty exists as it has previously not been possible for patients with SBS-IF who are stable on PS to achieve PS independence. As such, we have run a scenario providing an upper-bound estimate of this uncertainty in which we have assumed two specialist visits per year for PS-independent adults and four specialist visits per year for PS independent children. These estimates of specialist visits were based on clinical feedback sought by Takeda. The results of this scenario are provided in **Table 14** below.

Table 14. Scenario analyses for additional specialist visits in health state PS0

Model component	Base case	Scenario	Teduglutide costs	ICER (£/QALY)
Adult base case			[redacted]	£16,652
PS independent resource use	No specialist visits	2 specialist visits per year	[redacted]	[redacted]
Paediatric base case			[redacted]	£4,811
PS independent resource use	No specialist visits	4 specialist visits per year	[redacted]	[redacted]

- Please provide further justification for why sepsis costs have been included in the health state costs rather than included as adverse events based on the data from STEPS.

Line sepsis can occur as a result of a central venous catheter infection during parenteral support (PS) administration. Clinical expert opinion sought as part of the short bowel syndrome costing study highlighted that the risk of line sepsis is increased by the frequency of catheter days[57, 58]. Therefore, it is important to model the changing risk of line sepsis linked to the number of days of PS a patient requires each week. Applying line sepsis as an adverse event linked only to teduglutide exposure but not linked to PS levels would lack the granularity necessary to model this outcome sufficiently. Therefore, we considered it a more accurate and more clinically reflective approach to include these costs as part of the health state costs. All other adverse events in our model are applied to the teduglutide and standard care arms regardless of health state, so this approach maintains consistency. To ensure there is no double counting when applying these line sepsis costs by health state, any line sepsis events recorded as adverse events are excluded from adverse events in the model. This change to avoid double counting was made in response to feedback from the previous appraisal of teduglutide.

- Please clarify how the measure of line sepsis requiring critical care was derived, what it represents, and how this has been costed.

The approach taken to estimate line sepsis costs was revised from the previous appraisal based on the feedback received by the ERG, the DSU and the NICE appraisal committee. The ERG previously proposed an approach to align clinical expert input from the Parexel short bowel syndrome costing studies[57, 58] with published evidence sources[59-61] of line sepsis rates for patients as a whole who require parenteral support (PS).

The costing study provided estimates of mean annual line sepsis rates of 0.135, 0.172 and 0.232, for low, moderate, and high levels of PS, respectively. However, a pooled estimate of 0.44 was taken from published literature for PS as a whole, and as suggested by the ERG, this value of 0.44 was used to calibrate the values for each health state to ensure a weighted average was equal to 0.44. The relative rates between high and moderate, and moderate and low estimated in the costing study were maintained and assumed to apply to PS3, PS5 and PS7, for low, moderate, and high, respectively. Interpolation was used to estimate values for the remaining health states.

For line sepsis requiring critical care, the feedback received during the previous appraisal was that the estimates from the costing study (20–50% of patients with line sepsis would be expected to require critical care) was likely to be an overestimate. The NICE Decision Support Unit (DSU) sought clinical expert advice from both doctors and nurses and concluded that 10% of patients with line sepsis would require critical care. We took this feedback onboard and have assumed 10% of patients with line sepsis will require critical care in our current base case analysis.

References

1. UK Government. Population of England and Wales Gov.UK2020 [Available from: https://www.ethnicity-facts-figures.service.gov.uk/uk-population-by-ethnicity/national-and-regional-populations/population-of-england-and-wales/latest.
2. ClinicalTrials.gov. Study in Japanese Pediatric Subjects With Short Bowel Syndrome (SBS) Who Are Dependent on Parenteral Support 2021 [Available from: https://clinicaltrials.gov/ct2/show/study/NCT02980666.
3. ClinicalTrials.gov. Study to Evaluate the Safety, Efficacy and Pharmacokinetics of Teduglutide in Japanese Subjects With PN-dependent Short Bowel Syndrome (SBS) 2021 [Available from: https://clinicaltrials.gov/ct2/show/study/NCT02340819.
4. Shire Pharmaceuticals Limited. Revestive 1.25 and 5 mg powder and solvent for solution for injection. Summary of Product Characteristics2020.
5. Jeppesen P, Pertkiewicz M, Messing B, Iyer K, Seidner D, O'Keefe S, et al. Teduglutide reduces need for parenteral support among patients with short bowel syndrome with intestinal failure. Gastroenterology. 2012;143(6):1473-81.
6. NPS Pharmaceuticals Inc. STEPS CSR. Clinical Study Report. Not published - Takeda confidential
2011.
7. Schwartz LK, O'Keefe SJ, Fujioka K, Gabe SM, Lamprecht G, Pape UF, et al. Long-term teduglutide for the treatment of patients with intestinal failure associated with short bowel syndrome. Clin Transl Gastroenterol. 2016;7:e142.
8. NPS Pharmaceuticals Inc. STEPS-2 CSR. Clinical Study Report. Not published - Takeda confidential data2013.
9. Joly F, Seguy D, Nuzzo A, Chambrier C, Beau P, Poullenot F, et al. Six-month outcomes of teduglutide treatment in adult patients with short bowel syndrome with chronic intestinal failure: A real-world French observational cohort study. Clin Nutr. 2020;39(9):2856-62.
10. Lam K, Schwartz L, Batisti J, Iyer KR. Single-Center Experience with the Use of Teduglutide in Adult Patients with Short Bowel Syndrome. JPEN J Parenter Enteral Nutr. 2018;42(1):225-30.
11. Martin A, Boehm V, Zappa M, Billiauws L, Bonvalet F, Nuzzo A, et al. Imaging as predictor of clinical response to teduglutide in adult patients with short bowel syndrome with chronic intestinal failure. The American journal of clinical nutrition. 2021;113(5):1343-50.
12. Pevny S, Maasberg S, Rieger A, Karber M, Blüthner E, Knappe-Drzikova B, et al. Experience with teduglutide treatment for short bowel syndrome in clinical practice. Clin Nutr. 2019;38(4):1745-55.
13. Puello F, Wall E, Herlitz J, Lozano ES, Semrad C, Micic D. Long-Term Outcomes With Teduglutide From a Single Center. JPEN J Parenter Enteral Nutr. 2020;45(2):318-22.
14. Schoeler M, Klag T, Wendler J, Bernhard S, Adolph M, Kirschniak A, et al. GLP-2 analog teduglutide significantly reduces need for parenteral nutrition and stool frequency in a real-life setting. Therap Adv Gastroenterol. 2018;11:1756284818793343.
15. Tamara PR, Alicia HA. Teduglutide in adult patients with short bowel syndrome. Eur J Clin Pharm. 2020;22(3):166-70.

16. Ukleja A, To C, Alvarez A, Lara LF. Long-Term Therapy With Teduglutide in Parenteral Support-Dependent Patients With Short Bowel Syndrome: A Case Series. JPEN J Parenter Enteral Nutr. 2018;42(4):821-5.
17. NPS Pharmaceuticals Inc. STEPS protocol. Not published - Takeda confidential; 2011.
18. British Intestinal Failure A. British Intestinal Failure Alliance (BIFA): Position statement: Home parenteral nutrition (HPN) 2016 [updated August 2016. Available from: http://www.bapen.org.uk/images/pdfs/news/bifa-position-statement-about-hpn.pdf.
19. Nightingale J, Woodward JM, Small B, Nutrition Committee of the British Society of G. Guidelines for management of patients with a short bowel. Gut. 2006;55 Suppl 4:iv1-12.
20. Jeppesen P. CONFIDENTIAL: Expert testimony on the unexpectedly high placebo rate in the pivotal 020/STEPS Study in relation to intestinal adaptation and baseline demographics of placebo/SOC arm. In: Ltd T, editor. 2018.
21. Thompson JS, Rochling FA, Weseman RA, Mercer DF. Current management of short bowel syndrome. Curr Probl Surg. 2012;49(2):52-115.
22. Guillen B, Atherton NS. Short Bowel Syndrome: StatPearls; 2021 [Available from: https://www.ncbi.nlm.nih.gov/books/NBK536935/.
23. Iyer K, Jeppesen PB, Pape UF, Lee HM, Olivier C. Differential baseline characteristics in short bowel syndrome due to vascular catastrophes are associated with varying response to teduglutide: Post hoc analysis. American Society for Parenteral and Enteral Nutrition Clinical Nutrition Week. Orlando, Florida: USA; 2017.
24. Jeppesen PB, Gabe SM, Seidner DL, Lee HM, Olivier C. Factors Associated With Response to Teduglutide in Patients With Short-Bowel Syndrome and Intestinal Failure. Gastroenterology. 2018;154(4):874-85.
25. Seidner DL, Gabe SM, Lee HM, Olivier C, Jeppesen PB. Enteral Autonomy and Days Off Parenteral Support With Teduglutide Treatment for Short Bowel Syndrome in the STEPS Trials. JPEN J Parenter Enteral Nutr. 2020;44(4):697-702.
26. European Medicines Agency (EMA). CHMP Assessment Report: Revestive 2012 [Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/002345/WC500129094.pdf.
27. Takeda UK Ltd. Revestive atHOME_PS reduction report. Not published - Takeda confidential data [DPD]; 2021.
28. NPS Pharmaceuticals Inc. 004 CSR. Clinical Study Report. Not published - Takeda confidential
2013.
29. NPS Pharmaceuticals Inc. STEPS-3 CSR. Clinical Study Report. Not published - Takeda confidential data2014.
30. NPS Pharmaceuticals Inc. 005 CSR. Not published - Takeda confidential data2010.
31. Carter BA, Cohran VC, Cole CR, Corkins MR, Dimmitt RA, Duggan C, et al. Outcomes from a 12-week, open-label, multicenter clinical trial of teduglutide in pediatric short bowel syndrome. J Pediatr. 2017;181:102-11 e5.
32. Kocoshis SA, Merritt RJ, Hill S, Protheroe S, Carter BA, Horslen S, et al. Safety and Efficacy of Teduglutide in Pediatric Patients With Intestinal Failure due to Short Bowel Syndrome: A 24-Week, Phase III Study. Journal of Parenteral and Enteral Nutrition. 2020;44(4):621-31.

33. Sulkowski JP, Minneci PC. Management of short bowel syndrome. Pathophysiology. 2014;21(1):111-8.
34. Compher C, Gilroy R, Pertkiewicz M, Ziegler TR, Ratcliffe SJ, Joly F, et al. Maintenance of parenteral nutrition volume reduction, without weight loss, after stopping teduglutide in a subset of patients with short bowel syndrome. J Parenter Enteral Nutr. 2011;35(5):603-9.
35. Sobocki J, Majewska K, Jurczak P, Omidi M. CLINICAL STATUS OF PATIENTS WITH PARENTERAL NUTRITION-DEPENDENT SHORT BOWEL SYNDROME 4 YEARS AFTER TEDUGLUTIDE TREATMENT. Clinical nutrition. 2016;35(S67).
36. Takeda UK Ltd. Confidential: Teduglutide NICE submission advisory board 2021 21st June 2021.
37. NHS England. Intestinal Failure Service (Adult) NHS.uk2019 [Available from: https://www.england.nhs.uk/publication/intestinal-failure-service-adult/.
38. Salazar E, Clermont-Dejean NM, Schwenger KJP, Noelting J, Lu Z, Lou W, et al. Patients With Severe Gastrointestinal Dysmotility Disorders Receiving Home Parenteral Nutrition Have Similar Survival As Those With Short-Bowel Syndrome: A Prospective Cohort Study. JPEN J Parenter Enteral Nutr. 2021;45(3):530-7.
39. Pironi L, Joly F, Forbes A, Colomb V, Lyszkowska M, Baxter J, et al. Long-term follow-up of patients on home parenteral nutrition in Europe: Implications for intestinal transplantation. Gut. 2011;60(1):17-25.
40. BresMed. P15133 Teduglutide – Modified Delphi Panel Report. Not published - confidential Takeda data; 2016.
41. Pironi L, Steiger E, Joly F, Wanten GJA, Chambrier C, Aimasso U, et al. Intravenous supplementation type and volume are associated with 1-year outcome and major complications in patients with chronic intestinal failure. Gut. 2020;69(10):1787-95.
42. Mathiesen SM, Fuglsang KA, Ranzato G, Scheike T, Jeppesen PB. Renal function in patients with intestinal failure receiving home parenteral support. JPEN J Parenter Enteral Nutr. 2021.
43. Burden ST, Jones DJ, Gittins M, Ablett J, Taylor M, Mountford C, et al. Needs-based quality of life in adults dependent on home parenteral nutrition. Clin Nutr. 2019;38(3):1433-8.
44. Jeppesen PB, Pertkiewicz M, Forbes A, Pironi L, Gabe SM, Joly F, et al. Quality of life in patients with short bowel syndrome treated with the new glucagon-like peptide-2 analogue teduglutide--analyses from a randomised, placebo-controlled study. Clin Nutr. 2013;32(5):713-21.
45. Wilburn J, McKenna SP, Heaney A, Rouse M, Taylor M, Culkin A, et al. Development and validation of the Parenteral Nutrition Impact Questionnaire (PNIQ), a patient-centric outcome measure for Home Parenteral Nutrition. Clin Nutr. 2018;37(3):978-83.
46. Gabe S. CONFIDENTIAL - Expert statement_Teduglutide NICE letter. In: Ltd TU, editor. 2021.
47. Berghöfer P, Fragkos KC, Baxter JP, Forbes A, Joly F, Heinze H, et al. Development and validation of the disease-specific Short Bowel Syndrome-Quality of Life (SBS-QoL) scale. Clin Nutr. 2013;32(5):789-96.
48. Stephen McKenna. CONFIDENTIAL_Expert statement_SBS-QoL evaluation. In: Takeda UK Ltd, editor. 2021.
49. US Food and Drug Administration. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims fda.gov2009 [Available

from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-reported-outcome-measures-use-medical-product-development-support-labeling-claims.
50. Chen K, Mu F, Xie J, Kelkar SS, Olivier C, Signorovitch J, et al. Impact of Teduglutide on Quality of Life Among Patients With Short Bowel Syndrome and Intestinal Failure. JPEN J Parenter Enteral Nutr. 2020;44(1):119-28.
51. Nordsten CB, Molsted S, Bangsgaard L, Fuglsang KA, Brandt CF, Niemann MJ, et al. High Parenteral Support Volume Is Associated With Reduced Quality of Life Determined by the Short-Bowel Syndrome Quality of Life Scale in Nonmalignant Intestinal Failure Patients. JPEN J Parenter Enteral Nutr. 2021;45(5):926-32.
52. Ballinger R, Macey J, Lloyd A, Brazier J, Ablett J, Burden S, et al. Measurement of Utilities Associated with Parenteral Support Requirement in Patients with Short Bowel Syndrome and Intestinal Failure. Clin Ther. 2018;40(11):1878-93.e1.
53. Richards DM, Irving MH. Assessing the quality of life of patients with intestinal failure on home parenteral nutrition. Gut. 1997;40(2):218-22.
54. European Medicines Agency. CHMP Assessment Report: Revestive 2012 [Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/002345/WC500129094.pdf.
55. NPS Pharmaceuticals Inc. 004 CSR. Not published - Takeda confidential 2013 21 May. Contract No.: CL0600-004.
56. NHS England. NHS National framework agreement for the supply of the home Parenteral nutrition & intravenous fluid for patients with severe intestinal failure Gov.uk2019 [Available from: https://www.contractsfinder.service.gov.uk/Notice/fce8e9bb-23ae-4446-ace1-d506e5a54921.
57. PAREXEL Access Consulting. Adult SBS Costing Study Not published - Takeda confidential data; 2017 3 March
58. PAREXEL Access Consulting. Paediatric SBS Costing Study Not published - Takeda confidential data; 2017 3 March
59. Bond A, Teubner A, Taylor M, Cawley C, Abraham A, Dibb M, et al. Assessing the impact of quality improvement measures on catheter related blood stream infections and catheter salvage: Experience from a national intestinal failure unit. Clin Nutr. 2018;37(6 Pt A):2097-101.
60. McCarthy M, Dunn JM, O'Sullivan S, Fong S, Al-Hilou H, Le Couteur J, et al. Outcome of the first twenty patients in a Home Parenteral Nutrition (HPN) service at Guys and St. Thomas' Hospital. Clin Nutr ESPEN. 2015;10(5):e201.
61. Gabe S. Complications of Central Venous Catheters: current perspectives 2015 [Available from: https://www.slideshare.net/stmarks_academicinstitute/complications-of-central-venous-catheters-current-perspectives.

Appendix G – NHS organisation submission template (DH and WG)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Teduglutide for treating short bowel syndrome [ID3937]

Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

The Department of Health and the Welsh Government provide a unique perspective on the technology, which is not typically available from the published literature. NICE believes it is important to involve NHS organisations that are responsible for commissioning and delivering care in the NHS in the process of making decisions about how technologies should be used in the NHS.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Short, focused answers, giving a Department of Health and Welsh Government perspective on the issues you think the committee needs to consider, are what we need.

About you

Your name: **Dr Simon Gabe**

Name of your organisation: **Lennard Jones intestinal failure unit, St Mark's hospital, LNWH Trust**

Please indicate your position in the organisation:

- a specialist in the treatment of people with the condition for which NICE is considering this technology?

- a specialist in the clinical evidence base that is to support the technology (e.g. participation in clinical trials for the technology)?

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

No funding from the tobacco industry

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences in opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Appendix G – NHS organisation submission template (DH and WG)

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Teduglutide for treating short bowel syndrome [ID3937]

The main treatment for short bowel syndrome is nutritional support (delivery of nutrients, electrolytes and fluids), which can be given through a tube directly into the stomach or intestine (enteral feeding) or vein (intravenous nutrition or support)
- Enteral tube feeding into the stomach or small bowel is infrequently used in this condition. The method of delivery depends on the length and function of the remaining intestine
- Intravenous nutrition is used for patients who have severe intestinal failure. When this is long-term (Type III intestinal failure) then this is often referred to as home parenteral nutrition as it is possible to manage patients on this form of life support at home. The majority of people self-administer intravenous nutrition at home, using a long-term intravenous tube inserted by a healthcare professional. These tubes are associated with life threatening complications such as blood infections and blood clots. Home parenteral nutrition is also associated with the development of intestinal failure associated liver disease (IFALD) and liver failure. Parenteral support places a huge burden on patients, because it requires them to be attached to an infusion pump for many hours each night, for several nights a week. Some people need treatment every night and are unable to work.

People with short bowel syndrome will also receive drugs to promote nutrient absorption, including antimotility agents (such as loperamide and codeine) to increase the time it takes food to travel through the intestines, and antisecretory agents (such as proton pump inhibitors) to reduce the production of gastric acid. Patients will be advised to restrict their oral fluid intake and change their diet to promote absorption.

In addition, where possible surgery is considered to reconstruct or lengthen the remaining parts of the bowel, to increase the surface area for absorption. People whose condition does not respond to treatment, or who develop serious complications from long-term parenteral support, may require an intestinal transplant, but this is considered only as a last resort.

In terms of variation of practice in England, the management is fairly well agreed. There are differences in management that may relate to experience of the clinicians and teams looking after patients in different locations. The widest experience for the management of these patients is at St Mark's hospital and Salford Royal Hospital, where there are currently 2 National Reference Centres looking after large volumes of patients. Around the country there may be up to 25-30 hospitals looking after patients with varying experience. Currently the NHS is settin up a networked service (HIFNET) relating to all patients with intestinal failure receiving intravenous nutrition support. A service definition has been set and the larger centres, which are surgical and medical severe intestinal failure (SIF) centres, are in the process of being allocated. The smaller medical home parenteral nutrition (HPN) centres have not yet been allocated. Ultimately the aim for NHS England is that this type of network will be able to ensure a consistent standard of practice across the country.

The management of patients with intravenous nutrition support is well established and there are good survival rates for this sort of management. However, complications do occur with infection or thrombosis associated with the central venous catheters as well as intestinal failure associated liver disease. This morbidity

adds to the cost of treatment. Nevertheless, the cost of this treatment overall is much less than the current cost of teduglutide. However, quality-of-life is a separate issue. The advantage of teduglutide is that it has the potential to get patients off intravenous nutrition support, or decrease the amount they require. This certainly does have the potential to improve the patient's quality-of-life.

The alternatives to teduglutide are listed above with management predominantly relating to continuing with intravenous nutrition support, together with standard medical management. Current alternatives include:
- Surgical re-continuity procedures: this can only be performed in patients that have residual bowel that is out of continuity. However, it is very effective at rendering patients independent of parenteral nutrition support when it is possible to be performed.
- Small bowel lengthening procedures: this is currently being assessed in England and so far only 2 adult patients have undergone this procedure. This approach should therefore be considered more experimental at this stage as it is rarely performed in this country and also in Europe. There is a greater experience in America and also in the paediatric population.
- Intestinal transplantation. Intestinal transplantation is performed in very selected patients with short bowel. It is mainly reserved to patients who develop life-threatening complications. It is high cost and has a lower survival rate overall than remaining on intravenous nutrition support.

To what extent and in which population(s) is the technology being used in your local health economy?

- is there variation in how it is being used in your local health economy?

Currently this treatment is not available on the NHS in our local health economy. I have had 2 patients who have received it on a compassionate use basis, having been in the trials assessing its use. This was some time ago and both patients have now died unfortunately. One patient did develop pancreatic cancer and the other patient died of his underlying condition.

- is it always used within its licensed indications? If not, under what circumstances does this occur?

I would expect that it would always be used within its licensed indications.

- what is the impact of the current use of the technology on resources?

For the patients who I did have on this treatment, one came off his intravenous nutrition support altogether and therefore there was a substantial benefit to the health economy as well as to his quality-of-life. The second patient halved his intravenous nutrition support requirements, decreasing the cost to the NHS. This also improved his quality-of-life as well as stomal output decreased substantially, helping to prevent leakages from occurring and improving his confidence. Both patients were able to work as a result of being the medication.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Teduglutide for treating short bowel syndrome [ID3937]

- what is the outcome of any evaluations or audits of the use of the technology?

I have only had 2 patients on this treatment and therefore have not been able to audit it apart from being able to describe these patients as above.

- what is your opinion on the appropriate use of the technology?

I can see that this will definitely have a place in a treatment algorithm. Patients who are stable on intravenous nutrition support with short bowel (who do not meet any exclusion criteria) would be offered this. It will be especially helpful for patients with a very high output jejunostomy as these patients are deficient of GLP 2 and this treatment will correct that deficiency. It will maximise potential absorption from the residual bowel and decrease their requirement for parenteral nutrition support. Another group of patients who need only small amounts of parenteral nutrition (often these are patients who have residual colon in continuity). These patients have been shown to be more likely to be able to come off parenteral nutrition support as a result of this treatment.

Potential impact on the NHS if NICE recommends the technology

What impact would the guidance have on the delivery of care for patients with this condition?

As above, ultimately it will decrease the number of patients requiring intravenous nutrition support. These patients would have to be cared for in a specialist setting by experienced clinicians to minimise side effects and complications of the treatment itself. This would naturally be done in integrated intestinal failure centres on HIFNET.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional resources (for example, staff, support services, facilities or equipment)?

As above, this should be restricted to be prescribed by experienced specialist centres such as the integrated intestinal failure centres on HIFNET. I do not think additional staff would then be required. There may be some requirement for additional resources as these patients need to be followed up more closely than patients who are just simply on intravenous nutrition support. This would be in terms of increased outpatient reviews as well as more blood tests and tests for colonic surveillance (colonoscopy or CT colonography)

Can you estimate the likely budget impact? If this is not possible, please comment on what factors should be considered (for example, costs, and epidemiological and clinical assumptions).

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Single Technology Appraisal (STA)

Teduglutide for treating short bowel syndrome [ID3937]

The budget impact is great if the cost of the treatment remains exceptionally high at around £190,000 per annum. However, if the NHS can achieve a price reduction then obviously this would change.

Would implementing this technology have resource implications for other services (for example, the trade-off between using funds to buy more diabetes nurses versus more insulin pumps, or the loss of funds to other programmes)?

I do not think that this technology would have resource implications for other services.

Would there be any need for education and training of NHS staff?

There would be need for education and training of NHS staff. This would naturally happen in the intestinal failure centres as described above. My understanding is that industry would be prepared to fund such an education programme.

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

The only real issue that is probably different to the question that is being asked is that as the cost of this treatment is extremely high, whether it would have an impact on treating other conditions due to less money being available in the NHS budget. To some extent this is a political question although not entirely. If the use of this medication is truly limited to patients with short bowel syndrome & intestinal failure then this would be a select group of patients and therefore the budget impact would be minimised. Nevertheless, it still would be large impact on a healthcare budget as far as I can see. It is imperative that a much lower cost for this treatment is achieved when negotiating with the company.

If treatment with this medication is available within a networked system (HIFNET) then I do not think that there would be any equality issues as patients can be referred to the appropriate hospital or centre that is closest to them.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Teduglutide for treating short bowel syndrome [ID3937]

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

n/a

Other Issues

Please include here any other issues you would like the Appraisal Committee to consider when appraising this technology?

……

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Teduglutide for treating short bowel syndrome [ID3937]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**xxxxxxxxxxxxxxxx**

2. Name of organisation	PINNT
3. Job title or position	Chair
4a. Brief description of the organisation (including who funds it). How many members does it have?	Support & advocacy for people living on home artificial nutrition. Main funding comes from member donations, fund raising events, corporate partners pay a small fee annually, donation to PINNT from consultancy and advisory projects which occur on an ad hoc basis. In excess of two-thousand.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	A five-thousand-pound donation from Takeda as emergency funding during COVID-19. Purpose: To aid our work when donations dropped/ceased during the pandemic when our network was tested in terms of providing support and information to our members.
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None.

5. How did you gather information about the experiences of patients and carers to include in your submission?	• **We contacted members who have ongoing lived experiences with HPN/IF and asked them to submit individual testimonies about life with SBS/IF/PN.** • **A previous survey of members with a question-and-answer format.**
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	The patient journey to SBS is varied and potentially protracted given the potential for high levels of interventions by medically and surgically. The most associated conditions are Crohn's and other Inflammatory Bowel diseases. For many patients, SBS may not be the only health condition that they are managing on a day-to-day basis. These 'pre-existing' conditions may already have placed restrictions on an individual's life. SBS/IF is both a complex and rare condition, the addition of parenteral nutrition as a treatment is an additional layer of complexness which brings both benefits and risks. Once a patient develops SBS their life will be changed immensely, sometimes under quite traumatic circumstances. In a short space of time someone can go from eating and drinking in the normal way to being dependent on parenteral nutrition (PN) via a central venous catheter (CVC). Thankfully PN is lifesaving, having said that it is also highly complex and can be life-threatening in terms of the additional risk of infections and complications. Any PN associated complications could mean hospital admissions which patients want to avoid. The ability for SBS people to continue to eat and drink normally will vary; whatever the individual outcome is it will come with additional issues such potential pain when eating, discomfort, vomiting/nausea, increased output and frequent trips to the toilet and possibly oral restrictions with fluid and food types. The impact of this on an individual is immense – emotionally, physically and practically. There are some people who are unable to eat and drink at all; the psychological impact is immense, in a world where food and drink is used to celebrate special occasions and bring family and friends together, we impose social isolation on many with SBS/IF/PN. PN keeps people with SBS alive, day in day out. Due to the administration regimen, it is highly restrictive to the person receiving it and their families. Daily movements are dictated by their treatment regime. In most cases planning for the day ahead starts the day before due to infusion times and relevant

	procedures. Sadly, many people with SBS are used to having to cancel plans at the last minute due to unexpected changes in their daily ability to cope. There are evidence-based procedures that need to be adhered to every time a bag of PN is set up and then disconnected upon completion of an infusion. Each step has been planned to safeguard the patient in terms of potential infection or complications. The procedure times will vary due to the ability of the individual person, it could be up to 30 minutes depending on the procedure the patient uses. Once connected a bag of PN, up to 4 litres, along with the pump, battery and PN rucksack need to be carried around by the individual. There is a false belief that PN is given purely overnight while the individual is asleep. The total weight of PN and relevant accessories can be up to and over 4kg. Some people will need help to connect to their PN, many are self-caring, some people receive nursing care (which restricts the whole process of PN due to the rotas in which the nursing services are available) others need help from their partners/carers. *'On bad days when I'm in excess pain or dehydrated, my wife helps as my concentration isn't sufficient. It can be difficult lifting 3500ml bag.'* Many patients experience high levels of pain due to their underlying condition(s); this is their new 'normal' given their situation but this in no way makes it more bearable. There are times when even this becomes excessive, and the usual pain relief becomes ineffective. Their pain threshold is pushed to the limit, even exceeded so their ability to cope and be independent is compromised even further. *'Only need help when unwell with symptoms or fatigue. Easy to make mistakes.'* *'Initially I found myself being continually tired. This was due to the fact I had to care for [her] and also carry out the procedure to connect her up to the TPN every day for approximately eighteen months. When she was well enough to do it herself, we still had days when she was very ill and whilst not as frequent, she still has bad days. For me personally, I have a continual worry in the back of my mind wondering whether if she is ok in my absence. I have had many down days however this has not in any way affected me as much as it has [her].'* Once the individual is connected an infusion rate is set into the feeding pump which controls how much PN is given at an hourly rate. The infusion rates and volumes will vary from patient to patient, one common factor is the need to visit the toilet during the infusion time. Sleep can be disturbed multiple times

	during the night for bowel and bladder emptying, the patient will need to get themselves and the equipment to the toilet in good time to avoid accidents. It's not only the patient who experiences disturbed sleep patterns but anyone else sharing the bedroom or even in the household. The pressure on families with a child on PN are even greater as their role is to safeguard over night in terms of being alert and vigilant to warning alarms if the feeding pump detects a problem. In some situations the carer of an adult will also need to be vigilant as they be the person who needs to be attentive to alarms to assist with any corrective measures that need to be taken. For both parents/guardians/carers, there is potential to assist with toilet trips during the night. Indeed, this can include mopping up leaks, spillages, changing night attire, changing the bed and cleaning up the mess caused by a problem with a stoma bag while safeguarding the integrity of the giving set and CVC to ensure there is no cross contamination. On average someone receiving PN will spend six days a week, twelve hours a day undergoing the administration of feed. This volume can vary over the years and some people may have a reduction in the volume of feed – this results in a greater level of freedom. For many patients the panacea is to reduce the volume of feed as much as they can to allow them to lead a less restricted life. *'More flexibility and freedom. Went from 5 nights to 4. Easier to travel as less baggage.'* *'More nights off I have from PN the better. I constantly have the goal of reducing PN. Gives me an aim.'* *'Reduction from 5 to 4 days a welcome change.'* In terms of administering the actual feed, this is carried out solely by the patient in over 75% of cases, with family members also supporting the administration as and when required. In addition to the time spent infusing the PN there is the need to be fully aware of the arrangements for delivery of both the PN and ancillaries required. Monitoring stock levels, ensuring the PN is safely stored and checking expiry dates is a vital part of the process for the individual and their carers. The expiry date must be adhered to on the PN due to the stability of the components that make us the solution. Adverse

	reactions could result in trips to hospital which patients want to avoid at costs. All products must be safe to infuse and use. In addition to this there will be the need for hospital visits related to the underlying condition and the PN, as well as any other medical conditions they may have. There is no standard PN patient; each arriving at the point of having SBS and needing PN at different times of their lives. The impact for each of them will be individual but there are common issues around acceptance/anger/frustration and personal expectations. It maybe they feel less fulfilled in the life they once hoped. HPN dictates a high level of commitment both in terms of time and concentration. There is no let up or break from the life-saving treatment and regimes. The impact of treatment does vary from patient to patient but generally speaking their ability to work is moderately to very affected, personal relationships and mental health are moderately affected and their ability to take part in recreational activities is moderately to very affected. *'[he] has definitely been limited in his career due to his condition. His condition restricts his travel day-to-day, so he has not been able to take a number of promotions as he can't do the commuting. He also gets very tired so working extended hours is not an option. Recreationally, his condition limits certain activities at the weekend and late nights are not an option due to needing to get on his TPN. He also rarely drinks as it makes him ill so missed out on social opportunities as feels restricted.'* *'My husband's life has certainly improved since commencing artificial nutrition. He remains unable to work and is unable to participate in sporting activities, but these are due to other medical ailments. All our family and close friends are aware of the artificial nutrition being received by my husband and offer support.'* There are also practical implications of HPN in terms of storage of a medical fridge, relevant ancillaries to perform the procedures and a dedicate area in which the procedures can be done safely. Organising an overnight stay away from home can be problematic and even more complicated if people are able and wish to travel overseas. The need for PN can restrict choices in terms of travel etc. Some have tried it and elect to continue; others elect not to do it due to the amount of meticulous planning needed. *'Only once, not regularly.'*

	'Too much organisation and worry, also I need a fridge large enough to take 3.5 litres PN feeds.' *'Takes a lot of planning, also hard and tiring*.' Patients are provided with packaging for cold-chain process (2-8^{O}C) in around 70% of cases which is needed for travel and safe storage at the holiday accommodation can be difficult to obtain. Transporting PN can mean the cold-chain boxes which can weight up to 16kg. There is an increasing number of patients who can use multi-chamber bags that do not need the cold-chain process. However, these may be restricted to a certain number of nights as they are not nutritionally complete. The risks of PN are widely known and patients and carers are trained to recognise them and take appropriate action to seek medical attention. A high proportion of people (68%) receiving parenteral nutrition have experienced a line infection. When this happens, they are instructed to go to their own centre or their nearest A&E department. It's imperative that line cultures are taken to determine if an infection is present before broad spectrum antibiotics are started. It may then be necessary for the patient to remain in hospital until an infection can be confirmed and appropriate action taken such as a course of appropriate antibiotics or central line removal and replacement, it will vary. From the perspective of the carer, a marked change in their loved one's general state of health and wellbeing is often felt. Changes in the ability of the patient to work, decreased energy levels, social impact. Many carers will dedicate their life to looking after their family member who has SBS and will forgo their own needs and wants to do so, giving up work to become a full-time carer in many cases. *'After [her] operation 2 years ago we knew it would be life changing. Living with a patient with a high output stoma and relying on IV fluids is difficult at times but in a way has made us stronger. A routine is imperative.'* *'Initially I found myself being continually tired. This was due to the fact I had to care for [her] and also carry out the procedure to connect her up to the TPN every day for approximately eighteen months. When she was well enough to do it herself, we still had days when she was very ill and whilst not as frequent, she still has bad days. For me personally, I have a continual worry in the back of my mind wondering whether if she is ok in my absence. I have had many down days however this has not in any way affected me as much as it has [her].'*

	Living with SBS and being dependent on PN is lifesaving but it comes with limitations within the boundaries of the condition and treatment. The impact of treatment and care will vary between individual people and their families; each has their own journey and perspective. If there is a chance that a new technology could have a positive outcome on the daily lives for those for living with SBS and for those supporting them, then an overall improve in quality of life could be achieved. For many it's a situation that impacts on the whole family unit and not solely on an individual. **The patient/carer quotes are taken from the PINNT Short Bowel Syndrome Survey 2016.**
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Home parenteral nutrition is seen by many as a welcomed life-saving intervention. It gives people with SBS/IF the ability to receive nutrients and fluids to sustain life given their complex rare diseases. Of late there have been concerns about the supply of compounded parenteral nutrition which is a worry for some.
8. Is there an unmet need for patients with this condition?	Yes, there is no alternative therapeutic option to parenteral nutrition.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Some have mentioned that this technology gives 'hope' for increased quality of life for those with SBS/IF dependent on PN. There is huge potential for reduced burden of care, reduce complications and a degree of freedom for carers given the demand on their time, both physically and mentally.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Some have read about the technology and realise there is potential for an adjustment period to the technology, as with any new drug. There may be a period of increased gut pain, painful injections or issues relating to the effects on current stomas.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	None that we can state.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	**None that we are aware of.**

Other issues	
13. Are there any other issues that you would like the committee to consider?	Each person is unique; expectation will vary and no two people with SBS/IF on HPN will be the same. The treatment is the common denominator, expectations and the ability to make choices will vary. Our testimonies and member survey clearly show this.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Reduced nights of PN = improved quality of life both for patients & carers. Mental health can be improved.
- Nights without PN can provide quality sleep which aids the ability to cope with SBS/IF, HPN and additional medical condition(s).
- The burden of care and treatment could be alleviated if people have greater freedom within the boundaries of their condition(s) & treatment.
- Offer a viable therapeutic alternative to PN.
- Allow greater flexibility & choice around the burden and precise planning of travelling with PN both in the UK and further afield.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

……

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Teduglutide for treating short bowel syndrome [ID3937]

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Short Bowel Survivor and Friends
3. Job title or position	Chair/ Trustee
4a. Brief description of the organisation (including who funds it). How many members does it have?	Short Bowel Survivor and Friends is a not – profit charity Registration Number: 114493544 It is funded by public money in the form of fundraising activities, gifts and donations At present we have 43 members including the steering committee
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	NONE

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	NONE
5. How did you gather information about the experiences of patients and carers to include in your submission?	Firstly, I am grandmother of a13 year old girl who was born with Atresia, leaving her with initially only 10cm of small bowel. I was trained in the administration of Home Parenteral Nutrition (PN) so as to be able to assist my daughter who was a single parent. The child had several rounds of surgery in the first 3 years of her life and on PN for 6 years. I therefore have first-hand knowledge and experience of the intense 'burden of care' SBS-IF imposes on families. In 2011/12 I was instrumental in setting up Short Bowel Survivor and Friends charity which offers help support and up to date information to SBS-IF families through our website and mutual support via our social media site. As part of my role, I visit new parents on request in need of support. I am also in contact with other similar groups such as NEC UK and attend Parents Advisory Meetings run by the National Perinatal Epidemiology Unit where we review recent research into conditions that cause SBS-IF
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Living with SBS-IF is a constant round of pain and discomfort, tiredness and lethargy from disturbed sleep affects not only the child but the whole family. For parents and carers there is the constant worry about the risk of line infection, sepsis and the prospect of liver failure. A simple illness with a raised temperature can induce fear and panic in the parents of a baby or young child – to say nothing of the fear of failed or lost line sites and for which bowel transplant becomes the only option for survival at present. Parents often spend long hours in hospital wating rooms for appointments with doctors and clinicians to have measurements taken and blood work done to check if the child is healthy or the PN prescription needs to be altered. Many drugs are prescribed to help alleviate the effects of the condition and the PN. At these meetings parents often say they feel stressed and sometimes feel frustrated and inadequate.

	Parents and carers get up 5 or 6 times in the night and have to strip off the child and bathe them due to the burning effects of the diarrhoea on the skin. School age children are often tired due to disturbed sleep and find it difficult to concentrate in lessons. The day to day lives of parents are also affected by the loss of sleep and anxiety which affects their ability to cope with in the workplace or the everyday duties of housework and laundry. They are very limited to the kind of activities they are able to participate in outside of the home especially in the evening when they must administer PN which requires they are at home with the child ready to ensure a safe sterile procedure in order to, avoid infection. PN can be anything up to 12 hours a night and 7 nights a week. It is almost impossible to get people to babysit a child on PN due to the complexity of the equipment and the needs of the child. Parents find it difficult to explain their child condition to others as people in general have little or no idea where the small bowel is or what it does or how vital it is for survival.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Most parents are initially horrified at the thought of having to administer PN at home by themselves. They think there is no way they will remember everything they need to do! By the time the child is ready to go home they will have had lots of training but its still a scary prospect. Parents are generally grateful for PN to keep their child alive and hopefully thriving. They still have a lot to cope with, machines that malfunction and beep madly in the night, worry about air in the line and the line becoming dislodged or tugged out. The amount of equipment needed for the procedure makes storage onerous. Space must be found for an extra fridge to keep the PN away from other foodstuffs. Deliveries of PN and equipment have to be ordered and managed. Delivery is something of a post code lottery according to some parents. Recently parents have experienced difficulties with the production and deliveries of PN.
8. Is there an unmet need for patients with this condition?	Procedure for dealing with SBS-IF seems to differ from one hospital to another. There are many causes of SBS-IF that require different skills and techniques. Surgeons and gastroenterologists have differing opinions about how best to treat the condition and parents often get caught up and confused by this. PN is part of standard ‘treatment’ by the NHS for SBS-IF, however it only alleviates the condition and its effects, it does not actually change the malfunction in the bowel.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The parents of two of the babies taking part in the recent trials for this technology are members of Short Bowel Survivors and Friends. They say they are happy and wish to continue with this 'Technology' both parents report that their child has gained weight. The mother of baby 'C' who is now 2 years old has commented that not only has it reduced the number of nights on PN but also reduced diarrhoea and vomiting and it has given me more freedom to spend time with my other child." The mother of baby 'G' also 2-year-old says "it has given him the quality of life that a 2-year-old deserves. He is down to 4 nights TPN a week. He has just had life changing bowel surgery and the drug was stopped. The difference without it is upsetting! His output is through the roof, 15 nappy changes instead 3 – 4 when he is on it. The results speak for themselves. I believe he needs this 'medicine' for him to have a normal functioning life" (It also had allowed her to go back to work).
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	For some parents the thought of injecting their child is difficult. As a grandparent I know that this technology is not suitable for every child. My granddaughter for example has a rogue Chromosome in her bone marrow which could be adversely affected. I understand that tumours could also be a problem

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	I think children less than 50% of their residual bowel could benefit and maybe those with 'ultra' short bowel could benefit following bowel lengthening surgery. Those with other conditions that pose a threat like chromosomal difficulties and incidence of tumours would I suggest be unlikely to benefit.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Should this technology be made available on the NHS it should be available to all for once it can be medically determined that they can benefit from it - regardless of their ethnicity, colour or creed or ability to pay.

Other issues	
Recent trials and those from the past appear to show that this technology works and is used in many other countries	Recent trials and those from the past appear to show that this technology works and is used in many other countries

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- SBS-IF is a life limiting condition which affects the whole family's ability to function normally
- PN is an alternative way to feed those who cannot absorb sufficient nutrition independently
- There is constant worry for the family about sepsis, liver failure, loss of line sites resulting in the need for bowel transplant
- PN as part of NHS Standard Care alleviates the difficulties, it does nothing to change the malfunctioning bowel
- Evidence from recent trials and those from the past appear to show that this technology works in treating SBS-IF

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

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Teduglutide for treating short bowel syndrome [ID3937]

Produced by Aberdeen HTA Group

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Declared competing interests of the authors

No competing interests to disclose.

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Rider on responsibility for report

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

This report should be referenced as follows:

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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.

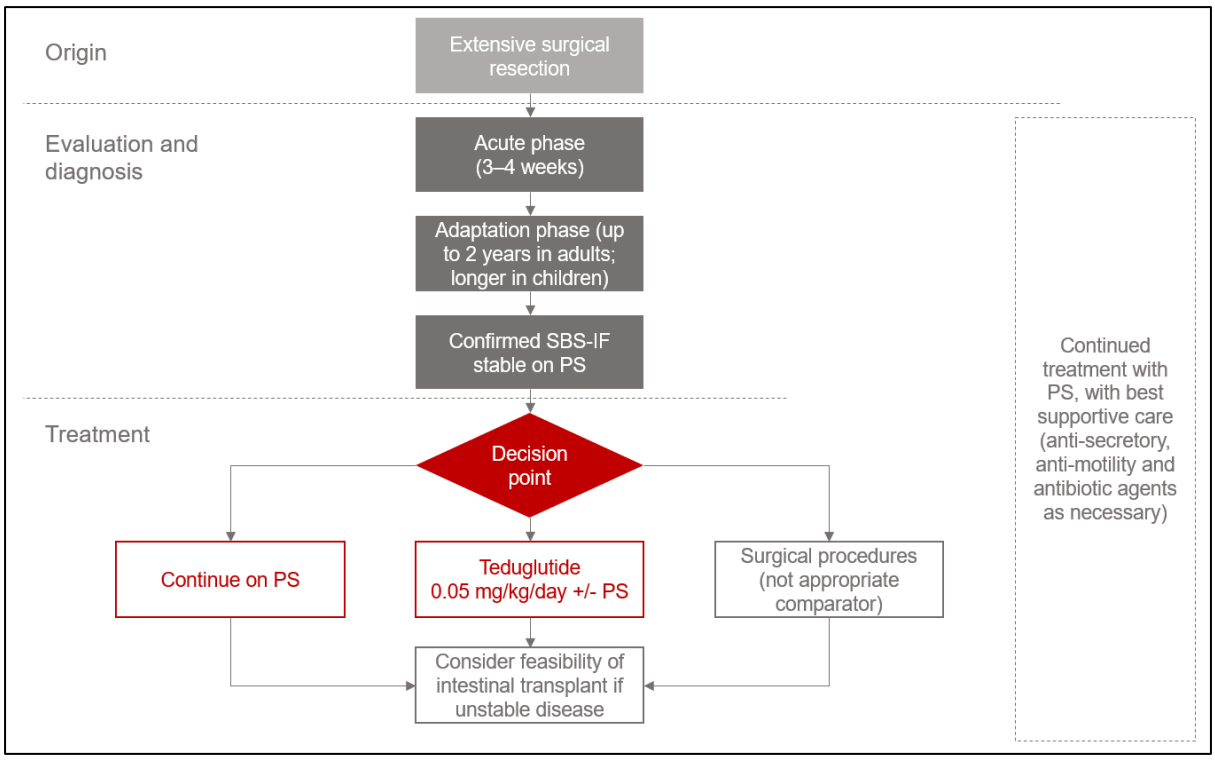


Figure 1 Company's proposed treatment pathway and positioning of teduglutide for adults and children with SBS-IF [reproduced from Document B, Figure 4 of the CS]

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.

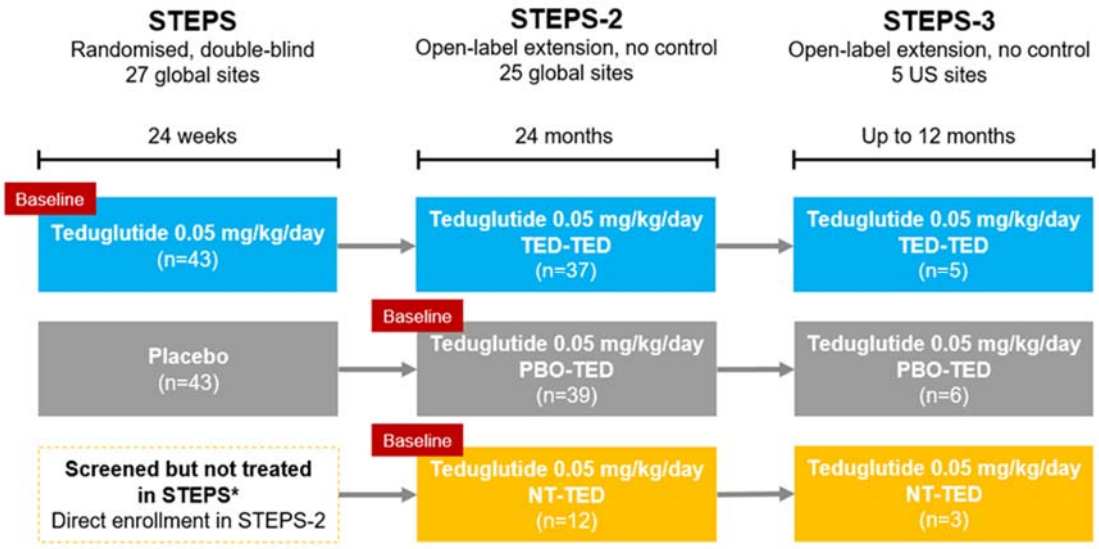
Methodology of the RCTs included in the CS and their extension studies

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)**		**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		NR	NR	NR	NR	1 (5.5)	NR	NR	NR
Gastric cancer	1 (2.3)	NR	NR	NR		NR	NR	NR	NR	NR	NR	NR	NR
Other	12 (27.9)	7 (16.3)	3 (8.6)	3 (18.8)		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		NR	NR	NR	2 (7.4)	3 (16.7)	NR	NR	NR
Patients with stoma, n (%)	21 (48.8)	17 (39.5)	NR	NR		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]		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]		NR	NR		3 (50.0)	6 (60.0)	NR	NR	0
Colostomy	4 (19.0)	1 (5.9)	NR	NR		2 (UC)[g]	NR	2 (13.3)	0	1 (10.0)	NR	NR	1 (33.3)
Descendostomy	0	0	NR	NR		NR	NR	0	1 (16.7)	0	NR	NR	0
Other (duodenostomy; jejunostomy + ileostomy)	0 (0)	2 (11.8)	NR	NR		NR	NR	0	1 (16.7)	0	NR	NR	0
End stoma, n (%)	21/42 (50.0)	NR	NR	NR		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)		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)		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		54	18	31	27	18	14	4	6
Mean (SD)	84.4 (64.6)	68.7 (63.9)	58 (44)	77 (53)		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		NR	NR	NR	NR	NR	NR	NR	NR
Average % (SD)	55.6 (20.8)	NR	NR	NR		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)		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)‡	1,531 (874)		2,295 (344)	NR	NR	NR	NR	NR	NR	NR
Weekly PS volume at baseline, L (SD)	12.6 (7.4)	NR	NR	NR		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/k g/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)ǂ	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

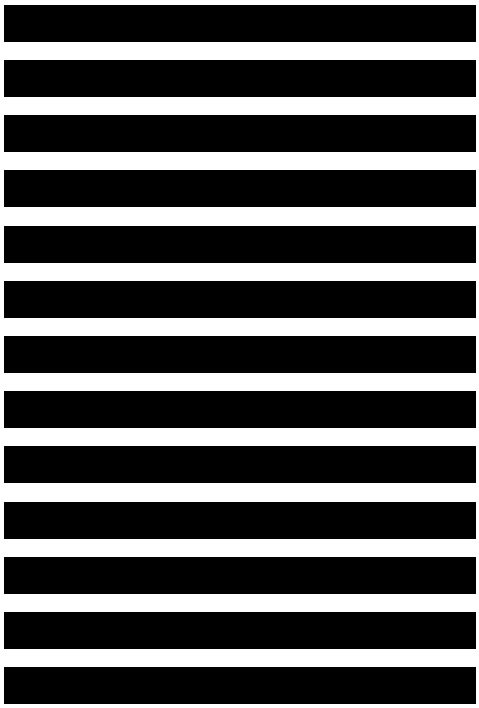
Clinical trials data

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.

7 References

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

2. Buchman AL, Scolapio J, Fryer J. AGA technical review on short bowel syndrome and intestinal transplantation. Gastroenterology. 2003;**124**(4):1111-34.

3. Pironi L, Hébuterne X, Van Gossum A, Messing B, Lyszkowska M, Colomb V, et al. Candidates for intestinal transplantation: a multicenter survey in Europe. Am J Gastroenterol. 2006;**101**(7):1633-43; quiz 79.

4. Bakker H, Bozzetti F, Staun M, Leon-Sanz M, Hebuterne X, Pertkiewicz M, et al. Home parenteral nutrition in adults: a European multicentre survey in 1997. ESPEN-Home Artificial Nutrition Working Group. Clin Nutr. 1999;**18**(3):135-40.

5. Goulet O, Ruemmele F. Causes and management of intestinal failure in children. Gastroenterology. 2006;**130**(2 Suppl 1):S16-28.

6. Squires RH, Duggan C, Teitelbaum DH, Wales PW, Balint J, Venick R, et al. Natural history of pediatric intestinal failure: initial report from the Pediatric Intestinal Failure Consortium. J Pediatr. 2012;**161**(4):723-8.e2.

7. Weale AR, Edwards AG, Bailey M, Lear PA. Intestinal adaptation after massive intestinal resection. Postgrad Med J. 2005;**81**(953):178-84.

8. Tappenden KA. Intestinal adaptation following resection. Journal of Parenteral and Enteral Nutrition. 2014;**38**(1S):23S-31S.

9. Jeppesen P, Pertkiewicz M, Messing B, Iyer K, Seidner D, O'Keefe S, et al. Teduglutide reduces need for parenteral support among patients with short bowel syndrome with intestinal failure. Gastroenterology. 2012;**143**(6):1473-81.

10. Carroll RE, Benedetti E, Schowalter JP, Buchman AL. Management and Complications of Short Bowel Syndrome: an Updated Review. Curr Gastroenterol Rep. 2016;**18**(7):40.

11. Iyer KR, Kunecki M, Boullata JI, Fujioka K, Joly F, Gabe S, et al. Independence From Parenteral Nutrition and Intravenous Fluid Support During Treatment With Teduglutide Among Patients With Intestinal Failure Associated With Short Bowel Syndrome. JPEN J Parenter Enteral Nutr. 2017;**41**(6):946-51.

12. Huisman-de Waal G, Schoonhoven L, Jansen J, Wanten G, van Achterberg T. The impact of home parenteral nutrition on daily life-a review. Clin Nutr. 2007;**26**(3):275-88.

13. Winkler MF, Hagan E, Wetle T, Smith C, Maillet JO, Touger-Decker R. An exploration of quality of life and the experience of living with home parenteral nutrition. JPEN J Parenter Enteral Nutr. 2010;**34**(4):395-407.

14. Winkler MF, Smith CE. Clinical, social, and economic impacts of home parenteral nutrition dependence in short bowel syndrome. JPEN J Parenter Enteral Nutr. 2014;**38**(1 Suppl):32s-7s.

15. Seidner DL, Schwartz LK, Winkler MF, Jeejeebhoy K, Boullata JI, Tappenden KA. Increased intestinal absorption in the era of teduglutide and its impact on management strategies in patients with short bowel syndrome-associated intestinal failure. JPEN J Parenter Enteral Nutr. 2013;**37**(2):201-11.

16. Buchman AL. Etiology and initial management of short bowel syndrome. Gastroenterology. 2006;**130**(2 Suppl 1):S5-s15.

17. Kim ES, Keam SJ. Teduglutide: A Review in Short Bowel Syndrome. Drugs. 2017;**77**(3):345-52.

18. McMellen ME, Wakeman D, Longshore SW, McDuffie LA, Warner BW. Growth factors: possible roles for clinical management of the short bowel syndrome. Semin Pediatr Surg. 2010;**19**(1):35-43.

19. McKeage K. Teduglutide: a guide to its use in short bowel syndrome. Clin Drug Investig. 2015;**35**(5):335-40.

20. European Medicines Agency. Revestive 1.25mg powder and solvent for solution for injection. Summary of Product Characteristics. Amsterdam: European Medicines Agency; 2017. Available from: https://www.ema.europa.eu/en/documents/product-information/revestive-epar-product-information_en.pdf.

21. Centre for Reviews and Dissemination. Systematic reviews: CRD's guidance for undertaking systematic reviews in health care. University of York: 2009. Available from: URL: http://www.york.ac.uk/inst/crd/SysRev/!SSL!/WebHelp/SysRev3.htm.

22. Jeppesen PB, Gilroy R, Pertkiewicz M, Allard JP, Messing B, O'Keefe SJ. Randomised placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome. Gut. 2011;**60**(7):902-14.

23. Schwartz LK, O'Keefe SJ, Fujioka K, Gabe SM, Lamprecht G, Pape UF, et al. Long-Term Teduglutide for the Treatment of Patients With Intestinal Failure Associated With Short Bowel Syndrome. Clin Transl Gastroenterol. 2016;**7**(2):e142.

24. Seidner DL, Fujioka K, Boullata JI, Iyer K, Lee HM, Ziegler TR. Reduction of Parenteral Nutrition and Hydration Support and Safety With Long-Term Teduglutide Treatment in Patients With Short Bowel Syndrome-Associated Intestinal Failure: STEPS-3 Study. Nutr Clin Pract. 2018;**33**(4):520-7.

25. O'Keefe SJ, Jeppesen PB, Gilroy R, Pertkiewicz M, Allard JP, Messing B. Safety and efficacy of teduglutide after 52 weeks of treatment in patients with short bowel intestinal failure. Clin Gastroenterol Hepatol. 2013;**11**(7):815-23.e1-3.

26. Zest. REVESTIVE atHOME Program Blueprint. Sydney, Australia: Zest; 2019.

27. Carter BA, Cohran VC, Cole CR, Corkins MR, Dimmitt RA, Duggan C, et al. Outcomes from a 12-Week, Open-Label, Multicenter Clinical Trial of Teduglutide in Pediatric Short Bowel Syndrome. J Pediatr. 2017;**181**:102-11.e5.

28. Kocoshis SA, Merritt RJ, Hill S, Protheroe S, Carter BA, Horslen S, et al. Safety and Efficacy of Teduglutide in Pediatric Patients With Intestinal Failure due to Short Bowel Syndrome: A 24-Week, Phase III Study. JPEN J Parenter Enteral Nutr. 2020;**44**(4):621-31.

29. Carter B, Hill S, Horslen S, Kocoshis S, Yoon M, Grimm A. Long-term retrospective follow-up of pediatric patients with short bowel syndrome–associated intestinal failure (SBS-IF) who completed 12 weeks of treatment in TEC-C13-003 [Poster presentation]. NASPGHAN/CPNP/APGNN Annual Meeting, Chicago, IL; 17-19 October: 2019. p. 76.

30. Mercer D, Carter B, Hill S, Horslen S, Kaufman S, Kocoshis S, et al. A prospective, open-label, long-term safety and efficacy study of teduglutide in pediatric patients with short bowel syndrome–associated intestinal failure: 6-month interim analysis (SHP633-304) [Poster presentation]. NASPGHAN/CPNP/APGNN Annual Meeting, Chicago, IL; 17-19 October: 2019. p. 77.

31. Seidner DL, Gabe SM, Lee HM, Olivier C, Jeppesen PB. Enteral Autonomy and Days Off Parenteral Support With Teduglutide Treatment for Short Bowel Syndrome in the STEPS Trials. JPEN J Parenter Enteral Nutr. 2020;**44**(4):697-702.

32. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health. 1998;**52**(6):377-84.

33. Ramos Boluda E, Redecillas Ferreiro S, Manrique Moral O, García Romero R, Irastorza Terradillos I, Nuñez Ramos R, et al. Experience With Teduglutide in Pediatric Short Bowel Syndrome: First Real-life Data. J Pediatr Gastroenterol Nutr. 2020;**71**(6):734-9.

34. Lam K, Schwartz L, Batisti J, Iyer KR. Single-Center Experience with the Use of Teduglutide in Adult Patients with Short Bowel Syndrome. JPEN J Parenter Enteral Nutr. 2018;**42**(1):225-30.

35. Ukleja A, To C, Alvarez A, Lara LF. Long-Term Therapy With Teduglutide in Parenteral Support-Dependent Patients With Short Bowel Syndrome: A Case Series. JPEN J Parenter Enteral Nutr. 2018;**42**(4):821-5.

36. Schoeler M, Klag T, Wendler J, Bernhard S, Adolph M, Kirschniak A, et al. GLP-2 analog teduglutide significantly reduces need for parenteral nutrition and stool frequency in a real-life setting. Therap Adv Gastroenterol. 2018;**11**:1756284818793343.

37. Joly F, Seguy D, Nuzzo A, Chambrier C, Beau P, Poullenot F, et al. Six-month outcomes of teduglutide treatment in adult patients with short bowel syndrome with chronic intestinal failure: A real-world French observational cohort study. Clin Nutr. 2020;**39**(9):2856-62.

38. NPS Pharmaceuticals I. A 24-Week Study of the Efficacy and Safety of Teduglutide in Subjects with Parenteral Nutrition-Dependent Short Bowel Syndrome A randomized, double-blind, placebo-controlled, parallel-group study [data on file]. Bedminster, NJ: NPS Pharmaceuticals, Inc.; 2011.

39. NPS Pharmaceuticals I. A Study of the Efficacy and Safety of Teduglutide in Subjects with Parenteral Nutrition-Dependent Short Bowel Syndrome [Data on file]. Bedminster, NJ: NPS Pharmaceuticals, Inc.,; 2013.

40. NPS Pharmaceuticals I. A Long-term, Open-label Study with Teduglutide for Subjects with Parenteral Nutrition Dependent Short Bowel Syndrome: Final Report [Data on file]. Bedminster, NJ: NPS Pharmaceuticals, Inc.; 2013.

41. Puello F, Wall E, Herlitz J, Lozano ES, Semrad C, Micic D. Long-Term Outcomes With Teduglutide From a Single Center. JPEN J Parenter Enteral Nutr. 2021;**45**(2):318-22.

42. Martin A, Boehm V, Zappa M, Billiauws L, Bonvalet F, Nuzzo A, et al. Imaging as predictor of clinical response to teduglutide in adult patients with short bowel syndrome with chronic intestinal failure. Am J Clin Nutr. 2021;**113**(5):1343-50.

43. Pevny S, Maasberg S, Rieger A, Karber M, Blüthner E, Knappe-Drzikova B, et al. Experience with teduglutide treatment for short bowel syndrome in clinical practice. Clin Nutr. 2019;**38**(4):1745-55.

44. Tamara P, Alicia H. Teduglutide in adult patients with short bowel syndrome. Eur J Clin Pharmacol. 2020;**22**(3):166-70.

45. Jeppesen PB. Expert testimony on the unexpectedly high placebo rate in the pivotal 020/STEPS Study in relation to intestinal adaptation and baseline demographics of placebo/SOC arm [Data on file]. Copenhagen, Denmark; 2018.

46. Jeppesen PB, Gabe SM, Seidner DL, Lee HM, Olivier C. Factors Associated With Response to Teduglutide in Patients With Short-Bowel Syndrome and Intestinal Failure. Gastroenterology. 2018;**154**(4):874-85.

47. Turner RB. Epidemiology, pathogenesis, and treatment of the common cold. Ann Allergy Asthma Immunol. 1997;**78**(6):531-9.

48. ICON Clinical Outcomes Assessments. Impacts on Carers of Patients with Short Bowel Syndrome-associated Intestinal Failure Receiving Parenteral Support - Study Report [data on file]. Dublin: ICON Clinical Outcomes Assessments; 2017.

49. National Institute for Health and Care Excellence. Position statement on use of the EQ-5D-5L value set for England (updated October 2019) 2019. Available from: https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/technology-appraisal-guidance/eq-5d-5l (Accessed 15 October 2021).

50. Ballinger R, Macey J, Lloyd A, Brazier J, Ablett J, Burden S, et al. Measurement of Utilities Associated with Parenteral Support Requirement in Patients with Short Bowel Syndrome and Intestinal Failure. Clin Ther. 2018;**40**(11):1878-93.e1.

51. Tadeka UK Ltd. Teduglutide NICE submission ad board [data on file]. London: Tadeka; 2021.

52. British Intestinal Failure Alliance. British Intestinal Failure Alliance (BIFA) Position Statement 2016 Home Parenteral Nutrition (HPN) 2016. Available from: https://www.bapen.org.uk/images/pdfs/news/bifa-position-statement-about-hpn.pdf (Accessed 15 October 2021).

53. Salazar E, Clermont-Dejean NM, Schwenger KJP, Noelting J, Lu Z, Lou W, et al. Patients With Severe Gastrointestinal Dysmotility Disorders Receiving Home Parenteral Nutrition Have Similar Survival As Those With Short-Bowel Syndrome: A Prospective Cohort Study. JPEN J Parenter Enteral Nutr. 2021;**45**(3):530-7.

54. Shire Pharmaceuticals Ltd. Database analysis to investigate potential links between parenteral nutrition volume/frequency with catheter line infections. London: Shire Pharmaceuticals Ltd; 2016.

55. British Intestinal Failure Alliance. British Intestinal Failure Alliance (BIFA) Position Statement Use of peptide growth factors for adult patients with intestinal failure 2018. Available from: https://www.bapen.org.uk/pdfs/bifa/position-statements/use-of-peptide-growth-factors-for-adult-patients-with-intestinal-failure.pdf (Accessed 15 October 2021).

56. Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol. 2012;**12**:9.

57. BresMed Health Solutions Ltd, Neves C, van Keep M. P15133 Teduglutide – Modified Delphi Panel Report [data on file]. Sheffield, UK: BresMed; 2016.

58. Cavicchi M, Beau P, Crenn P, Degott C, Messing B. Prevalence of liver disease and contributing factors in patients receiving home parenteral nutrition for permanent intestinal failure. Ann Intern Med. 2000;**132**(7):525-32.

59. Pape UF, Iyer KR, Jeppesen PB, Kunecki M, Pironi L, Schneider SM, et al. Teduglutide for the treatment of adults with intestinal failure associated with short bowel syndrome: pooled safety data from four clinical trials. Therap Adv Gastroenterol. 2020;**13**:1756284820905766.

60. Sowerbutts AM, Burden S, Griffiths J, Abraham A, Farrer K, Leahy G, et al. Glucagon-like peptide 2 analogues in the treatment of intestinal failure: A qualitative exploration of the views of patients and their families in decision making. Clin Nutr ESPEN. 2021;**44**:263-9.

61. Wilburn J, McKenna SP, Heaney A, Rouse M, Taylor M, Culkin A, et al. Development and validation of the Parenteral Nutrition Impact Questionnaire (PNIQ), a patient-centric outcome measure for Home Parenteral Nutrition. Clin Nutr. 2018;**37**(3):978-83.

62. Burden ST, Jones DJ, Gittins M, Ablett J, Taylor M, Mountford C, et al. Needs-based quality of life in adults dependent on home parenteral nutrition. Clin Nutr. 2019;**38**(3):1433-8.

63. European Medicines Agency. Revestive EPAR summary for the public. Amsterdam: European Medicines Agency; 2017. Available from: https://www.ema.europa.eu/en/documents/overview/revestive-epar-summary-public_en.pdf.

64. Berghöfer P, Fragkos KC, Baxter JP, Forbes A, Joly F, Heinze H, et al. Development and validation of the disease-specific Short Bowel Syndrome-Quality of Life (SBS-QoL™) scale. Clin Nutr. 2013;**32**(5):789-96.

65. Lloyd A, Kerr C, Breheny K, Brazier J, Ortiz A, Borg E. Economic evaluation in short bowel syndrome (SBS): an algorithm to estimate utility scores for a patient-reported SBS-specific quality of life scale (SBS-QoL™). Qual Life Res. 2014;**23**(2):449-58.

66. Howard L. Home parenteral nutrition: survival, cost, and quality of life. Gastroenterology. 2006;**130**(2 Suppl 1):S52-9.

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

68. Raghu VK, Binion DG, Smith KJ. Cost-effectiveness of teduglutide in adult patients with short bowel syndrome: Markov modeling using traditional cost-effectiveness criteria. Am J Clin Nutr. 2020;**111**(1):141-8.

69. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013 Process and methods [PMG9]: 5.3 Measuring and valuing health effects 2013. Available from: https://www.nice.org.uk/process/pmg9/chapter/the-reference-case#measuring-and-valuing-health-effects (Accessed 15 October 2021).

70. Decision Support Unit. NICE DSU technical support document 11: alternatives to EQ-5D for generating health state utility values. Sheffield: University of Sheffield; 2011. Available from: http://nicedsu.org.uk/wp-content/uploads/2016/03/TSD11-Alternatives-to-EQ-5D_final.pdf.

71. Jeppesen PB, Chen K, Murphy R, Shahraz S, Goodwin B. Impact on caregivers of adult patients receiving parenteral support for short-bowel syndrome with intestinal failure: A multinational, cross-sectional survey. JPEN J Parenter Enteral Nutr. 2021.

72. ICON Clinical Outcomes Assessments. Short Bowel Syndrome (SBS) Multi-national Survey [data on file]. Dublin: ICON Clinical Outcomes Assessments; 2020.

73. Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. Catalogue of EQ-5D scores for the United Kingdom. Med Decis Making. 2011;**31**(6):800-4.

74. Wyld M, Morton RL, Hayen A, Howard K, Webster AC. A systematic review and meta-analysis of utility-based quality of life in chronic kidney disease treatments. PLoS Med. 2012;**9**(9):e1001307.

75. National Institute for Health and Care Excellence. Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy: TA352 2015. Available from: http://www.nice.org.uk/guidance/TA352. (Accessed September 2021).

76. Bermingham SL, Ashe JF. Systematic review of the impact of urinary tract infections on health-related quality of life. BJU Int. 2012;**110**(11 Pt C):E830-6.

77. Brown RE, Hutton J, Burrell A. Cost effectiveness of treatment options in advanced breast cancer in the UK. Pharmacoeconomics. 2001;**19**(11):1091-102.

78. Beusterien KM, Szabo SM, Kotapati S, Mukherjee J, Hoos A, Hersey P, et al. Societal preference values for advanced melanoma health states in the United Kingdom and Australia. Br J Cancer. 2009;**101**(3):387-9.

79. Decision Support Unit. NICE DSU technical support document 12: the use of health state utility values in decision models Sheffield: University of Sheffield; 2011. Available from: http://nicedsu.org.uk/wp-content/uploads/2016/03/TSD12-Utilities-in-modelling-FINAL.pdf.

80. Royal College of Paediatrics and Child Health. UK-WHO growth charts - 2-18 years 2013. Available from: https://www.rcpch.ac.uk/resources/uk-who-growth-charts-2-18-years (Accessed 18 October 2021).

81. PAREXEL Access Consulting. Parexel SBS costing study for adults: final report [data on file]. Newton, MA: PAREXEL Access Consulting; 2017.

82. National Institute for Health and Care Excellence. Scenario: Management of acute renal or ureteric colic 2020. Available from: https://cks.nice.org.uk/topics/renal-or-ureteric-colic-acute/management/management/ (Accessed 5 October 2021).

83. Tappenden P, Chilcott JB. Avoiding and identifying errors and other threats to the credibility of health economic models. Pharmacoeconomics. 2014;**32**(10):967-79.

84. NHS England. National Cost Collection for the NHS 2019/20. Available from: https://www.england.nhs.uk/national-cost-collection/ (Accessed 19 October 2021).

85. Kind P, Hardman G, Macran S. UK population norms for EQ-5D. CHE Discussion Paper 172. York: Centre for Health Economics; 1999.

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Teduglutide for treating short bowel syndrome [ID3937]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 2 November 2021** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Clinical effectiveness issues

Issue 1 Primary endpoint in 004

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page xiv: The ERG report states 'Data from STEPS and 004 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)…'. This was not the definition of the primary endpoint in 004	Change to: '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)…'	The primary endpoint of 004 was not clinical response defined as a ⩾20% reduction in parenteral support volume at week 20, maintained to week 24 but a graded response score which took into account both the magnitude and durability of PS volume reduction.	Change accepted

Issue 2 Days per week of PS reduction in 004

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page xv: The ERG report states 'Data from STEPS and 004 showed that…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'. This comparison was not significant in 004, only in STEPS	Change to: 'Data from STEPS and 004 showed that… 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''	This comparison was significant in STEPS but not in 004	Change accepted

Issue 3 Summary of the ERG's approach to modelling SoC transitions

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page xvi: It is noted that '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 trial'. However, their approach is actually to hold the 6 month health state for the remainder of the model horizon, not remainder of the trial	Change to: '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'	Provides clarity with regards the alternative approach which the ERG has explored	Change accepted

Issue 4 Patient numbers in C13

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 12: number of patients receiving 0.0125 mg/kg/day in C13 is listed as n=12, when this study arm included n=8 patients	Change n=12 to n=8 (in-line with what is correctly reported in ERG report Table 6)	Factual error that should be corrected for accuracy	Change accepted

Issue 5 Description of PS weaning in C13 and C14

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 12: C13 and C14 are described as having 'PS weaning	Refer to 'PS weaning guidance' instead of 'PS weaning protocols' when referring to these	In C13 and C14, the investigators were provided with weaning	We have amended text as follows

protocols' when in fact investigators were only provided with weaning guidance	studies (this is correctly described in other sections of the ERG report, e.g. C14 is described as having 'no strict weaning algorithm' on page 46).	guidance, but the decision to wean at study visits was ultimately at the investigator's and patient's discretion. A correction for clarity, but relevant given that the weaning protocols in STEPS and 004 were full protocols and therefore it is important to distinguish the guidance provided to investigators in C13/C14 with the protocolised weaning in place in STEPS/004	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/m2. 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

Issue 6 Number of study sites in STEPS-3

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 16: STEPS-3 is listed as taking place across 15 sites in the US, but only took place across 5 sites (all in US)	Change 15 to 5 (as correctly reported in Figure 2)	Factual error that should be corrected for accuracy	Change accepted

Issue 7 Inclusion of real-world studies in meta-analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 16 and 19: Joly 2020 and Tamara 2020 are listed as 'No' in the column 'Used in the meta-analysis'; both studies were included in the meta-analysis	Change both Joly 2020 and Tamara 2020 to 'Yes' in the column 'Used in the meta-analysis'	Factual error that should be corrected for accuracy; we want to be clear that our meta-analysis used all sources of published real-world evidence.	Change accepted

Issue 8 Mislabelling of study TED-C14-006 (C14)

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 21: the table lists TED-C14-004 as a study that we present efficacy and safety results for, but this is not correct. The study in question is TED-C14-006	Change TED-C14-004 to TED-C14-006	Factual error that should be corrected for accuracy and clarity. This is important because TED-C14-004 is another study (in Japanese patients) that we have not covered in our dossier	Change accepted

Issue 9 Inclusion of paediatric studies in meta-analysis

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 21 and 22: TED-C13-003 (C13), SHP633-303, TED-C14-004 (a typo, should read TED-C14-006; C14) and SHP633-304 are all listed as 'Yes' in the column 'Used in the meta-analysis' but they were not included in the meta-analysis	Change these four entries to 'No' in the column 'Used in the meta-analysis'	Factual error that should be corrected for accuracy and clarity. Whilst we do present pooled safety analysis for these studies, they were not included in out meta-analysis.	Change accepted

Issue 10 Table 7 in ERG report and Table 15 in company dossier

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 27, footnote g: The ERG highlights a difference between the proportion of the STEPS TED arm reported as having 'Other' reasons for resection in Table 10 and Table 15 of our dossier, implying that this may be a discrepancy but it is not	Delete footnote g	To clarify why there is this discrepancy: in Table 15 of our submission, we reduced the number of 'reasons of resection' to save space. One patient in STEPS had 'cancer' as a reason listed in Table 10, this patient was moved to the category 'Other' in Table 15 (cancer was not included as an individual category in Table 15). This explains why the number of patients with 'Other' reasons of resection increases from Table 10 to Table 15	Thank you for clarifying that point. We have removed this footnote

Issue 11 Proportion of patients gaining PS independence in Ramos Boluda 2020

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 30: 87% (13/15) are listed as having gained independence in Ramos Boluda 2020 (real world study in children with SBS). This 87% (13/15) refers to patients who achieved a ≥20% reduction in PS by week 24; whilst 44% (n=7/16) gained PS independence at 24 weeks	Change 'In the real-world study, 87% (13/15) of patients achieved PS independence, and 44% (n=7/16) at 24 weeks' To: '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'	Factual error that should be corrected for accuracy	Change accepted

Issue 12 Proportion of patients gaining PS independence in C13

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 31: the ERG report states that 'None achieved PS independence' in a sentence following description of study C13. This is not the case, 3/15 patients (20%) achieved independence by week 12 (as stated in the previous sentence)	Delete the sentence	Factual error that should be corrected for accuracy	Change accepted

Issue 13 Patient deaths in SHP633-304 (clarification point)

Description of problem	Description of proposed amendment	Justification for amendment
Page 31 and 33: the ERG correctly point out that the CSR reports two deaths unrelated to treatment in SHP633-304, when we only state one in Table 21 of our submission. In the adverse reactions section of our dossier, we reported data only from the pooled analysis of all studies (Pape 2020). The data cut-off for inclusion in the pooled analysis was July 2018, and at the time, SHP633-304 was ongoing. The second patient died in December 2019. The ERG are right to point out this discrepancy	None	None

Issue 14 Comparison of discontinuation rates in STEPS/STEPS-2/004/005 and placebo

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 32: the ERG state that 'more teduglutide patients experienced adverse events leading to treatment discontinuation (19.7% of the STEPS/STEPS-2/004/005 teduglutide group, and 9.2% of the STEPS/004 teduglutide group versus 6.8% of the STEPS/004 placebo group)' This is a misleading statement. It is not appropriate to compare the percentage of patients who discontinued teduglutide in STEPS/STEPS-2/004/005 (19.7%) to placebo in STEPS/004 (6.8%) as the former group were treated for longer (up to 30 months vs 24 weeks for the placebo group), and so had more opportunity to discontinue treatment. The comparison of 9.2% discontinuing teduglutide in STEPS/004 to 6.8% discontinuing placebo in STEPS/004 is appropriate as both are measured over 24 weeks. No statistical comparison is presented in Pape 2020, likely because there is no statistical difference between arms, so we do not believe it is	Replace with 'a similar proportion of treatment discontinuations were observed in the teduglutide and placebo groups in STEPS/004.'	Factual error that should be corrected for accuracy; it is not correct to say that more patients discontinue teduglutide compared to placebo	We have amended the two statements to include the length of time on treatment. We have also taken the opportunity to report the numbers of patients in the two teduglutide groups who received the licensed dose of 0.05 mg/kg/day and how many received the 0.10 mg/kg/day dose. "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

correct to say that 'more teduglutide patients experienced adverse events leading to discontinuation' The same issue is present of page 33 where the ERG states that 'adverse events leading to discontinuation occurred more frequently in teduglutide patients compared with placebo patients'			39 received 0.10 mg/kg/day) treated for up to 30 months were reported to experience adverse events leading to discontinuation." "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."

Issue 15 Percentage of serious AEs in paediatric studies

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 33: the ERG state that 'In children, 40.4% experienced a serious adverse event' however this should be reported as 77.5%. A severe adverse event (rather than serious) was experienced by 40.4% of children.	Change 40.4% to 77.5%	Factual error that should be corrected for accuracy	Change accepted

Cost effectiveness issues

Issue 16 Measurement of carer utilities

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 37: the ERG state 'Carer utilities are measured using the EQ-5D-5L instrument. These have been cross walked to provide EQ-5D-3L values.' Page 38: the ERG state 'Carer utilities are sourced from 47 UK caregivers of SBS-IF patients'. These statements are only partially correct. Our model uses two sources of carer utilities – one from a survey of 47 carers using the EQ-5D and one from a Delphi panel (as accurately described on page 62 of the report)	Change to 'Carer utilities were obtained from two sources. One source used the EQ-5D-5L, which was mapped to EQ-5D-3L, and the other source used direct elicitation from a Delphi panel of 9 clinical experts.' Change to 'Carer utilities are sourced from 47 UK caregivers of SBS-IF patients and from a Delphi panel of 9 clinical experts'	Factual error that should be corrected for clarity	Text within table 10, page 38 changed to: "*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."* "*Carer utilities are sourced from a study of 47 UK caregivers of SBS-IF patients[48] and a Delphi panel of 9 clinical experts."*

Issue 17 Description of teduglutide marketing authorisation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 40: the ERG state 'The population considered in the company submission is in line	Delete the following text: '…and receiving at least 3 days per week of	Factual error to be corrected for accuracy and clarity	Change accepted

with teduglutide's marketing authorisation, SBS-IF patients aged 1 year and above who are stable following a period of intestinal adaption after surgery and receiving at least 3 days per week of parenteral support (in line with the inclusion criteria of the STEPS trial)' This is potentially misleading as the marketing authorisation for teduglutide is not limited to patients receiving PS for 3 days per week	parenteral support (in line with the inclusion criteria of the STEPS trial)'		

Issue 18 Survival modelling

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page xviii: the ERG state '…the projected mortality rate drops below that of the general population whilst a substantial proportion of the cohort remains alive.' This statement implies that the model applies a mortality rate less than that of the general population. However, the model does ensure the rate does not drop below that of the general	Change to: 'the projected mortality rate in the model becomes equivalent to the general population mortality rate whilst a substantial proportion of the cohort remains alive'	Lack of clarity could cause misinterpretation of the application of mortality in the model.	This statement was not focussed on the modelling, but rather the face validity of the chosen curve for extrapolation. To avoid any confusion, we have modified the text as follows: "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

population.			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"

Issue 19 ERG preferred assumptions

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page xxii: The order of preferred assumptions 3 and 4 in Table 2 is not in line with the cumulative results.	Switch the text in the 'Preferred assumptions' and 'Section in ERG report' columns for issues 3 and 4 to align with the cumulative results. Also, in the list of preferred assumptions above Table 2, assumptions 3 and 4 should be switched to align with Table 2.	Factual error that should be corrected for accuracy and clarity as the cost, QALY and ICER results are aligned to the wrong scenarios.	Change accepted

Issue 20 Paediatric company base case results

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 73: the ERG state 'For the paediatric population, the company base case ICER is lower at £4,811 per QALY gained, due to a lower incremental cost	Amend to [redacted]	Factual error that should be corrected for accuracy.	Change accepted

[redacted], The number should be [redacted]			

Issue 21 PS costs

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 68: The ERG state 'The provision of PS bags which includes the bags themselves, delivery, nurse time, fragmin, ondansetron and taurolock is agreed through private contracts with trusts.' This is not correct and could cause confusion regarding how the costs should be applied in the model. The Home Parenteral Nutrition (HPN) framework contract lists ondansetron as a medication but notes that it is not within the band price. Fragmin is not listed. This should be clarified to ensure clarity in which cost inputs are confidential and will be amended in the confidential appendix.	Change to: 'The provision of PS bags, which includes the bags themselves, delivery, nurse time, and taurolocks is agreed through private contracts with trusts.'	Factual error that should be corrected for accuracy and clarity.	Accept change.

Issue 22 ERG additional analysis text

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 81: The ERG states '…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, lower health state utility values and lower carer utility values…' This should state higher health state utility values and higher carer utility values.	Change to: '…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…'	Factual error that should be corrected for accuracy and clarity.	Change accepted

Issue 23 ERG results text

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 84: The ERG states 'Teduglutide dominates standard of care…' in the ERG preferred base case for the paediatric population (table 25)' However, the ERG's preferred base case does not show dominance in the paediatric population; the preferred ICER is £5,797.	Change to: '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)'	Factual error that should be corrected for accuracy and clarity.	Change accepted, and footnotes removed from Table 25 and 26 as unnecessary.

Issue 24 ERG's sensitivity analyses

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 86: The ICERs in Table 26 are described in the table header as cumulative. However, the results reported are not.	The heading 'Cumulative ICER' in Table 26 should be replaced with 'ICER'	Factual error that should be corrected for accuracy and clarity.	Change accepted

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG response
Page 30, Table 9	Table 9 title and all contents are labelled AIC. Only the PSP data need to be AIC	Keep the PSP column as marked AIC, remove AIC marking on the title and all other columns	Change accepted
Page 64, paragraph 2	The sentence 'This survey reported an average EQ-5D-5L…' is not marked up, but contains confidential data	'This survey reported an average EQ-5D-5L value of [redacted]	Change accepted but note to company: the same value is not marked as AIC on page 122 of the company submission with revised mark-up, dated 060921.
Page 9, paragraph 4	The ERG state "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 (see Table XX below for	Table XX is not present in the ERG report, but if so, it should be marked AIC as the data are not published	Reference to table XX has been removed.

	information on baseline characteristics)”		

NICE National Institute for Health and Care Excellence

Technical engagement response form

Teduglutide for treating short bowel syndrome [ID3937]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

About you

Table 1 About you

Your name	Sarah Campbell-Hill
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Takeda UK Limited
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

Key issues for engagement

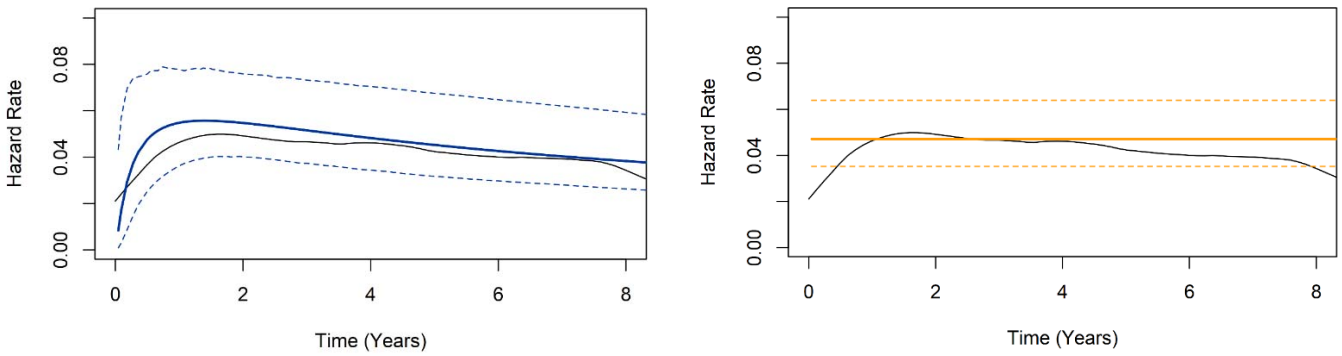
Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Modelling of health state transitions (and the placebo response in STEPS)	Yes	**Modelling of health state transitions/placebo effect** The ERG have identified uncertainty, particularly with regards the reductions in PS that patients could achieve with standard care in the real world. This uncertainty stems primarily from the observation of a treatment effect in the placebo arm of STEPS. Our model does not allow health state transitions for patients receiving standard care, and we are pleased to note that this is a position the ERG considers plausible (ERG report; page xvi). To briefly re-iterate, we argue that the treatment effect seen in the placebo arm of STEPS is not plausible in the real-world, and can instead be attributed to the PS weaning algorithm used in the study. The rationale for this is discussed in detail in Document B, B.2.6.1.4 (pages 51-53), but in summary [redacted].

		It should also be noted that patients in STEPS underwent 8 to 16 weeks of PS stabilisation and optimisation with the aim of ensuring 'that all patients received and tolerated a stable minimal level of PS before treatment'[1]. This process means that any reductions in PS observed in the placebo arm cannot be attributed to further optimisation of patients' care. It is reasonable to assume that patients with SBS-IF in England who are candidates for teduglutide would also be stabilised and optimised on PS prior to starting treatment. This is because a) teduglutide is indicated only in patients who are stable[2] and b) the NHS England Service Specification for Severe Intestinal Failure mandates that patients are managed by a multi-disciplinary team in specialist intestinal failure centres[3], so patients care (including PS) would be optimal to begin with. To explore the uncertainty around this placebo effect, the ERG have provided a scenario where the placebo effect observed in STEPS is applied to the standard care arm for the lifetime horizon of the model. The ERG state that this is likely overly conservative; we would argue it is not clinically plausible. This scenario requires that patients who are optimised and stabilised on PS by experts in specialist IF centres, spontaneously reduce their required PS volume by 21% (the average treatment effect observed in the placebo arm of STEPS) within 6 months and maintain this reduction for up to 50 years (adults) or 94 years (paediatrics), without any reversion to baseline. We would argue that even if spontaneous reductions in PS requirements are possible, such reductions could not be sustained over a patient's lifetime. This is because without improvement in intestinal absorption, reductions in PS (for patients who are optimised and stabilised on PS) are not healthy and would lead to dehydration, nutritional deficiency and weight loss. In STEPS, signs that patients who received placebo were becoming unhealthy were already evident at 6 months. Clinical experts suggest that in the intensified environment of a clinical trial or, very occasionally, when a patient exerts maximum effort, they may be able to reduce their PS from a stable baseline on standard care, but this requires inordinate effort, dedication and application on the part of the patient (not unlike trying to sustain drastic changes to one's oral diet) and it is only achievable short-term. In the context that spontaneous reductions in PS are only sustainable short-term, we have calculated (using a revised base case that is outlined below) that the placebo effect observed in STEPS would need to be sustained for almost 7 years in the standard care arm before our ICER exceeds the threshold of £30,000 per QALY (for adult patients; the paediatric base case is dominant including a placebo effect for 7 years. Full results in Appendix TE_4, page 31 of this document). As noted, spontaneous PS reductions of this duration are clinically not plausible. We would instead suggest a plausible upper bound for uncertainty is to

		assume a placebo effect in the standard care arm for 6 months, as observed in STEPS. Using our revised base case, the adult ICER for this scenario is £10,589 per QALY (teduglutide dominates in children). In sum, spontaneous reductions in PS for patients receiving standard care would be very rare in England: due to the exceptional standard of care that patients receive, they are optimised and stable on PS. Without improvements in intestinal absorption, reductions in PS for these patients would likely lead to malnutrition and dehydration (as evidenced in STEPS), and so the reduction would not be sustainable. It would therefore be implausible to model PS reductions for standard care over a lifetime horizon. We suggest that applying the placebo effect from STEPS to the standard care arm for 6 months represents a plausible upper bound of uncertainty. **Transition matrices and treatment stopping rule** On page 49 of the ERG's report, the ERG comment that "*It was not clear if the calculation of the transition matrices beyond 12 months accounted for the stopping rule applied in the model.*" In our submission, transition matrices were calculated based on all patients receiving teduglutide in STEPS-2 up to month 30 (see page 99 of Document B for further details). As such, patients who would be stopped by our stopping rule (discontinue treatment if no change in days per week of PS by month 12) continue to inform transition matrices beyond the 12 month point. We acknowledge that this is an oversight in our submission. Using data from patients *beyond the point they would have stopped treatment* creates an unrealistic estimation of treatment effectiveness beyond month 12. It is also inconsistent with our approach to treatment discontinuation: in our model, only patients who are not stopped by the stopping rule are allowed to inform discontinuation modelling after month 12 (Document B, section B.3.3.3, page 104 for more details). To address this, we have recalculated the transition matrices from month 12 to month 30, removing patients who would be stopped by the treatment stopping rule. These updated matrices can be seen in Appendix TE_1 (page 20 of this document). Notably, the health state occupancy predicted by the model aligns well with the observed health state occupancy from the STEPS/PSP data with these revised transitions (see Appendix TE_2, page 24 of this document).

		Our new base case ICERs are detailed more fully in the 'Summary of changes to the company's cost-effectiveness model', on page 14 of this document. Scenario analyses based on the revised base cases are available in Appendix TE_3, on page 25.
Health state utility by frequency of parenteral support	Yes	The ERG identified uncertainty in the utility benefit associated with a day per week reduction in PS. We agree with the ERG that patients and carers are best placed to comment on this uncertainty. In the patient testimonials submitted by PINNT as part of this appraisal (Technical Engagement Papers, pages 249–258), 23 patients and 2 caregivers outline the effect PS has on their life. The desire for an additional day free of PS could not be more clearly or emotively expressed across all 25 testimonials, regardless of the patients' number of days of PS per week. We note the ERG's position that using the vignette study introduces uncertainty, but are pleased that they agree it represents the only source of patient utility data which meets the test of face validity (showing a relationship between days per week of PS and patient quality of life). The ERG's concern is that that the vignette study potentially exaggerates the quality of life benefits of PS reductions. To explore this uncertainty, the ERG conducted analyses where the range in patient utility between 'PS independence' (PS0) and 'PS 7 days per week' (PS7) was reduced by 10% and 20%. We have further explored this using our revised base case. Our analyses show that the range in utility between PS0 and PS7 can be *reduced to zero* (that is, reduced by 100%) for adult patients, and our ICER is £26,559 per QALY; below the upper-bound cost-effectiveness threshold of £30,000 per QALY. For paediatric patients, even with 100% reduction in utility range, the ICER remains dominant (full results for adults and children in Appendix TE_4, page 31 of this document). We also note that the ERG consider there to be some uncertainty in the relationship between carer quality of life and days per week of PS. To further explore this, we analysed the impact of reducing the range in caregiver utility between high PS use (caregiver utilities were defined by high/medium/low/no PS use rather than PS7–PS0 as for patients) and PS independence. The caregiver utility range could also be reduced by 100% while still remaining below the £30,000 per QALY threshold (again, full results for adults and children in Appendix TE_4, page 31 of this document). Although we have provided both of these calculations for the purpose of exploring uncertainty, we are keen to emphasise that they are completely implausible. The utility gain for patients and carers when patients reduce a day of PS is definitively not zero. We have provided these calculations to illustrate that even with totally implausible scenarios for utilities, teduglutide remains cost-effective.

		In summary, patients and carers unanimously voice that a day reduction in PS is of huge benefit. However, to explore uncertainty around the magnitude of the utility gain associated with days off PS, we have provided scenarios where the utility gain is reduced to zero. These scenarios are implausible, however, they still return ICERs below the £30,000 per QALY cost-effectiveness threshold. For this reason, we are confident that the uncertainty around health state utilities is manageable.
Modelling of overall survival	Yes	The ERG argue that the log-normal curve we have used extrapolate survival data is not appropriate, as it predicts a hazard rate below general population mortality from year 24 of the model (patient age 74) onwards. They prefer the exponential extrapolation, where the hazard rate stays higher than general population mortality until year 31 (patient age 81). We argue that the benefit of making this correction is small (only 7 extra years before mortality reaches general population mortality), and not worth the change given the exponential extrapolation of adult survival is a poor fit overall to the underlying data. Figure 1 below illustrates the hazard functions described by the log-normal extrapolation (company-preferred) and the exponential (ERG-preferred) compared to the hazard function of the Salazar 2021 survival data[4]. The hazard function of Salazar 2021 survival data is not constant (black line in both figures). Our preferred log-normal extrapolation predicts a hazard rate that closely follows the observed rate from Salazar 2021. The ERG-preferred exponential extrapolation assumes a constant hazard rate, which as can be seen, is a poor fit to the shape of the data. **Figure 1 Hazard function predicted by log normal (blue, company-preferred) and exponential (orange, ERG-preferred) compared to Salazar 2021 (black)** 

		It is also worth noting that although the Akaike Information Criterion (AIC) statistics for the two models were almost identical (log-normal 334.62; exponential 334.48), the log-normal value is penalised more harshly by the *n* parameter term, as it is a two-parameter model, whereas the exponential is a simpler one-parameter model. This penalty is given to avoid over-fitting caused by more complex models. However, as can be clearly seen by the hazard plots, the exponential is actually underfitting (as it is overly simplistic), rather than the log-normal overfitting. The fact that the more complex log-normal model has equivalent AIC to the simpler exponential model is actually an indication that the log-normal is a closer fit to the data than the exponential model. We would also note that even using the ERG's preferred exponential extrapolation as a scenario to evaluate uncertainty around cost-effectiveness, the adult ICER is £12,918 per QALY (using our revised base case), comfortably below the £30,000 per QALY threshold.
Modelling of complications (Intestinal failure related liver disease and chronic kidney disease)	Yes	The ERG note that by not modelling a mortality risk for intestinal failure associated liver disease (IFALD) and chronic kidney disease (CKD), we introduce potential bias in our model. This bias may be in favour of teduglutide (by overestimating the costs and disutility of IFALD and CKD as patients do not die of them) or may favour standard care (by missing a survival benefit for teduglutide). We believe our approach is necessary and appropriate for two reasons: • Firstly, clinical feedback suggests that due to the exceptional standard of care in the UK, deaths due to IFALD and CKD in patients with SBS-IF are very rare. Aligned with this, the adult survival data we have used in our model (Salazar 2021) reported only 3 deaths (of 45 observed with 10 years of follow up; 6.7%) related to IFALD and none related to CKD. This is in-line with values reported elsewhere in the literature (albeit not exclusively in SBS-IF populations) for PS-related deaths: 2.9% to 8.8% deaths from IFALD, 0% deaths from CKD[4-7]. • Secondly, as the real-world data we use to inform mortality in our model (Salazar 2021 for adults, Pironi 2011 for children), already includes deaths from complications, separately modelling mortality for IFALD and CKD would introduce double counting and open us up to greater criticism. We would also note that while the direction of bias is difficult to determine, the magnitude of bias is small and therefore the uncertainty should be palatable. In a scenario where the risks of IFALD and CKD are not assumed to change with days per week of PS (implying no difference in incidence between the teduglutide and standard care arms, which effectively 'removes' IFALD/CKD from the model), the adult ICER is £13,943 per QALY using our revised base case, comfortably below the £30,000 per QALY threshold

		(teduglutide remains dominant for the paediatric base case). The impact is small because of the rarity of the complications: our model predicts that liver cirrhosis will only affect a maximum of 2.4% of patients and CKD Stage V only a maximum of 3.8% of patients receiving standard care during the model's entire time period (the proportion of patients with liver cirrhosis/CKD Stage V in the teduglutide arm is even lower). While the impact on the ICER of removing IFALD/CKD from the model is small, assuming no link between days per week of PS and IFALD/CKD is not clinically realistic. In accord with clinical feedback we have received, we note that the ERG's clinical expert was supportive of a link between days per week of PS and IFALD/CKD incidence. In sum, our approach to modelling complications reflects the rarity of deaths related to IFALD/CKD and avoids double counting. Removing complications from the model has a small impact on the ICER due to the rarity of IFALD/CKD in patients with SBS-IF.
Modelling of adverse events	No	**Approach to modelling adverse events** To clarify our approach to modelling adverse events, our model makes use of data from STEPS and STEPS-2 covering treatment emergent adverse events occurring in at least 5% of patients. For the teduglutide group, two time periods were modelled, with the first capturing the events that occurred in STEPS, followed by a separate period to cover the events captured within STEPS-2. This separation of the trial periods ensures a more accurate reflection of the rates of adverse events over time. The observed events in the teduglutide group of STEPS were used to estimate a rate per individual (i.e. dividing the number of events by the sample size [n=43]) to get a rate per person for the 6 month period of the STEPS study. These values were then divided by 6 to get a per-cycle rate of adverse events to input into the model. It is worth noting that the initial source of data were event rates (not probabilities of an individual experiencing at least one adverse event), and therefore, dividing by 6 and assuming a constant rate of adverse events for the period is the most plausible approach. The same approach was taken using the STEPS-2 study to represent the post-6 month period (and using data only from the subgroup who had received teduglutide in STEPS i.e. the TED-TED group; see document B, B.2.3.2, page 34). However, the number of events per person was divided by 24, as the total numbers of events were observed over the 24 month period of the STEPS-2 study.

		For the standard care group, the same approach was used for the first 6 month period using the adverse events observed in the placebo group of STEPS. As no further evidence is available from the STEPS programme to inform adverse events on standard care beyond the first 6 months (and no other sources of data were available), we have assumed the event rate remains constant. The ERG also noted that the pooled safety data we presented in Document B did not make the case for reducing rates of adverse events over time with teduglutide. To provide reassurance of this: the total number of events observed in STEPS for the teduglutide group was 247 from 42 patients who received teduglutide[9]. This represents 5.88 adverse events per person over the 6 month period, and therefore, a rate of 0.98 adverse events per month per person. In STEPS-2, a total of 386 events were observed for 37 patients (who received teduglutide in both STEPS and STEPS-2)[10]. This represents 10.43 events per-person for the 24 month period of STEPS-2, and therefore a rate of 0.43 per month per person. **Justification of observed trends in adverse event rates** The ERG note that data from STEPS and STEPS-2 show that a) adverse events with teduglutide decrease over time and b) the safety profile of teduglutide after 6 months is more favourable than standard care (ERG report, page xx). They have asked for justification of these trends. We believe the trends are plausible. In general, adverse events in patients with SBS-IF treated with teduglutide can be related to one of four sources: • Teduglutide treatment • Use of PS • Underlying SBS-IF • 'Other' (general adverse events, or events related to the cause of SBS-IF, e.g. Crohn's disease). We cannot establish causality for any single adverse event, but we can address the ERG's concern by looking at the sources as a whole:

		• Adverse events related to teduglutide will only be experienced in the teduglutide arm. It is reasonable to expect these to decrease over time as events related to the immunogenicity of teduglutide would decrease, and in general tolerance of the therapy by patients is likely to improve. • Adverse events related to use of PS would be experienced in both teduglutide and standard care arms. Over time, the teduglutide arm reduces their use of PS, and so the rate of adverse events associated with PS would also be expected to decrease. The rates of these adverse events in the standard care arm would be expected to remain constant in-line with their PS needs. • Adverse events related to underlying SBS-IF would be experienced in both teduglutide and standard care arms. Clinical feedback suggests that teduglutide improves patients feeling of 'general wellbeing', citing for example that patients put on more muscle mass during treatment. It would therefore be reasonable to expect adverse events associated with underlying SBS-IF to decrease with teduglutide treatment. We would not expect the standard care arm to have any change with regards adverse events from underlying SBS-IF. • Adverse events from 'other' causes are likely to remain the same between teduglutide and standard care arms Taken altogether, it is not unreasonable to think that the rates of adverse events in the teduglutide arm would a) decrease over time and b) be lower than in the standard care arm after 6 months of teduglutide treatment. This is because patients in the teduglutide arm will achieve lower PS requirements, so experience fewer adverse events associated with PS. They may also have fewer adverse events associated with underlying SBS-IF. Furthermore, adverse events associated with teduglutide itself are likely to decrease over time.
Health state costs (specialist visits for people who reached independence	Yes	**Specialist visits at PS0** In our original submission, we assumed adult patients would have 3 gastroenterologist visits per year when receiving PS (4 for children receiving PS) and 0 visits per year once PS independent. In our response to the ERG's clarifications we provided a scenario assuming 2 specialist visits per year for PS independent adults and 4 specialist visits per year for PS independent children. This was based on clinical feedback that patients with SBS-IF who gain independence from PS would be likely to have fewer gastroenterology visits than those on PS.

from parenteral support and costs related to line sepsis)		In their report we note that the ERG has received separate clinical advice that all SBS-IF patients typically receive 3–4 clinic visits per years regardless of their PS requirements. We are happy to embrace this alternative feedback and implement the ERG's preferred assumption of an equal number of gastroenterology visits between patients independent and dependent on PS. Our revised base case (outlined in 'Summary of changes to the company's cost-effectiveness model', on page 14 of this document) now assumes no change in gastroenterology visits for patients who gain independence from PS. **Line sepsis** Line infection leading to sepsis can occur at the point of line insertion, and also during line use[11] (amongst other situations e.g. contaminated infusion). More days per week on PS means more frequent line insertion and greater duration of line use, so it is reasonable to assume more days per week of PS would lead to higher incidence of line sepsis. We also note that the ERG's clinical expert was supportive of this position, given patients with more days per week on PS face greater exposure to infection (ERG report, p 71). We were not able to identify literature that examined a connection between days per week of PS and incidence of line sepsis. We do note however that almost all literature on sepsis events in patients receiving PS reports the rate of line sepsis in the units 'per 1000 catheter days'[11-14] (as opposed to 'per patient year'). This indicates that time spent on a catheter is widely recognised as linked to sepsis incidence, and reporting 'per 1000 catheter days' controls for this important variable. As days per week of PS is equivalent to 'catheter days', it is appropriate to vary rates of line sepsis by days per week of PS in our model.

Additional issues

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Ondansetron dosing	NA – raised by the ERG at the technical engagement meeting with the Company	No	The ERG asked us to clarify the basis for the dosing of the co-medication ondansetron in our model. Usage of ondansetron was based on the results of a resource use study. The aim of the study was to determine the treatment pathway and associated costs of managing SBS-IF in the UK[16]. Four gastroenterologists, 5 nurses, 1 pharmacist and 1 dietician, all experts in SBS-IF (and representing the specialist centres of St Marks Hospital, Salford Royal Hospital, Barts Health NHS Trust, University College London, Queen Elizabeth Hospital and the University of East Anglia), were interviewed for the purpose of this study[16]. Results of this study suggested that patients on PS would receive 16 mg of ondansetron IV daily whilst patients independent of PS would not receive ondansetron. Our model aligns with these findings.

Summary of changes to the company's cost-effectiveness estimate(s)

We have made five changes to our original adult base case (7 to our paediatric base case). As outlined in the 'key issues' table above, the ERG flagged an inaccuracy with our calculation of transition matrices that has now been corrected. In addition, we have incorporated the first 3 out of 4 of the ERG's preferred assumptions (ERG report page xxii) into our new adult and paediatric base cases; we acknowledge all as plausible assumptions. Finally, we have amended the cost of renal colic, which the ERG flagged as under-costed (but did not include as a preferred assumption). The paediatric base case is further updated with new costs for colonoscopies and greater use of the smaller teduglutide vial, both in line with the ERG's preferred assumptions.

The revised adult base case results show an incremental cost of [redacted] for people treated with teduglutide and an increase in QALYs of [redacted], resulting in an ICER of £9,691. For the paediatric population, the base case analysis shows that teduglutide results in cost savings of [redacted] and a gain in QALYs of [redacted], meaning that teduglutide represents a dominant treatment strategy.

Takeda's internal insights suggest that approximately [redacted] of the SBS-IF population anticipated to receive teduglutide will be paediatric. This means that for the licensed population as a whole, the combined results represent a weighted incremental cost of [redacted] for patients treated with teduglutide, and a weighted QALY gain of [redacted]. This represents a weighted base case ICER of £4,290 per QALY.

Table 4 Changes to the company's cost-effectiveness estimate (adult base case)

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
			Company base case in original submission: £16,652
Modelling of health state transitions	Post-stopping rule, transition matrices were estimated using all patients in STEPS-2 who received teduglutide up to 30 months	Post-stopping rule, transition matrices are now estimated using only patients in STEPS-2 who would not be stopped by the stopping rule who received teduglutide up to 30 months	Changes original base case from £16,652 to £9,031
Correct disutility cell referencing error	The ERG identified a cell referencing error in our model: the adverse event 'urinary tract infection' was being assigned an incorrect utility value	In line with the ERGs preferred assumption '1' (ERG report page xxii), we have corrected this in our updated base case	Changes original base case from £16,652 to £16,344 [Cumulative with above: £8,870]
Equal gastroenterology visits for PS0	Our model assumed 3 gastroenterology visits per year for adult patients receiving PS and 0 visits for adults who gained independence from PS	In line with the ERGs preferred assumption '2' (ERG report page xxii), our model now assumes 3 gastroenterology visits per year for all adult patients regardless of whether or not they receive PS	Changes original base case from £16,652 to £17,266 [Cumulative with above: £9,513]
Recalculation of utility decrement applied for line sepsis	The utility decrement applied for line sepsis was relative to a utility value of 1.00	In line with the ERGs preferred assumption '3' (ERG report page xxii), the utility decrement applied for line sepsis is now relative to	Changes original base case from £16,652 to £16,752 [Cumulative with above: £9,626]

		the EQ-5D population norm (0.86)	
Increased cost of renal colic	We used the NHS reference cost for renal colic, which does not include intervention. This was costed at £839.	The ERG highlighted that intervention should be included in the costs for renal colic. We have added these, resulting in an increase in cost of renal colic to £975.	Changes original base case from £16,652 to £16,720 [Cumulative with above: £9,691]
Updated base case	**Incremental costs:** [redacted]	**Incremental QALYs:** [redacted]	**ICER:** £9,691

Sensitivity analyses around revised adult base case

We have also provided updated sensitivity analyses for the adult base case (see Appendix_TE3, page 25 of this document). All scenarios bar one fall under the £30,000 per QALY upper threshold for cost-effectiveness. The exception is a scenario assuming no further teduglutide discontinuations after 12 months of treatment, however this scenario is clinically implausible.

The probability of teduglutide being cost-effective vs standard care is 67% at a £30,000 per QALY willingness-to-pay threshold, and 59% at a £20,0000 per QALY threshold. The probability of teduglutide dominating in the adult base case is 42%.

Table 5 Changes to the company's cost-effectiveness estimate (paediatric base case)

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
			Company base case in original submission: £4,811
Modelling of health state transitions	Post-stopping rule, transition matrices were estimated using all patients in STEPS-2 who received teduglutide up to 30 months	Post-stopping rule, transition matrices are now estimated using only patients in STEPS-2 who would not be stopped by the stopping rule who received teduglutide up to 30 months	Changes original base case from £4,811 to teduglutide dominates
Correct disutility cell referencing error	The ERG identified a cell referencing error in our model: the adverse event 'urinary tract infection' was being assigned an incorrect utility value	In line with the ERGs preferred assumption '1' (ERG report page xxii), we have corrected this in our updated base case	Changes original base case from £4,811 to £4,736 [Cumulative: teduglutide dominates]
Equal gastroenterology visits, haematology tests, tests of inflammatory markers, clinical biochemistry tests per year for PS0	Our model assumed 4 gastroenterology visits, 4 haematology tests and 4 inflammatory markers and clinical biochemistry tests per year for children on PS, and 0 for children who gained independence from PS.	In line with the ERGs preferred assumption (ERG report, Table 25, page 85), our model now also assumes 4 gastroenterology visits, 4 haematology tests and 4 inflammatory markers and clinical biochemistry tests per year for children regardless of whether or not they receive PS	Changes original base case from £4,811 to £5,357 [Cumulative: teduglutide dominates]

Recalculation of utility decrement applied for line sepsis	The utility decrement applied for line sepsis was relative to a utility value of 1.00	In line with the ERGs preferred assumption '3' (ERG report page xxii), the utility decrement applied for line sepsis is now relative to the EQ-5D population norm (0.86)	Changes original base case from £4,811 to £4,837 [Cumulative: teduglutide dominates]
Cost of paediatric colonoscopy applied (FE37C Endoscopic or Intermediate, Lower Gastrointestinal Tract Procedures, between 5 and 18 years)	Our model used the same value for paediatrics as per the adult base case.	The ERG's suggested paediatric-specific cost has now been applied.	Changes original base case from £4,811 to £5,280 [Cumulative: teduglutide dominates]
Smaller vial cost of teduglutide for paediatrics.	Our model only applied the smaller vial cost of teduglutide until the age of 6.	Now this smaller vial cost is applied until the age of 8, as per the ERG's suggestion.	Changes original base case from £4,811 to teduglutide dominates [Cumulative: teduglutide dominates]
Increased cost of renal colic	We used the NHS reference cost for renal colic, which does not include intervention. This was costed at £839.	The ERG highlighted that intervention should be included in the costs for renal colic. We have added these, resulting in an increase in cost of renal colic to £975.	Changes original base case from £4,811 to £4,865 [Cumulative: teduglutide dominates]
Updated base case	**Incremental costs:** [redacted]	**Incremental QALYs:** [redacted]	**ICER:** Teduglutide dominates

Sensitivity analyses around revised paediatric base case

In all scenarios bar one, teduglutide is dominant vs standard care in the paediatric population. The exception is a scenario assuming no further teduglutide discontinuations after 12 months of treatment (ICER £9,945), however this scenario is clinically implausible.

The probability of teduglutide being cost-effective vs standard care is 93% at a £30,000 per QALY willingness-to-pay threshold, and 87% at a £20,0000 per QALY threshold. The probability of teduglutide dominating in the paediatric base case is 68%.

Appendix TE_1: Updated transition matrices from months 12–30

As outlined in our response to key issue #1 (modelling of health state transitions), we have recalculated transition matrices post-stopping rule (post-12 months) to exclude data from patients in STEPS-2 who would have been stopped by the stopping rule (data from the PSP are not included, as this was only used to inform transition matrices up to month 12). Transition matrices are estimated for 6 month intervals.

Tables 1 to 6 below outline the recalculated transition matrices for the 12–18, 18–24 and 24–30 month period. Tables 1, 3 and 5 show the number of patients in STEPS-2 (excluding those who would be stopped by the stopping rule) occupying each health state (PS0–PS7) at the beginning and end of the 6 month period. Tables 2, 4 and 6 show the recalculated transition matrices; these show the probability of either remaining in the starting health state or improving by one health state per each 4-weekly cycle. For more discussion of our model structure, see Document B, section B.3.2.2 (page 93) and for more detail on calculating transition matrices, see Document B B.3.3.2 (page 99).

Table 1 Patient distributions at the start and end of the 12 to 18 month interval

Health state	PS0	PS1	PS2	PS3	PS4	PS5	PS6	PS7	Total
Patients at start of interval	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients at end of interval	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 2 Transition probabilities (4-weekly) for 12 to 18 month period (STEPS-2 data)

Health state	PS0	PS1	PS2	PS3	PS4	PS5	PS6	PS7
PS0	[redacted]	-	-	-	-	-	-	-
PS1	[redacted]	[redacted]	-	-	-	-	-	-
PS2	-	[redacted]	[redacted]	-	-	-	-	-
PS3	-	-	[redacted]	[redacted]	-	-	-	-
PS4	-	-	-	[redacted]	[redacted]	-	-	-
PS5	-	-	-	-	[redacted]	[redacted]	-	-
PS6	-	-	-	-	-	[redacted]	[redacted]	-
PS7	-	-	-	-	-	-	[redacted]	[redacted]

Table 3 Patient distributions at the start and end of the 18 to 24 month interval

Health state	PS0	PS1	PS2	PS3	PS4	PS5	PS6	PS7	Total
Patients at start of interval	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients at end of interval	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 4 Transition probabilities (4-weekly) for 18 to 24 month period (STEPS-2 data)

Health state	PS0	PS1	PS2	PS3	PS4	PS5	PS6	PS7
PS0	[redacted]	-	-	-	-	-	-	-
PS1	[redacted]	[redacted]	-	-	-	-	-	-
PS2	-	[redacted]	[redacted]	-	-	-	-	-
PS3	-	-	[redacted]	[redacted]	-	-	-	-
PS4	-	-	-	[redacted]	[redacted]	-	-	-
PS5	-	-	-	-	[redacted]	[redacted]	-	-
PS6	-	-	-	-	-	[redacted]	[redacted]	-
PS7	-	-	-	-	-	-	[redacted]	[redacted]

Table 5 Patient distributions at the start and end of the 24 to 30 month interval

Health state	PS0	PS1	PS2	PS3	PS4	PS5	PS6	PS7	Total
Patients at start of interval	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients at end of interval	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 6 Transition probabilities (4-weekly) for 24 to 30 month period (STEPS-2 data)

Health state	PS0	PS1	PS2	PS3	PS4	PS5	PS6	PS7
PS0	[redacted]	-	-	-	-	-	-	-
PS1	[redacted]	[redacted]	-	-	-	-	-	-
PS2	-	[redacted]	[redacted]	-	-	-	-	-
PS3	-	-	[redacted]	[redacted]	-	-	-	-
PS4	-	-	-	[redacted]	[redacted]	-	-	-
PS5	-	-	-	-	[redacted]	[redacted]	-	-
PS6	-	-	-	-	-	[redacted]	[redacted]	-
PS7	-	-	-	-	-	-	[redacted]	[redacted]

Appendix TE_2: Health state occupancy of updated model compared to STEPS/PSP

In our response to clarification question B5 (Clarification Responses, page 30), we compared the health state occupancy predicted by our model to the health state occupancy from pooled STEPS/STEPS-2/PSP data. With patients stopped by the stopping rule now removed from the calculation of transition matrices, we have produced an updated comparison. Table 7 shows the health state distributions predicted by our updated model at 6-monthly timepoints. Table 8 shows corresponding health state occupancy from pooled STEPS/STEPS-2/PSP data.

Table 7. Health state distributions produced by the updated model (base case)

Health state distributions (model)	PS0	PS1	PS2	PS3	PS4	PS5	PS6	PS7
Baseline	0%	0%	0%	11%	14%	10%	13%	52%
6 months	3%	2%	8%	11%	20%	13%	16%	29%
12 months	7%	5%	9%	12%	17%	13%	9%	28%
18 months	9%	8%	10%	4%	18%	14%	8%	28%
24 months	19%	0%	8%	5%	21%	12%	5%	28%
30 months	24%	2%	4%	11%	17%	7%	5%	28%
Abbreviations: PS*x*, *x* days per week on parenteral support								

Table 8. Health state distributions as per STEPS, STEPS-2 and the PSP

Health state distributions (observed)	PS0	PS1	PS2	PS3	PS4	PS5	PS6	PS7
Baseline	[redacted]							
6 months	[redacted]							
12 months	[redacted]							
18 months	[redacted]							
24 months	[redacted]							
30 months	[redacted]							
Abbreviations: PS*x*, *x* days per week on parenteral support; PSP, patient support programme								

Appendix TE_3: Sensitivity analyses for updated base case

Scenario analyses for our updated base case ICER are presented below for both the adult and paediatric population

Table 9 Summary of scenario analyses (adults)

Model component	Base case	Scenario	Relevant section of Document B	ICER (£/QALY)
Base case				£9,691
Discount rate	3.5% for both costs and QALYs	1.5% for both costs and QALYs.	B.3.2	£2,318
Data source	STEPS/STEPS-2 and PSP data pooled	STEPS/STEPS-2 only	B.3.3.1	£13,174
Standard care health state transitions	Not applied	Applied based on placebo in STEPS with reversion to baseline at 6 months	B.3.3.1	£10,589
Survival modelling	Salazar 2021 (Log-normal)	Salazar 2021 (Exponential)	B.3.3.4	£12,918
		Salazar 2021 (Log-logistic)		£11,609
		Amiot 2013 (Gen.gamma)		£14,596
		Amiot 2013 (Log-normal)		£16,598
		Amiot 2013 (Log-logistic)		£17,150
Treatment discontinuation model	Weibull	Log-normal	B.3.3.3	£12,063
		Log-logistic		£10,230
Treatment discontinuation assumptions after stopping rule.	Rate based on extrapolated survival model	No further discontinuation after stopping rule	B.3.3.3.2	£31,356
Heath-state utility data source	Ballinger 2018	Lachaine 2016	B.3.4.5	£12,101

Complications	Based on Delphi panel rates	Assumes benefit only achieved for PS 0 (based on Delphi panel rates applied to baseline PS for all others)	B.3.3.5	£10,443
		No complications		£13,943
Adverse events	All adverse events	Serious adverse events only	B.3.4.3	£13,079
Carer quality of life	Mid-point of Delphi panel and survey	Delphi panel	B.3.4.4	£8,465
		Survey		£11,332
Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; PS, parenteral support; PSP, patient support programme				

Table 10 Summary of scenario analyses (paediatrics)

Model component	Base case	Scenario	Relevant section of submission	ICER (£/QALY)
Base case				Teduglutide dominates
Discount rate	3.5% for both costs and QALYs	1.5% for both costs and QALYs.	B.3.2	Teduglutide dominates
Data source	STEPS/STEPS-2 and PSP data pooled	STEPS/STEPS-2 only	B.3.3.1	Teduglutide dominates
Standard care health state transitions	Not applied	Applied based on placebo in STEPS with reversion to baseline at 6 months	B.3.3.1	Teduglutide dominates
Treatment discontinuation model	Weibull	Log-normal	B.3.3.3	Teduglutide dominates
		Log-logistic		Teduglutide dominates
Treatment discontinuation assumptions after stopping rule	Rate based on extrapolated survival model	No further discontinuation after stopping rule	B.3.3.3.2	£9,945

Heath-state utility data source	Ballinger 2018	Lachaine 2016	B.3.4.5	Teduglutide dominates
Complications	Based on Delphi panel rates	Assumes benefit only achieved for PS 0 (based on Delphi panel rates applied to baseline PS for all others)	B.3.3.5	Teduglutide dominates
		No complications		Teduglutide dominates
Adverse events	All adverse events	Severe adverse events only	B.3.4.3	Teduglutide dominates
Carer quality of life	Mid-point of Delphi panel and survey	Delphi panel	B.3.4.4	Teduglutide dominates
		Survey		Teduglutide dominates
Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; PS, parenteral support; PSP, patient support programme				

Figure 1. One-way sensitivity analyses (adult base case)

Figure 2. One-way sensitivity analyses (paediatric base case)

Figure 3. Probabilistic sensitivity analysis (adult base case)

Figure 4. Cost effectiveness acceptability curve (adult base case)

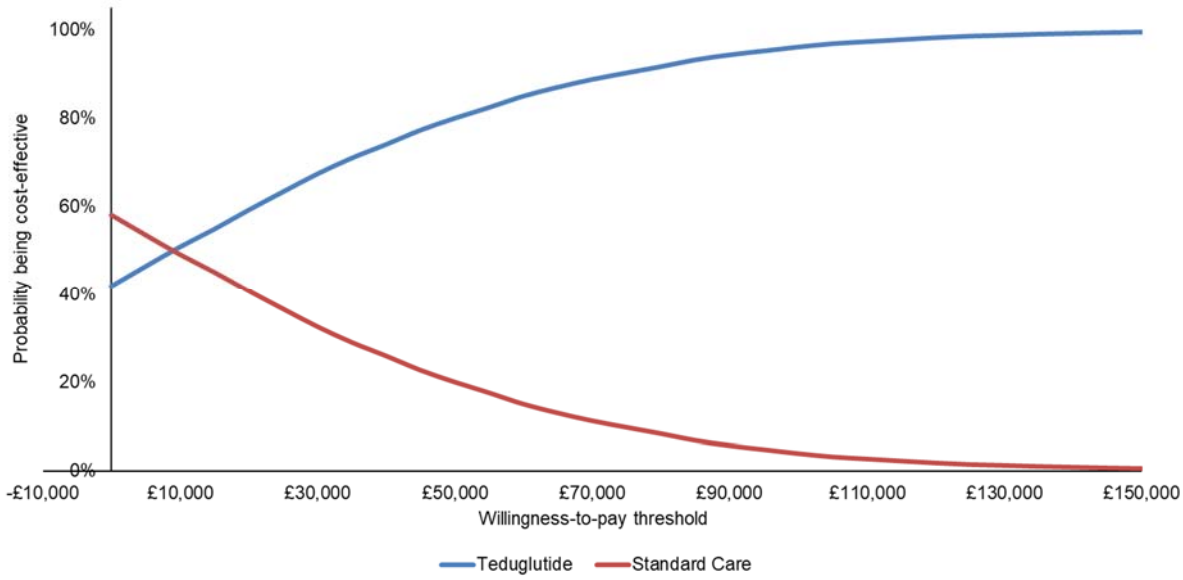
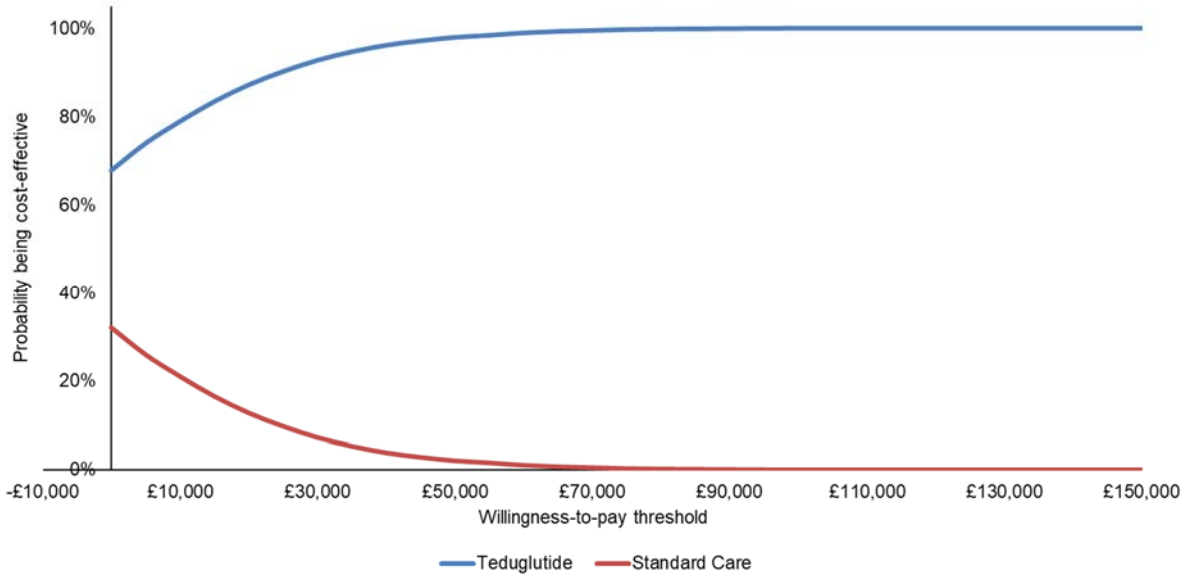


Figure 5. Probabilistic sensitivity analysis (paediatric base case)

Figure 6. Cost effectiveness acceptability curve (paediatric base case)



Appendix TE_4: Explorations of standard care PS reductions and health state utility using revised base case

Summaries of the analyses conducted to explore uncertainty around the placebo effect in STEPS and the range in utilities for patients and carers are presented in the tables below.

Table 11. Placebo duration scenarios

Duration of placebo effect	ICER (adult base case)	ICER (paediatric base case)
None (base case)	£9,691	Teduglutide dominates
6 months	£10,589	Teduglutide dominates
1 year	£12,204	Teduglutide dominates
2 years	£15,576	Teduglutide dominates
3 years	£18,797	Teduglutide dominates
4 years	£21,870	Teduglutide dominates
5 years	£24,805	Teduglutide dominates
6 years	£27,611	Teduglutide dominates
7 years	£30,294	Teduglutide dominates

Table 12. Patient health state utility decrement scenarios

Reduction applied to decrements	ICER (adult base case)	ICER (paediatric base case)
None (base case)	£9,691	Teduglutide dominates
10%	£10,348	Teduglutide dominates
20%	£11,101	Teduglutide dominates
30%	£11,972	Teduglutide dominates
40%	£12,991	Teduglutide dominates
50%	£14,200	Teduglutide dominates
60%	£15,658	Teduglutide dominates
70%	£17,448	Teduglutide dominates
80%	£19,701	Teduglutide dominates
90%	£22,621	Teduglutide dominates
100%	£26,559	Teduglutide dominates

Table 13. Carer decrement scenarios

Reduction applied to decrements	ICER (adult base case)	ICER (paediatric base case)
None (base case)	£9,691	Teduglutide dominates
10%	£9,978	Teduglutide dominates
20%	£10,283	Teduglutide dominates
30%	£10,607	Teduglutide dominates
40%	£10,952	Teduglutide dominates
50%	£11,321	Teduglutide dominates
60%	£11,715	Teduglutide dominates
70%	£12,137	Teduglutide dominates
80%	£12,591	Teduglutide dominates
90%	£13,080	Teduglutide dominates
100%	£13,609	Teduglutide dominates

References

1. Jeppesen PB, Pertkiewicz M, Messing B, Iyer K, Seidner DL, O'Keefe SJD, et al. Teduglutide reduces need for parenteral support among patients with short bowel syndrome with intestinal failure. Gastroenterology. 2012;143(6):1473-81.
2. Shire Pharmaceuticals Limited. Revestive 1.25 and 5 mg powder and solvent for solution for injection. Summary of Product Characteristics2020.
3. NHS England. Intestinal Failure Service (Adult) england.nhs.uk: NHS; 2019 [Available from: https://www.england.nhs.uk/publication/intestinal-failure-service-adult/; https://www.england.nhs.uk/wp-content/uploads/2019/07/170077S-Intestinal-Failure-Service-Specification.pdf.
4. Salazar E, Clermont-Dejean NM, Schwenger KJP, Noelting J, Lu Z, Lou W, et al. Patients With Severe Gastrointestinal Dysmotility Disorders Receiving Home Parenteral Nutrition Have Similar Survival As Those With Short-Bowel Syndrome: A Prospective Cohort Study. JPEN J Parenter Enteral Nutr. 2021;45(3):530-7.
5. Amiot A, Messing B, Corcos O, Panis Y, Joly F. Determinants of home parenteral nutrition dependence and survival of 268 patients with non-malignant short bowel syndrome. Clin Nutr. 2013;32(3):368-74.
6. Lloyd DA, Vega R, Bassett P, Forbes A, Gabe SM. Survival and dependence on home parenteral nutrition: experience over a 25-year period in a UK referral centre. Aliment Pharmacol Ther. 2006;24(8):1231-40.
7. Dibb M, Soop M, Teubner A, Shaffer J, Abraham A, Carlson G, et al. Survival and nutritional dependence on home parenteral nutrition: Three decades of experience from a single referral centre. Clin Nutr. 2017;36(2):570-6.
8. McKee RF, Knight K, Leitch EF, Stevens P. Changes in adult home parenteral nutrition practice over 25 years. Clinical Nutrition ESPEN. 2021;45:170-6.
9. NPS Pharmaceuticals Inc. STEPS CSR. Clinical Study Report. Not published - Takeda confidential
2011.
10. NPS Pharmaceuticals Inc. STEPS-2 CSR. Clinical Study Report. Not published - Takeda confidential data2013.
11. McWhirter D. Parenteral nutrition line sepsis: the difficulty in diagnosis. Proc Nutr Soc. 2010;69(4):508-10.
12. Martincich I, Cini K, Lapkin S, Lord H, Fernandez R. Central Venous Access Device Complications in Patients Receiving Parenteral Nutrition in General Ward Settings: A Retrospective Analysis. JPEN J Parenter Enteral Nutr. 2020;44(6):1104-11.
13. Ferrie S, Carey S, Ryan R, Sandroussi C, Jones L, Storey D, et al. Parenteral nutrition with standard solutions: not the best solution for everyone? A retrospective audit of 300 patients. J Infus Nurs. 2014;37(6):424-31.
14. Gillanders L, Angstmann K, Ball P, O'Callaghan M, Thomson A, Wong T, et al. A prospective study of catheter-related complications in HPN patients. Clin Nutr. 2012;31(1):30-4.
15. Dyson JK, Thompson N, Northern Nutrition N. Adult parenteral nutrition in the North of England: a region-wide audit. BMJ Open. 2017;7(1):e012663-e.
16. PAREXEL Access Consulting. Adult SBS Costing Study Not published - Takeda confidential data; 2017 3 March

NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form

Teduglutide for treating short bowel syndrome [ID3937]

Thank you for agreeing to comment on the evidence review group (ERG) report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary (section 1) at the beginning of the ERG report. You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR
- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Clinical expert statement

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm** on **9 December 2021**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Clinical expert statement

NICE National Institute for Health and Care Excellence

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating short bowel syndrome and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Susan Hill
2. Name of organisation	Department of Gastroenterology, Great Ormond Street Hospital for Children NHS Foundation Trust, London
3. Job title or position	Consultant in paediatric gastroenterology, specialising in nutrition and intestinal failure rehabilitation
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with short bowel syndrome? ☐ A specialist in the clinical evidence base for short bowel syndrome or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	none

8. What is the main aim of treatment short bowel syndrome ? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The main aim of treatment of short bowel syndrome associated with intestinal failure is to cure the condition. The child needs to attain sufficient enteral function to gain weight and grow normally without the need for parenteral nutrition (PN) support and for the central venous catheter (CVC) for administering it to be removed. Once the catheter has been removed the patient is no longer at risk of the life-threatening complications associated with an indwelling central venous device such as bloodstream infection and thrombotic episodes. The child changes from a patient with major organ failure and dependency on the burden of 'hi-tech' medicine to an effectively normal healthy child.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	A clinically significant treatment response is reduction of the need for parenteral nutrition (PN) by one night/week, i.e. about 20%. In patients with the most severe IF a clinically significant treatment response enables them to remain well for a 36-hour period free of infusions at least once a week. In a patient who is partially dependent on PN and already tolerating some nights without an intravenous nutrition or fluid infusion the 20% reduction in PN infusion enables them to have an extra night each week free of an infusion. And if a child can manage one night a week off PN they can have two nights a week off at separate times during the week. In other words the ability to have one night off PN enables the child to reduce PN from 7 to 5 nights a week (if needed extra nutrients can be given on intervening nights)
10. In your view, is there an unmet need for patients and healthcare professionals in short bowel syndrome?	Yes. We do not have a treatment that significantly improves intestinal function. Up until now the only available treatment has been to support good health rather than to significantly improve intestinal function. Patients and their families are so conditioned to finding that any sudden change in their health is a change for the worse that they find it difficult to believe when I have offered them the chance to trial a new medication that might offer them the chance of a night or two a week completely free of a PN infusion.

11. How is short bowel syndrome currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which?	• Are any clinical guidelines used in the treatment of the condition, and if so, which? Current recommendations are that short bowel syndrome associated intestinal failure (SBS-IF) is treated in a specialist centre by a multidisciplinary team with experience in treating the condition (www.rcpch.ac.uk)A centre would usually treat patients with SBS-IF along with patients with IF associated with other underlying aetiologies in the same service. BIFA (British Intestinal Failure Association) of BAPEN (British Association for Parenteral and Enteral Nutrition) produced a position statement in 2016 stating that an IF centre should treat a minimum of 10 children or 20 adults with IF at any one time to expect to maintain sufficient expertise (https://www.bapen.org.uk/images/pdfs/position-statements/position-statement-on-hpn.pdf). The statement also stipulated the composition of an IF multidisciplinary team and the team practices, relationships, external interactions and which IF outcomes should be audited. I specialise in paediatrics. There are European guidelines for management of parenteral nutrition (PN) that include guidelines for management of long-term/home PN for SBS (**ESPGHAN/ESPEN/ESPR/CSPEN guidelines on paediatric parenteral nutrition** *Clin Nutr.* 2018; **37**: 2306-2429). We are developing specific SBS guidelines through the ESPGHAN Committee of Nutrition that we plan to submit for publication in 2022.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? The pathway of care is well developed. The first line treatment internationally is long-term home PN. Intestinal transplant is reserved for those cases in which PN fails. The pathway of care broadly consists of:

	1. initial stabilisation of the patient following presentation (usually post-surgical resection of an ischaemic portion of small intestine), 2. A period of aiming to establish oral/enteral nutrition whilst weaning the patient from PN and 3. to discharge the patient to their home if they fail to wean from PN in the first few weeks after presentation. 4. to continue supportive treatment with PN with care by formally trained parents/carers + still aiming to reduce and stop PN if at all possible. + 5. To continue to monitor the patient at home + 6. trouble shoot any complications that develop 7. Continue attempting to reduce PN and increase oral/enteral intake as tolerated Internationally agreed reasons for PN failure and the need to move to a new pathway for intestinal transplant assessment include: - 1. Loss of central venous access with thrombosis of major blood vessels - 2. intestinal failure associated liver failure - 3. Major fluid losses that are difficult to stabilise - 4. Quality of life Once a patient has had an intestinal transplant, they will need medical support for the rest of their life whereas if they had had the opportunity to wean off PN they would have had the possibility of a normal healthy life.

• What impact would the technology have on the current pathway of care?	You ask about differences of opinion. I find that there is agreement on management amongst the most experienced multidisciplinary intestinal failure rehabilitation services in Europe and even on a worldwide basis. What impact would the technology have on the current pathway of care? Teduglutide treatment would be incorporated into the current pathway of care in the stable patient who had ceased to wean from PN by > 10% for > 3 months. I would expect it to reduce the length of time of the pathway of care. The child would still be treated in the same pathway, but initially with more frequent assessment than usual since their condition could rapidly improve on treatment. Use of teduglutide would: - enable children with SBS and chronic IF who have reached their maximum potential to wean from PN with the current supportive management to have the opportunity to wean even further from PN - in some cases PN treatment would be stopped completely and the central venous catheter removed - it could be used to enhance weaning in children in a precarious situation with significant problems such as liver disease or limited central venous access to wean from PN - It would reduce the need for intestinal transplant. The children who would benefit from teduglutide are a small minority of all short bowel syndrome cases who are unable to reduce or stop PN even with the best possible supportive treatment. They are the patients who have reached a 'plateau' in their natural ability to wean from PN, i.e. have reached their maximum potential for oral/enteral absorption and are unable to survive and grow without PN support. The impact would vary according to the child's dependency on PN. It would be best to consider the patients in two separate groups:

	1. Those with virtually total dependency on PN requiring it 7 nights a week and 2. Those with partial PN dependency who have the ability to absorb a portion of their nutrients enterally, but still need a central venous catheter to give enough nutrition to support normal growth and development. 1. The impact on patients totally dependent on PN would be: - an improved quality of life and reduced cost of care in the child who would otherwise be connected up to an infusion into the central venous system every 12-14 hours (or in some cases, even longer) out of 24 hours. These cases ae unable to remain well for > 12 hours free from a central venous infusion and have their indwelling central venous catheter connected to plastic tubing attached to a plastic bag of nutrients with bag of PN and pump attached for infusion. - Parents/carers have considered their quality of life has improved even when teduglutide has reduced diarrhoea and the need for excessive nappy changes. For example, one of my teduglutide trial patients was opening their bowels X8-10/day and needed nappy changes promptly since stool would cause excoriation if left in contact with skin for more than a few minutes. Once on teduglutide the parents were delighted that bowel frequency was X 2-4 /day and the stool no longer led to skin excoriation. 2. The impact in patients with partial PN dependence would be: - every extra night free of the PN infusion with pump and the bag of nutrients attached is highly valued. - Patients who start teduglutide when they are already only partially dependent on PN have a higher chance of stopping PN completely. - once PN can be stopped completely the central venous catheter can be removed. They are then free of the worry of acute potentially life-threatening complications.

	If PN can be stopped completely and the central venous catheter removed the child is no longer at risk of: - catheter related bloodstream infection (CRBSI). When a child with a central venous catheter for PN administration develops a fever of ≥38c they need to go straight to hospital for a blood sample to be taken for culture and antibiotics to be commenced to treat a possible (CRBSI) that needs to be continued for at least 48 hours whilst the result of the blood culture is awaited. In other words, with every inter-current childhood illness associated with a fever ≥38c the child has to spend at least 48 hours in hospital with the worry of possible CRBSI. In some cases of CRBSI that do not respond to antibiotic treatment the child then has to undergo an anaesthetic for removal of the catheter. The whole event can be distressing and disruptive for the whole family with repercussions such as parents having to take time off work and the child missing school. - Other potentially life-threatening complications including thrombotic episodes and pulmonary emboli - failure of long-term home PN treatment when intestinal transplant with a shortened life expectancy and loss of the potential for a life free of specialist medical care
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? The patients would need less NHS resources. On starting treatment, they would still need to be managed by a specialist multidisciplinary intestinal failure rehabilitation team. If they wean off PN they no longer need the specialist intestinal failure rehabilitation service and can be followed up by a simpler gastroenterology nutrition service. It would be usual to just have a dietitian and specialist nutrition gastroenterology consultant • How does healthcare resource use differ between the technology and current care?

• How does healthcare resource use differ between the technology and current care?	In patients still on PN the care would be less demanding: - If a patient can manage a night off/36 hours without PN they do not need such urgent care as the child on PN every night. For example, if the catheter blocks, they can wait until normal working hours to have it dealt with rather than urgent admission to hospital for intravenous fluids. Once they have weaned off PN they would use less NHS funded resources including: - Change to a simpler gastroenterology nutrition service. It would be usual to just have a dietitian and specialist nutrition gastroenterology consultant involved in the child's care rather than the wider multidisciplinary team required for intestinal failure rehabilitation. - Less monitoring - There would no longer be the need for hospital admission for every fever >38c - the patient no longer needs NHS funding for a private homecare company to manufacture and deliver the PN to the home + rent out the infusion pump to the patient - There would be reduced waste. A large amount of single use plastic waste is associated with PN: - single use plastic bag for the sterile nutrients for each infusion -single use giving set for each infusion -other single use equipment such as syringes, gloves and other plastic parts
• In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic)	• In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) Teduglutide should only be used in a specialist setting by a specialist intestinal failure rehabilitation team with expertise in optimising the intestinal

• What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	function of a patient with short bowel syndrome associated intestinal failure (www.rcpch.ac.uk). • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training) Teduglutide treatment can be given by the patient's intestinal failure rehabilitation team with their current skills. A nurse with expertise in sub-cutaneous injections needs to teach the parents/carers to administer the teduglutide. It is essential that the team are committed to closely monitoring the patient with weekly assessment (some face to face and at other times by video or phone) after starting the treatment since the potential rate of improvement in intestinal function is much more rapid than any previous improvement. The team needs to advise on reducing the PN the patient infuses as intestinal absorption improves and encourage normal eating (in most cases)
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Do you expect the technology to provide clinically meaningful benefits compared with current care? Yes, I do expect the treatment to provide clinically meaningful benefits for adults and children with short bowel syndrome and associated intestinal failure. Teduglutide is the first potentially curative treatment for intestinal failure associated with short bowel syndrome • Do you expect the technology to increase length of life more than current care? Yes. Although most patients with short bowel syndrome can expect a good life expectancy there are a few children who have a shortened life expectancy. These are patients who would have had problems if they remained on PN: - Those who would have failed long-term PN care without the support of teduglutide in weaning from it and would have undergone intestinal

	transplant. Please see my response to question 11 above for the reasons for failure of home PN. - Patients who would have had a severe catheter related bloodstream infection and ended up with life changing problems such as severe neurological impairment. Do you expect the technology to increase health-related quality of life more than current care? Most definitely yes for the following reasons: 1. Significantly more children were able to reduce parenteral nutrition (PN) by ≥ 20% in the 24-week paediatric study (Kosochis et al.J Parenter Enteral Nutr.2020;44:621-631) - If PN is reduced by 20% the child should manage a 36 hour period without an infusion, i.e. manage a night without PN - If a child can manage a night without PN it is possible for them to have two nights a week off and to be given all their intravenous requirements on the other 5 nights/week - 5 nights of PN means less central venous catheter connections and disconnections and consequently less risk of catheter related bloodstream infections (CRBSI) - The burden of care is significantly improved for parents/carers. They can expect a better night's sleep on the two nights without PN - Less need to pass urine and stool at night (which many children do when attached to PN) + no need to sort out any pump alarms/other problems at night - Parents/carers have more energy for the working day after a night when they don't need to get up and attend to the child - Children can expect a better night's sleep which means they will be more alert and better able to concentrate during the school day

	- Less risk of a severe CRBSI that can be life-threatening or result in life changing neurological impairment - Older children enjoy the possibility of sleepovers with friends which are not possible when infusing PN overnight
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? It is much simpler treatment to administer teduglutide than to give an infusion of PN. Teduglutide is just one sub-cutaneous injection a day which is equivalent treatment to giving growth hormone to a child with growth deficiency or an insulin injection for a child with insulin dependent diabetes. In contrast administering PN is hi-tech treatment that has potentially life-threatening consequences each time the PN is connected to the central venous catheter. The child's central venous system has to be accessed in a sterile manner for each infusion of PN in order to minimise the risk of infection. Parents are taking on a hi-tech treatment that is usually only given in a specialist unit by specially trained nurses. It is not possible to leave the home unless a carer is present who has been trained in central venous catheter safety.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Yes. There would be recommendations for when to start and stop treatment. We have a national intestinal failure network for paediatric intestinal failure rehabilitation specialists and would recommend that potentially suitable cases should be discussed by that group.

	Teduglutide would be recommended when: - the natural ability of the shortened small intestine to improve has ceased and the patient is unable to reduce their need for PN by > 10% in the previous 3 months, despite being in good health - The child needs to be able to tolerate oral/enteral diet/nutrition. If they are unable to do so there is no point in giving teduglutide - The intestine needs to be patent with no evidence of obstruction. If the child has not had a radiological contrast study in the previous year or so it should be repeated to ensure there is no intestinal structuring or obstruction or excessive dilatation. If there are abnormalies the child should be referred for surgical correction and not for teduglutide. Only when they have fully recovered from the surgery should the need for teduglutide be reassessed Teduglutide should be stopped when: - If teduglutide has not had a positive effect on improving intestinal absorption after 6-12 months and the child has been otherwise well during that time the need to continue treatment should be reassessed - In some cases, a second trial of treatment should be re-considered if there has been a change in the child's condition since the original trial of treatment
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen	Yes, as far as I am aware the QALY would not have considered all benefits that treatment with teduglutide offers. Also, it was done in adults. Children have more complications and any problem affects the whole family (parents and siblings) as well as the child himself. A child must be urgently taken to hospital every time they have a fever of ≥ 38c. Children have a higher rate of intercurrent febrile illnesses and a higher rate of central venous catheter related bloodstream infections (CRBSI) than adults. With each fever they need to be admitted to hospital for a minimum of 48 hours to be

may be more easily administered (such as an oral tablet or home treatment) than current standard of care	given intravenous antibiotic treatment whilst the result of a blood culture (taken on arrival) is awaited. The child will miss school, and a parent will usually have to take time off work. The parent usually needs to be available to support the hospitalised child and administer any intravenous medication via the central venous catheter. Nursing staff on many paediatric wards are not qualified to handle central venous catheters and even if they are qualified to do so the risk of damage to the catheter or introducing further infection is increased when accessed by a greater number of people – even if appropriately trained). It is not just the length of life. When a child or adult weans off PN and has the central venous catheter removed their life is transformed. They are granted the opportunity of a normal life without 'hi-tech' support. And they no longer have the constant worry of an acute complication of PN treatment that might require urgent admission to hospital. They also have the possibility of improved sleep and as a result a higher level of energy. Teduglutide treatment is well tolerated by children and parents/carers who were previously receiving/administering a hi-tech treatment, PN. Whereas previously they were connected to their treatment for 12 hours or so up to as often as 7 nights/week, once on teduglutide they will substitute at least some of those evenings and nights attached to treatment with a once daily sub-cutaneous injection. Patients can be divided into two groups, yhose who gain a night or two a week off PN and those who fully gain independence of PN 1. Aspects of quality of life that families appreciate with some nights/week off PN include: - Once daily injection instead of 12 or more hours attached to an infusion - A better night's sleep - Less nappies to change overnight in small children

	- Less overnight disturbances to visit the toilet in older children - Patients on teduglutide treatment can usually enjoy a wider variety of food than they were able to before starting treatment - Improved enjoyment of food - Less attention needed to ensure exactly the right food quantity and variety is available - Older children enjoy sleepovers with their friends and overnight school trips - Parents can go out for the evening - The family can go away for a night without taking the PN and equipment with them 2. Children who wean fully from PN enjoy all the above and in addition: - No longer need to be acutely hospitalised if they develop a fever ≥38c - Parents/carers and children can all sleep better every night - No longer anxious about the possibility of less common complications such as liver disease, venous thrombosis, and loss of vascular access if the central venous catheter needs to be replaced - Enjoy a family holiday without the worry of a fridge available for storing the PN, the possibility of needing to go to the nearest hospital if the child is febrile and taking a huge amount of equipment with them on holiday
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition?	Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? Most definitely, yes.

• • Does the use of the technology address any particular unmet need of the patient population?	It is as innovative as growth hormone for growth failure, thyroxine for hypothyroidism or insulin for insulin dependent diabetes. It is giving a hormone that the body is not producing in adequate quantities. • Is the technology a 'step-change' in the management of the condition? Although it may not be totally curative, it is the first potentially curative treatment for chronic intestinal failure associated with short bowel syndrome. Does the use of the technology address any particular unmet need of the patient population? Yes. It offers a new chance of reduced dependence on hi-tech treatment and if the child weans off treatment, a new life free of medical equipment, a central venous catheter and nights attached to a pump and infusion with potentially life-threatening complications which may develop acutely at anytime.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The most common adverse events described in the paediatric trials were gastrointestinal symptoms (seen in children with short bowel syndrome on standard of care) and those associated with intercurrent childhood infections. There was also some soreness at the injection site, but the severity was minimal in comparison to the acute, potentially life-threatening complications associated with treatment with PN
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • • What, in your view, are the most important outcomes, and were they measured in the trials?	Do the clinical trials on the technology reflect current UK clinical practice? I am a paediatrician and am only able to comment on the paediatric trials. The paediatric trials do reflect current UK practice. The paediatric intestinal failure rehabilitation specialists who participated in the trials were consulted and we agreed as to how to best manage the condition. Our advice was taken on how to clinically manage the patients in the paediatric trials. • What, in your view, are the most important outcomes, and were they measured in the trials? • Yes, they were. The main endpoint of the trials was 20% reduction in PN which should easily be sufficient for an extra night each week off PN in

• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	virtually all cases. For patients and medical professionals an extra night a week off PN is considered an important outcome. Of course the ultimate aim of treatment is to wean the child completely from PN and in some cases this has been possible. However, realistically it is unlikely to be achievable in all cases of short bowel associated intestinal failure. • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? Surrogate outcomes were not used in the paediatric trials • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently? I am not aware of any new adverse events in paediatrics
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	I would hope that any relevant evidence would be found by a good systematic review
22. How do data on real-world experience compare with the trial data?	In the first paediatric real-world publication the improvement of intestinal function appeared to be even better than in the paediatric and adult trials (Ramos Boluda E, et al. JPediatrGastroenterolNutr2020;71:734-7390).
24. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil	An interesting finding is that in paediatrics teduglutide appears to improve intestinal function in all the different conditions that most commonly predispose to short bowel associated intestinal failure. My impression is that the patients who do best are those with families who comply most diligently with medical advice. One important aspect is that the child is offered regular meals and snacks (e.g. 3 meals and 2 snacks per day) in order to enable the intestinal remnant to absorb as much as possible when treatment is commenced.

partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	In view of the need for good dietary care, the child from a family that does not encourage the child to eat regularly is less likely to do well. No No If anything use of teduglutide should benefit children with severe neuro-disability in association with intestinal failure. The burden of care of administering long-term home PN can be too great for the families of some of this group of children. Teduglutide is far simpler to administer, has a hugely reduced burden of care in comparison to PN and might enable such a child to wean from PN and go home to his family.

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Modelling of health state transitions (and the placebo response in STEPS) – Would you expect people with short bowel syndrome to experience any sustainable reduction in parenteral support (PS) with current standard of care (that is, in the absence of	Some children can continue to gain enteral autonomy for many months post-intestinal resection. Once a child has reached a plateau i.e. has been unable to reduce their PN dependency by >10% for at least 3 months at a time when otherwise well when managed to the highest standard by a specialist intestinal failure rehabilitation service I would not expect a significant improvement with current standard of care. You ask about the STEPS study in adult patients. My response is that it might be possible to reduce PN for a short period of time, but I would not expect the reduction to be sustainable if patients had been complying with medical advice at the start of the study. I note that there was weight loss in the standard of care (SOC) patients in the STEPS trial. The weight loss suggests that overall SOC patients had pushed themselves too hard to reduce PS and over-stretched themselves. It is possible that the SOC patients were not feeling quite as well as usual whilst they tried so hard to reduce PS and would have increased the PS again with time. A weaning algorithm can be a helpful guide when weaning PN, but the opinion of an experienced clinician taking a holistic approach should be prioritised over the algorithm. The STEPS study is an example of

Clinical expert statement

teduglutide treatment)? Would a weaning algorithm for teduglutide affect the need for PS?	how an algorithm might lead to over-treatment in some patients and under-treatment in others. My interpretation of the adult STEPS trial algorithm is that urine output was over-relied on without taking into account other factors and ended up distorting the management of the patients since the SOC patients tended to lose weight whilst the teduglutide treatment cases tended to gain weight. I would have expected well managed adults with intestinal failure to have maintained a reasonably steady weight over the 6 month trial period. The differing changes in weight between the SOC and teduglutide treatment groups suggest that the teduglutide treatment patients were given too much PN (and might have been able to wean more rapidly) and the SOC patients too little PN. There are many factors that need to be taken into consideration when weaning a patient from PN. For example, physical activity was not taken into account in the studies I saw a child this week who had recently lost weight on PN who had been more active during the school term than when at home in the school holidays and appeared to have needed increased PN.
Health state utility by frequency of PS – How would you expect people with short bowel syndrome and their carers quality of life to change after reducing their number of days on PS?	The effects of reducing the nights of PS in children and their carers would include: - more relaxed with a more flexible lifestyle and the opportunity to participate in new activities. - the chance to sleep overnight at a friend's home; children have told me about the pleasure of doing so on several occasions when they have had a night a week off PN - Parents can go out for an evening which can be difficult with a child on PN since the infusion usually needs to be infused over a minimum of 12 hours for safety reasons. The parent can of course connect the PN late some evenings after they have been out, but if they do so the child will be connected to the infusion for longer the following morning which would be difficult if it were a school day - Parents/carers can have a drink in the evening knowing they are less likely to be disturbed in the night. - Parents and the child can expect to have an improved energy level and be more alert during the day for school and work. - The family appreciate having less PN and ancillary equipment to take with them on holiday. - The family can go away for a night without PN equipment.

	- One of my patients attended a school play prior to their first night off PN this week and was excited to not have to rush home before the end to connect PN
Modelling of overall survival – would you expect people with short bowel syndrome to have an increased risk of death compared to the general population in the long-term? Are long-term short bowel syndrome complications linked to increased risk of mortality?	**would you expect people with short bowel syndrome to have an increased risk of death compared to the general population in the long-term?** You are asking about long-term short bowel syndrome (SBS) problems and not intestinal failure (IF) problems. My understanding is that children and adults with SBS have a near normal life expectancy once they have gained enteral autonomy and weaned off parenteral nutrition (PN) and the central venous catheter (CVC) has been removed. Increased risk of mortality would come from: - 1. Lack of monitoring and/or management of micronutrient deficiencies - 2. Intestinal bacterial overgrowth and associated D-lactic acidosis - 3. Increased incidence of renal calculi 1. When we monitor our children with SBS who were previously dependent on PN in some cases we find low blood levels of copper, vitamin A, vitamin E, vitamin D, vitamin K and/or vitamin B12. Symptoms can be severe if the child is not monitored and given supplements as needed. For example, I was referred one child (who had been lost to follow up from another service) who had presented to an ophthalmologist with loss of vision with severe vitamin A deficiency. Most children with SBS have lost a portion of their terminal ileum and are at risk of vitamin B12 deficiency. Regular intramuscular vitamin B12 injections can be arranged via the patient's GP. If deficiencies are diagnosed and appropriate oral/enteral supplements of other micronutrients provided people with SBS can expect to lead a normal life. 2. Abnormalities of the intestinal bacteria often referred to as 'intestinal bacterial overgrowth' can lead to staggering gait, lowered level of consciousness and if severe the patients can become comatose. If unrecognised the condition can be fatal.

	3. I would not expect an increased mortality from renal calculi.
Modelling of complications (Intestinal failure related liver disease (IFALD) and chronic kidney disease (CKD)) – Would you expect the proportion of people who experience IFALD and CKD to be linked to the number of days on PS? Is it reasonable to assume teduglutide would reduce IFALD and CKD? Are IFALD and CKD linked to an increased risk of mortality?	**Would you expect the proportion of people who experience IFALD and CKD to be linked to the number of days on PS?** Yes, I would expect the risk of IFALD and CKD to be greater in people on more nights/week PN IFALD is a condition that is most commonly associated with unstable, hospitalised patients with IF. It is most common in premature infant since the immature liver is most vulnerable to any insults. The risk lessens with - reduced dependency on PN - less nights/week on PN - when the patient is stable and not having other intercurrent problems such as catheter related bloodstream infections/CRBSI. - well managed patients at home on long-term PN **Is it reasonable to assume teduglutide would reduce IFALD and CKD?** Teduglutide should reduce the risk of IFALD since it reduces PN dependency. It should also reduce the risk of CKD since intestinal fluid absorption improves on treatment. The reduced intestinal fluid losses and less variability in intestinal fluid loss lower the risk of dehydration and secondary renal failure. **Are IFALD and CKD linked to an increased risk of mortality?** There is a mortality associated with IFALD. The patients at greatest risk are those who developed SBS in the neonatal period and have already developed liver disease prior to discharge home on PN. It is also possible for significant IFALD to develop in the older child/adult even after many months of stability on PN at home.

	When the patient with IFALD remains dependent on PN for many months and it is not possible to wean them off PN the liver disease can progress. These people are then assessed for liver and intestinal transplant. A number of such patients have died on the paediatric transplant waiting list in England. CKD may be a concern in adults with SBS and IF. I am not aware of chronic kidney disease/CKD as a major problem in children with SBS associated IF. In our service we monitor for CKD including monitoring creatinine and cystatin C level and we have not had any cases in association with SBS (in stable patients on PN at home).
Modelling of adverse events – Would you expect a diminishing adverse event rate over time for people having teduglutide? Would you expect the safety profile of teduglutide to be more favourable than standard of care in the long-term?	**Would you expect a diminishing adverse event rate over time for people having teduglutide?** Yes, I would expect a diminishing adverse event rate over time for people on teduglutide treatment. **Would you expect the safety profile of teduglutide to be more favourable than standard of care in the long-term?** Yes. I would expect the safety profile to be more favourable than standard of care in the long-term. However, I would only expect an improvement in patients in whom teduglutide has been effective in reducing PN dependency, i.e. the favourable outcome would be related to the reduced PN dependency. People with SBS who respond to teduglutide and manage to reduce PN by even one or two nights a week are effectively swapping an overnight infusion into the bloodstream just above the heart with a daily intramuscular injection. The safety of an intramuscular injection is far greater than a central venous infusion.
Health state costs (specialist visits for people who reached independence from PS and costs related	**1) Would you expect people who have reached independence from PS to require gastroenterology (multi-professional) specialist visits? If so, how many visits per year would you expect be needed?**

to line sepsis) – 1) Would you expect people who have reached independence from PS to require gastroenterology (multi-professional) specialist visits? If so, how many visits per year would you expect be needed? 2) Would you expect the incidence of line sepsis to increase with an increase in the frequency of PS? Is there any data to inform correlation between the number of days on PS and the risk of sepsis?	1. I would expect people who have reached independence from PS to require less gastroenterology support. In particular, they no longer need the multi-professional specialist visits. Instead they initially need 3-6 monthly out-patient assessment for growth and monitoring of nutritional related laboratory investigations. After a year or so the visits can be reduced to 6-monthly and in many cases, annually. Each appointment need only be with a gastroenterology specialist doctor and does not need a multidisciplinary team. A dietitian may also be needed if nutritional concerns arise. Indeed, this has been my experience in children who have been in the teduglutide studies. A child who is still on teduglutide, but weaned off PN no longer needs: - a central venous catheter/CVC - the multidisciplinary IF service - homecare company funded by the NHS to supply and deliver to the home bags of PN and all ancillary equipment - emergency admissions to hospital with potential CRBSI with every fever ≥38c - emergency attention to the central venous catheter if it becomes blocked or develops a hole Once the child has weaned off PN for approximately 6 months and has had the central venous catheter **2) Would you expect the incidence of line sepsis to increase with an increase in the frequency of PS? Is there any data to inform correlation between the number of days on PS and the risk of sepsis?** Yes – I would expect the risk of septicaemia to be higher when PN is administered more frequently We found a significantly higher infection rate when we audited the rate of CRBSI in our patients, ***CRBSI patients had significantly more PN infusions/week P <0.0001*** REF: *Puoti, Maria Giovanna, Chiara D'Eusebio, Zafar Zaidi, Hannah Littlechild, Emily King, Jutta Koglmeier, and Susan Hill. "P13 Clinical Features Significantly Associated with Higher Risk of Catheter-related Blood Stream Infection (CRBSI) in Children on Long-term Parenteral Nutrition (PN)." Frontline Gastroenterology 12.Suppl 1 (2021): A19-20. Web.*

	Every time the catheter is accessed to connect or disconnect a bag of PS there is a risk of contaminating the catheter with bacteria that may lead to a septicaemia.
Are there any important issues that have been missed in the ERG report?	We have just had a paper accepted (REF:Jones B, O'Sullivan B, Amin SP et al Patient level costing analysis of paediatric short bowel syndrome care in a specialist tertiary centre 2022 Pediatric Surgery International) looking at the annual specialist centre in-patient costs for children with SBS on PN treatment. The costs are purely for complications and in addition to the cost of: - the homecare company charge to the NHS for the PN and ancillary equipment - community nursing support when problems arise that can be dealt with in the community, such as extra blood tests, skin swab for an infected looking CVC site. - local hospital support for acute admissions with a fever/other problems that do not need immediate attention at the specialist centre I have posted the draft abstract below and should have a full reference soon: **Abstract** *Purpose* To undertake a pilot study estimating patient-level costs of care for paediatric short bowel syndrome (SBS) from the healthcare provider perspective. *Methods* A pilot group of patients with anatomical SBS was selected at a single specialist tertiary centre in the United Kingdom. The Patient Level Information and Costing System (PLICS) was used to extract costing data for all hospital-based

	activities related to SBS, from implementation of PLICS in 2016 to April 2021. Patient-specific and pooled data were reported descriptively in per patient-year terms. *Results* Five patients had full PLICS data available for the 5-year study period and 2 patients had 4 years of data. The median cost for hospital care of SBS was £52,834 per patient-year (range: £1804 to £331,489). The key cost drivers were inpatient beds, pharmacy, and staffing costs, which made up >60% of annual costs. In the first 3 years following index admission (n=2), there was a steady decline in annual cost of care to a level comparable with patients with established SBS. *Conclusion* Patient-level cost of care analysis for SBS is feasible using PLICS. Hospital-related costs vary widely between and within individual patients over time. Key drivers of cost are related to complications of SBS. I would also like to add a 5th point to the 4 summary points on the original form please as follows 'one night a week off PN is a significant improvement for both the person affected with short bowel syndrome and intestinal failure and for the multi-professional team managing their care'.

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Teduglutide is the first potentially curative as opposed to supportive treatment for children and adults with short bowel syndrome associated intestinal failure (SBS-IF)
Teduglutide should be administered in a specialist setting by an experienced multidisciplinary intestinal failure rehabilitation team in a patient who has received optimal treatment for their intestinal failure
Teduglutide can reduce the risk of life-threatening complications associated with long-term home PN and if treatment fails can prevent the need small intestinal transplant by improving intestinal function
Teduglutide has a life transforming effect when it supports a child in weaning completely from PN; the child can live a normal healthy life without the support of hi-tech treatment

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Teduglutide for treating short bowel syndrome [ID3937]

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The evidence review group (ERG) report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with short bowel syndrome or caring for a patient with short bowel syndrome. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary (section 1) at the beginning of the ERG report.

A patient perspective could help either:

- resolve any uncertainty that has been identified OR

- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Patient expert statement

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm** on **9 December 2021**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Living with this condition or caring for a patient with short bowel syndrome

Table 1 About you, short bowel syndrome, current treatments and equality

1. Your name	Carolyn Wheatley
2. Are you (please tick all that apply)	☒ A patient with short bowel syndrome? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with short bowel syndrome? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	PINNT
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: Chair of support and advocacy groups, PINNT, for people on home artificial nutrition in the UK and a broader network.

	☒ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with short bowel syndrome? **If you are a carer (for someone with short bowel syndrome) please share your experience of caring for them**	I've lived with short bowel syndrome (SBS) for 37 years due to pseudo-obstruction/motility disorder resulting in intestinal failure. My condition was undiagnosed for 7 years, I deteriorated and consequently had disease related malnutrition. Having lost half my body weight with no viable way to 'feed' me orally, to correct and correct this, parenteral nutrition (PN) was deemed my only option. I embraced the prospect of a life-saving treatment. My first central line was sited and a few weeks later I had pioneering surgery and a jejunostomy stoma fashioned. My enthusiasm waned when reality struck; I had traded one body image dilemma for another. A central venous catheter (CVC) and stoma bag would now be permanently attached to my body. While my CVC was a vehicle to provide my life-saving nutrition and hydration, it requires meticulous adherence to procedures to minimise the risk of infection, fracture and complications. I had to learn medical techniques and adhere to them as well as having adopted the roll of the nutrition team to be vigilant and responsive to all aspects of my treatment and care, especially early signs of complications and infections. I struggled with acceptance, I felt burdened by the overwhelming need to get it right and keep myself well and safe. I was fully self-caring. 12-14 hours every day connected to a machine (longer if extra fluids are required), poor quality of life/body image, low self-esteem, no social life yet thankful for my treatment. I have adjusted over time, the reality of my PN remains the same, still connected to a pump for 12/14 hours every day, still rigorous about procedures to reduce/minimise the risk of sepsis, visual and mental reminders of the reality of home PN. Fully aware it's lifesaving but also life-threatening. Stoma: My jejunostomy stoma relieved the embarrassment of diarrhoea, assisted relieving my constipation which reduced pain and bloating. However, I've traded

	that for a high output stoma. Transition is fast, unpredictable and can leak and explode causing personal dilemmas and embarrassing situations, all affecting psychological well-being. I've accepted that PN has corrected my disease-related malnutrition and the stoma has aided my ability to manage my SBS, neither have cured me though. Living with SBS and PN is possible due to a lot of personal compromise and planning. The on-going symptoms of the underlying condition combined with the burden of treatment and care have a major impact of my quality of life. I have become accustomed to compromising when it comes to socialising, having SBS is not food and fluid friendly, it's about risks versus consequences. Travelling has always been a passion, it is a stressful process due to the requirement to transport PN in specially temperature-controlled boxes. Boxes weight up to 15kg for three bags of PN and are 44cm sq. Life continues but the quality and burden of life with SBS and PN is a different matter. Life is governed by time management, adherence to medical procedures and accepting the parameters within which I can live.
7a. What do you think of the current treatments and care available for short bowel syndrome on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	**7a.** PN is a recognised specialised treatment to support those with SBS. In most cases, it is welcomed but has the potential to be overwhelming in terms of the responsibility, the homecare process and the burden of the treatment. Clinically it is effective, but not always easy to accept and adjust to. The physical and psychological impact may not be fully recognised at the beginning of the treatment. Some people mourn the life they had or the potential they believe is lost because they recognise PN is their only option with restrictions. People struggle with a hidden condition, PN improves what is seen externally but does not convey the organ failure and dependency on a lifesaving treatment which disfigures both the mind and body. **7b.** They align with the comments in 7a.

8. If there are disadvantages for patients of current NHS treatments for short bowel syndrome? Please describe these	Being dependent on a time consuming, complex, high-risk lifesaving treatment which impacts not only the person receiving it, but parents, partner, siblings, family and friends brings many disadvantages. Lifestyle choices, education, social interaction, intimacy, sleep deprivation, personal development, mobility, travel, confidence, self-esteem and psychological well-being. PN also brings concerns about infections, potential lengthy hospital admissions for treatment or CVC replacements and time away from family and their family units.
9a. If there are advantages of teduglutide over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does teduglutide help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	**9a.** There are numerous advantages of teduglutide, the ability to make choices about lifestyle, education, social interaction, intimacy, improve sleep deprivation, enhance personal development, increase mobility, allow greater choice and flexibility for travel and holidays, improve confidence, improve self-esteem and psychological well-being. A reduction in the nights of PN would allow all those impacted by the PN, the person on PN and the carer/parent/family to benefit from quality sleep, less disruption due to potential pump alarms and toilet visits while having to mobilise essential feeding pumps and stands. It also reduces the number of nights people worry about performing clinical procedures that have the potential to introduce an infection or sepsis (reduce risk). Often the carers/parents/family members are overlooked in terms of the impact of SBS and PN. The overall advantages can improve their lives. They are relieved from the burden of care, often bringing independence for them too and reduced anxiety. **9b.** I'm stating two**:** 'choice' – 'reduce risk.' Both contribute to 'improved quality of life,' which will have a positive impact on all the disadvantages listed. **9c.** Depending on the individual situation it has potential to overcome and improve a number of the disadvantages listed in 8.
10. If there are disadvantages of teduglutide over current treatments on the NHS please describe these. For example, are there any risks with teduglutide? If you are concerned about any potential side effects you have heard about, please describe them and explain why	I am unable to comment on question 10 as I have not heard any concerns about it.

11. Are there any groups of patients who might benefit more from teduglutide or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	I am not qualified to comment on this question.
12. Are there any potential equality issues that should be taken into account when considering short bowel syndrome and teduglutide? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	I see no potential equality issues in respect of SBS and teduglutide.
13. Are there any other issues that you would like the committee to consider?	No.

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the ERG report are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the ERG report, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from ERG report

Modelling of health state transitions (and the placebo response in STEPS) – Would you expect people with short bowel syndrome to experience any sustainable reduction in parenteral support (PS) with current standard of care (that is, in the absence of teduglutide treatment)? Would a	I am aware of people who have a reduction of PN but sadly it is not always sustainable, it can have an adverse effect on their mental health to revert to previous feeding regime.

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weaning algorithm for teduglutide affect the need for PS?	
Health state utility by frequency of PS – Have you or someone you care for experienced a reduction in the number of days of PS after receiving teduglutide? If so, how has your/their quality of life changed?	Not personally but I have met and spoken to people who have experienced a reduction in the number of days of PN after starting teduglutide. • 1 night reduction, adult: Less emphasis on time! One night a week he doesn't have to rush home from work to get his PN out the fridge to adjust to room temperature before commencing his infusion which is time managed around the infusion time to get up for work the next day. His one night off has allowed him the opportunity to venture out and fulfil his ambition to gain further qualifications which in turn has given him a social life. Time focused on personal development and new mates, not PN, the clock and a complex condition. His self-esteem and self-worth have improved with a focus on what he can do, not what he would like to do or can't do. • 2 nights reduction (one during the week, one at the weekend), child: after school clubs are now enjoyed which focus on friendships and sibling quality time. The family unit is stronger without choices about which parents stays at home while the PN is done. One night reduction at the weekend (their choice) means two days of freedom, overnight stays with family and friends, no need to pack PN and all the ancillaries needed, not seeking a safe space to connect and disconnect the child which reduces the anxiety of time away from home, worrying about forgetting all the essential medical supplies. • 2 nights, adult: She manages by having two consecutive nights off which has enabled her to take a part time job. Her husband says he sees the change in her, more confident and greater motivation to go out and socialise. They have quality time together, date nights and enjoy spontaneous weekends away. Her husband jokes they can now travel light (no PN and medical supplies), and he has admitted to sleeping more soundly on her nights off as the pump disturbed him and he isn't listening for alarms and alerts from the pump.
Modelling of overall survival – would you	I am not qualified to comment on this question.

expect people with short bowel syndrome to have an increased risk of death compared to the general population in the long-term? Are long-term short bowel syndrome complications linked to increased risk of mortality?	
Modelling of complications (Intestinal failure related liver disease (IFALD) and chronic kidney disease (CKD)) – Would you expect the proportion of people who experience IFALD and CKD to be linked to the number of days on PS? Is it reasonable to assume teduglutide would reduce IFALD and CKD? Are IFALD and CKD linked to an increased risk of mortality?	I am not qualified to comment on this question.

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Modelling of adverse events – Would you expect a diminishing adverse event rate over time for people having teduglutide? Would you expect the safety profile of teduglutide to be more favourable than standard of care in the long-term?	I am not qualified to comment on this question.
Health state costs (specialist visits for people who reached independence from PS and costs related to line sepsis) – 1) Would you expect people who have reached independence from PS to require gastroenterology (multi-professional) specialist visits? If so, how many visits per year would you expect be needed? 2) Would you expect the incidence of line sepsis to increase	I am not qualified to comment fully on this question. Each time a connection or disconnection is performed there is a risk of sepsis. The core principles of training are to reduce the risk of sepsis in terms of the rigorous procedures taught. This is part of the burden of care, maintaining precise and accurate techniques is a factor within the burden of care for the patient/carer/parents. The consequences of sepsis weight heavy on everyone involved on home PN.

with an increase in the frequency of PS? Is there any data to inform correlation between the number of days on PS and the risk of sepsis?	
Are there any important issues that have been missed in the ERG report?	I cannot emphasis enough the value of a reduction of nights of home PN. Having SBS is a complex rare disease which is multifactorial both in terms of the condition itself and the impact of those living with it. One day less or more gives hope in terms of health improvement, freed time from complex and rigorous procedures, opportunities and prospects in terms of person goals. For carers/parents nights off PN brings similar outcomes as listed above but the additional burden of responsibility is reduced if only for 24–48 hours. This time is priceless to benefit from resemblance of what normal life can be or used to be.

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Reduced nights of PN reduces the risk of sepsis.
- The burden of risk is reduced for the patient/carer/parents with a reduction of PN.
- Patients/carers/parents would benefit from an improved quality of life, freedom from complex medical procedures allowing quality time and opportunities for people which in turn can contribute to mental health improvements for everyone and the ability to make choices not usually afforded to them.
- Nights without PN can correct sleep deprivation as sleep is needed to maintain good mental and physical health thus aiding the ability to cope with SBS/IF, PN and additional medical condition(s) and life.
- This is the first viable therapeutic alternative to PN

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see NICE's privacy notice.

NICE National Institute for Health and Care Excellence

Patient expert statement and technical engagement response form

Teduglutide for treating short bowel syndrome [ID3937]

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments and feedback on the key issues below are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources. The evidence review group (ERG) report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking you about living with short bowel syndrome or caring for a patient with short bowel syndrome. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary (section 1) at the beginning of the ERG report.

A patient perspective could help either:

- resolve any uncertainty that has been identified OR

- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise. We have given guidance on the issues in which we expect this to be the case and advice on what you could consider when giving your response.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Your response should not be longer than 15 pages.

Patient expert statement

Please note, **part 1** can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Deadline for comments by **5pm** on **9 December 2021**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees

Part 1: Living with this condition or caring for a patient with short bowel syndrome

Table 1 About you, short bowel syndrome, current treatments and equality

1. Your name	Mary Elizabeth Foss
2. Are you (please tick all that apply)	☐ A patient with short bowel syndrome? ☐ A patient with experience of the treatment being evaluated? ☒ A carer of a patient with short bowel syndrome? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience:In my voluntary work with the charity supporting families dealing with SBS IF ☒ I have completed part 2 of the statement **after attending** the expert

Patient expert statement

	engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with short bowel syndrome? **If you are a carer (for someone with short bowel syndrome) please share your experience of caring for them**	In 2008 my Granddaughter D was born prematurely with atresia and only 10cm of short bowel. She needed immediate surgery to survive. I was trained by the hospital to assist with PS as her mother was a single parent. At approximately 9 months D was discharged from hospital. Unfortunately, my daughter had fallen on the icy road and broke her arm at the elbow. This meant I had to attend to all D's PS and care for the first 6 weeks. After which I supported my daughter with PS for some considerable time. Even with the greatest of care D was to experience several episodes of hospitalisation due to line infection. Apart from 6 nights on Parenteral Nutrition and a gastrostomy tube feed, it became clear she was failing to thrive and at about 30 months it was decided that she needed bowel lengthening surgery. It took quite some time for the bowel to adapt after surgery. PS then continued until the age of 6 years when the central line was removed. Throughout those 6 years I witnessed the awful pain and discomfort she suffered due to bloating and swelling of the abdomen, also the constant diarrhoea, and lethargy due to disturb sleep from having to be changed as often as 6 or 7 times in the night, sometimes having to be bathed and a complete change of clothing and bed linen. I saw that dealing with PS was an all-consuming nightmare for my daughter. The ever-present worry about sepsis and liver failure - plus the constant rounds of hospital visits, dealing with doctors, clinicians and medication caused her immense stress. The ordering and storing of the huge amount of medical equipment and materials which sadly made D's room look more like a hospital ward than a child's bedroom!

	Even now at the age of thirteen D remembers how the beeping of the pumps would wake her in the night and make her feel upset! Apart from this first-hand experience - since 2011 my voluntary role with Short Bowel Survivor and Friends charity has not only allowed me to support families dealing with SBS-IF but I believe it has given me a unique insight into the day-to-day problems these families face.
7a. What do you think of the current treatments and care available for short bowel syndrome on the NHS?	The current care provided by the NHS is simply a system whereby child or adult patients with SBS-IF are artificially fed. Medication may be provided in an attempt to alleviate some of the symptoms. The level and quality of the service provided appears to be something of a 'Post-Code Lottery! For most parents learning to coping with PS is daunting task. They are being asked to do what they see the trained nurses in hospital do - but in their own home - and on their own! They have the constant worry about sepsis and liver failure to deal, with along with huge amounts of equipment and materials (including an extra fridge! How many of us have room for one of those?) Not all families cope well! - especially if they are continually wakened in the night with feed pumps beeping or an upset child needing to be changed frequently throughout the night. This can and does affect the whole family, leading to frayed tempers, lack of concentration at work or school and there is still a house to clean, laundry to be done and meals to be made!
7b. How do your views on these current treatments compare to those of other people that you may be aware of?	Most parents are grateful for PS despite all the trauma and stress as there seems little or no choice! Not all families cope, many do struggle as the immense burden of care has caused family relationships to break down. Many parents say they feel isolated, exhausted and that the NHS generally doesn't care! They worry for the future health of their child. They face problems with delays of PN or equipment delivery - Hospital appointments, and medication. The average family have little or no chance of

	respite, whereas those who can afford to pay for help and support say for overnight feeds can continue with employment and their social life.
8. If there are disadvantages for patients of current NHS treatments for short bowel syndrome? Please describe these	Lack of choice other than PS as supplied by NHS in the UK – except Scotland. PS provides nutrients but only if the relevant structures in the body can absorb them. E.g., Those born with ultra-short bowel. Sadly, there are insufficient surgeons who can perform bowel lengthening surgery in the UK. Patients' and carers lives are severely restricted by hours of being hooked up to feed pumps which affects their freedom due to the need for privacy Patients' carers and other members often suffer disturbed sleep leading to lethargy and depression. Many suffer embarrassing toileting issues leading to a lack of confidence and lower self-esteem.
9a. If there are advantages of teduglutide over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others?	The advantage of teduglutide is that it can make changes to improve the function of the bowel to better absorb the necessary nutrients needed for growth. Long term this could remove the need to rely on PS. eventually becoming self-reliant in terms of extracting nutrients from normal food. The removal of the central line for intravenous feed also eliminates the risk of sepsis and possibly liver failure associated with Parenteral Nutrition. This in turn removes the risk to vital line sites around the body and the subsequent need for transplants. For both patients and carers this alternative treatment takes little time and much less equipment compared to the standard NHS parenteral support. It would relieve the burden of care on families by freeing them from long hours tied to the home in the administration of PS. Even 2 or 3 nights of freedom can make a huge difference. A chance to socialise with others at any age is a boost to their confidence and wellbeing. Likewise, a

9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why	sleep-over for kids with their friends without the usual embarrassments associated with PS, can boost confidence and general moral! Without constant disturbed sleep carers may be able to continue with or return to full employment thereby supporting themselves and others in society. Children will be less tired and better able to focus on school and take full advantage of their education. Reduction of the risk of sepsis and liver failure by removal of central line Protection of line sites – reduces the need of a transplant Improved absorption of nutrients within the bowel and associated structures therfore reducing or removing the body's dependence on PS
9c. Does teduglutide help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	Relief from the risk of sepsis by removal of central line in favour simple subcutaneous injections Less risk to line sites and the possibility of needing a transplant. Eliminates a huge amount of equipment and materials needed for PS Frees up time used for ordering and re-ordering and storing equipment and materials. No waiting in for deliveries of equipment and Parenteral Nutrition. No need for an extra fridge to store bags of Parenteral Nutrition. Improves the patient's personal space Opportunity to practise self-care in private Freedom to socialise with friends, have families' outings, visit to the cinema etc Return to work, or education, volunteer to help others in the community Improved quality of sleep helps children better able to benefit from lessons in school
10. If there are disadvantages of teduglutide over current treatments on the NHS please describe these.	I understand that patients who have tumours may not be able to benefit from teduglutide There may be a reluctance on the part of a parent or carer to administer the drug for religious or ideological reasons

Patient expert statement

For example, are there any risks with teduglutide? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from teduglutide or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	There may be some adult patients who have difficulties with mobility and or dexterity, however this would also have been the case with administration of PS Treating patients with cognitive impairment would require sensitive support whatever the treatment regime required. The fact that the delivery would be quicker and require less equipment may be an advantage in these circumstances,
12. Are there any potential equality issues that should be taken into account when considering short bowel syndrome and teduglutide? Please explain if you think any groups of people with this condition are particularly disadvantaged Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	People suffering from rare diseases and the disabilities and difficulties that they cause, deserve the best treatment available regardless of their of their age, gender, race, religion or sexual orientation and regardless of their ability to pay.
13. Are there any other issues that you would like the committee to consider?	

Part 2: Technical engagement questions for patient experts

Issues arising from technical engagement

The issues raised in the ERG report are listed in table 2. We welcome your comments on the issues, but you do not have to provide a response to every issue, such as the ones that are technical, that is, cost effectiveness-related issues. We have added a comment to the issues where we consider a patient perspective would be most relevant and valuable. If you think an issue that is important to patients has been missed in the ERG report, please let us know in the space provided at the end of this section.

For information: the patient organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report, the patient organisation responses will also be considered by the committee.

Table 2 Issues arising from ERG report

Modelling of health state transitions (and the placebo response in STEPS) – Would you expect people with short bowel syndrome to experience any sustainable reduction in parenteral support (PS) with current standard of care (that is, in the absence of teduglutide treatment)? Would a	It may be possible for people to have a sustained reduction in the level of PS in the absence of teduglutide dependant on the length of residual bowel after surgery although this may involve many years and a great deal of suffering and disruption to family life.

Patient expert statement

weaning algorithm for teduglutide affect the need for PS?	
Health state utility by frequency of PS – Have you or someone you care for experienced a reduction in the number of days of PS after receiving teduglutide? If so, how has your/their quality of life changed?	[we consider patient perspectives may particularly help to address this issue] Yes, there ae two families where there has been a marked reduction in PS. Both cases are single parents. 1. In the first of these it has allowed the mother to spend more time with her older child who she had missed for over 12 months due to hospitalisation. 2. In the second case; it made it possible for the mother to return to work as a nurse thereby helping to continue her training, helping others in the community and the NHS. It also improved her own self-worth.
Modelling of overall survival – would you expect people with short bowel syndrome to have an increased risk of death compared to the general population in the long-term? Are long-term short bowel syndrome complications linked to increased risk of mortality?	The risks due to sepsis, liver failure and the loss of line sites are ever present due to intravenous feeding.

Modelling of complications (Intestinal failure related liver disease (IFALD) and chronic kidney disease (CKD)) – Would you expect the proportion of people who experience IFALD and CKD to be linked to the number of days on PS? Is it reasonable to assume teduglutide would reduce IFALD and CKD? Are IFALD and CKD linked to an increased risk of mortality?	In my opinion the risk of (IFLD) and (CKD) is linked to the type and volume of Parenteral Nutrition and the number of hours, days and weeks a patient is infused with it.
Modelling of adverse events – Would you expect a diminishing adverse event rate over time for people having teduglutide? Would you expect the safety profile of teduglutide to be more favourable than standard of care in the long-term?	Not being a Clinical Expert, I can only surmise that as the biggest risks are removed for those eligible for treatment with teduglutide I would therefore expect diminishing adverse events over time.

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Health state costs (specialist visits for people who reached independence from PS and costs related to line sepsis) – 1) Would you expect people who have reached independence from PS to require gastroenterology (multi-professional) specialist visits? If so, how many visits per year would you expect be needed? 2) Would you expect the incidence of line sepsis to increase with an increase in the frequency of PS? Is there any data to inform correlation between the number of days on PS and the risk of sepsis?	If having reached independence from PS the patient will still need some level of monitoring. They will naturally still have a short Bowel unless they have had a transplant. The bowel may grow to some extent after prematurity but in general the percentage of bowel length will remain shorter than normal length - therefore patients will still need monitoring but perhaps on a reduced scale – possibly 6 monthly then yearly unless a specific problem occurs which cannot be dealt with by the GP.
Are there any important issues that have been missed in the ERG report?	Even when understanding ERG need for QUALY's it is also important to consider the quality of life issues for these families as well as the cost of the medication.

Patient expert statement

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Constant worry about the risk of line infection=sepsis, liver failure and loss of line sites leading to the need for transplants
- Living with SBS-IF is a constant round of pain, discomfort, tiredness/ lethargy from disturbed sleep impacting on the child's ability to focus in school and adults in work.
- Patients on PS/PN can be hooked up for 12ours at a time for up to 7 nights a week disrupting normal family life
- The benefits of exchanging PS for a simple subcutaneous injection to the day-to-day life for the patient and their care cannot be underestimated
- Without the huge amounts of clinical apparatus and materials needed for PS a child's personal space can be more like a normal bedroom.

Thank you for your time.

Your privacy

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Teduglutide for treating short bowel syndrome [ID3937]

ERG critique of the company's response to technical engagement

Produced by Aberdeen HTA Group

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Contains [redacted]

In their response to the technical engagement report, the company addressed each of the issues raised in the ERG report and provided some revised economic analyses. This addendum to the ERG report provides a brief critique of the company response on each of the issues. It should be read in conjunction with the company's response document dated 9 December 2021.

1. Modelling of health state transitions (and the placebo response in STEPS)

This issue relates to the company's interpretation of the observed changes in PS requirement in the STEPS trial, that: 1) the reduction in PS observed in the placebo arm of STEPS[1] was a temporary artefact of the weaning algorithm applied, and would not be observed in routine practice for a SBS-IF population stable on parenteral support; and 2) the weaning algorithms applied in STEPS[1] and STEPS-2[2] lead to underestimation of the reduction in PS frequency that patients can expect and tolerate in the absence of weaning algorithms (See Company submission, Document B, B.2.6.1.4). Based on these arguments, the company applied the STEPS baseline PS requirement (days per week) over the time horizon in the SoC arm of the model, and pooled data from the teduglutide arm of STEPS with real-world observational data from the Australian patient support programme to model expected reductions in PS days in the teduglutide arm. The ERG found these arguments to be plausible given the nature of the condition, but remained concerned about the lack of control for the modelled teduglutide response. The ERG noted that further comments from clinical experts on the plausibility of the company's assumptions would be beneficial.

In their response to technical engagement, the company have reiterated their justification for the assumptions applied (see company response). They further note that, in STEPS, patients underwent 8 to 16 weeks of PS stabilisation and optimisation prior to randomisation, suggesting that the placebo arm response could not be due to further optimisation of care. They also argue that candidates for teduglutide treatment in England would also be stabilised and optimised on PS prior to starting treatment given the mandated standard of care and the indication for teduglutide (…"stable following period of intestinal adaptation").[3]

In light of these arguments, the company further suggest that the ERG's scenario of applying the placebo arm response in the SoC arm of the model, and carrying it forward for the duration, is clinically implausible. They argue that if spontaneous reductions in PS requirement are possible within the intensified environment of a clinical trial, or with maximum effort in routine practice, they are not sustainable over a patient's lifetime. Therefore, the company have provided a threshold analysis to establish how long the placebo effect in STEPS would have to be maintained in the SoC arm of the model, before the ICER for teduglutide rises above £30,000 per QALY.

The ERG acknowledges the company's arguments, and accepts their points relating to the implausibility of the ERGs conservative scenario. However, the ERG scenario was less about modelling plausible long-term reductions in PS in the SoC arm, and more about providing a degree of control for the reductions applied in the teduglutide arm. Of note, the

company use 12 months' worth of observational data for patients who received teduglutide in routine practice as part of the Australian PSP. The observed 12-month reductions in PS from this uncontrolled observational study feed into the modelled reductions in the teduglutide arm of the model, which are ultimately carried forwards indefinitely for those who remain on treatment. The ERG had concerns about the lack of a control group in the Australian PSP study, and potential for some of the observed benefit to also be unsustainable in the long-term. Therefore, the placebo arm response from STEPS was applied to the SoC arm of the model as a conservative control scenario. Ideally, the preferred way to address this uncertainty would have been to subtract the placebo arm response (or a proportion of it) from the teduglutide arm transition probabilities, but this is more complex to do with independently fitted transition matrices and would have yielded similar results.

Regardless, the ERG believes its scenario is overly conservative. However, the uncertainty is less about how long the placebo response in STEPS could be sustained for, and more about the extent to which mechanisms similar to those responsible for the placebo response in STEPS could also be partly responsible for reductions in PS that are estimated for teduglutide based on pooled STEPS, STEPS2 and Australian PSP data. The ERG is generally satisfied that the response observed in the teduglutide arm of STEPS and STEPS2 is sustainable and down to increased absorptive capacity of the gut as indicated by maintained fluid intake and weight, but is less sure about the PSP data where larger reductions were observed in the context of heavy censoring and no allowance for any potential reversal of PS reductions in the applied transitions probabilities. In this respect, removing the 12 months PSP data from the calculation of transition probabilities in teduglutide arm provides a conservative scenario for addressing this uncertainty.

It is worth noting that the single clinical expert response to technical engagement also concurred with the company's explanation for the PS reductions observed in the placebo arm of STEPS.

Related to the calculation of transition probabilities, the ERG queried whether patients who were assumed to have stopped treatment in line with the modelled 12 month stopping rule, had been removed from the pool for calculating transition probabilities beyond 12 months. In their response, the company acknowledged that they were not, and that this was an oversight resulting in unrealistic estimation of treatment effectiveness beyond month 12. They have therefore re-estimated the transition probabilities for months 12 to 30, using only data for those not meeting the 12-month stopping rule applied in the model. This reduces the ICER, and presumably reflects the fact that those who reduce their PS requirement by

12 months are more like to experience further reductions beyond 12 months compared to those who achieve no reduction by 12 months. The ERG believes that the revised approach is more in keeping with the proposed stopping rule, but notes that it does result in less data being available to inform the transitions beyond 12 months.

2. Health state utility by frequency of parenteral support.

The ERG acknowledged the company's source of utility data as the only available source to support the suggested inverse relationship between the number of PS days and health-related quality of life. The ERG further acknowledges that there is some data to support this relationship based on a measure designed specifically to capture the impact of HPN on a patient's ability to fulfil their human needs.[4-5] However, the ERG has concerns regarding potential for the company's vignette-based study to overstate the relationship between a reduction in PN days and improvements in health state utility, and also note the lack of comparability of the derived disease specific utility values with those applied in other technology appraisals. Therefore, the ERG conducted some scenarios to assess the impact of reducing the range in patient utility between 'PS independence' (PS0) and 'PS 7 days per week' (PS7) by 10% and 20%. The company have explored this further using their revised model base case, and note that the range can actually be reduced by 100% (i.e. to zero) and the ICER still falls below £30,000 per QALY in adults, and remains dominant in the paediatric population. In these scenarios the modelled utility gains for carers deliver large enough QALY gains to keep the ICER favourable.

The ERG also expressed uncertainty about the modelled relationship between number of PS days and carer disutility, as this was informed primarily based on clinical expert estimates rather than data collected using a validated instrument. The

[redacted]

. The company have further addressed this uncertainty in the technical engagement response by reducing the range in caregiver disutility between high PS use (PS6-7 days) and PS independence (PS0). They note that the range can also be reduced by 100% and the ICER remains below £30,000 in adults and dominant in the paediatric population. These scenarios show that under the company's revised base case, either carer disutility or patient health state utility gains can be completely removed from the model, and the ICER remains favourable. However, the ERG agrees with the company that neither of these scenarios are particularly plausible, and would suggest scenarios that reduce the range in health state utility and carer disutility simultaneously would better characterise the joint uncertainty associated with the utility inputs in the model.

The clinical expert and patient expert responses received during technical engagement provide further insights that provide support for the company's position that a reduction in PN days can be expected to improve the health-related quality of life of both patients and carers – (see clinical and patient expert TE responses). However, the magnitude of the improvements on the health state utility scale remains an area of uncertainty.

3. Modelling of overall survival

The ERG was concerned that the company's log-normal extrapolation of overall survival resulted in the hazard of death falling below that of the age/sex matched general population while a sizable proportion of the cohort was still alive. Whilst this was overridden in the model by applying general population mortality from this point onwards, the ERG questioned if it was plausible for a proportion of patients with SBS-IF on long-term parenteral support to achieve mortality rates in line with the general population. To mitigate this, the ERG applied the more pessimistic exponential curve in its preferred base case.

The company have argued in their response that the exponential curve provides a poor fit to the observed hazard rate in the survival data used to inform the model,[6] which does suggest an initially increasing then decreasing hazard of death over time.

The ERG accepts the company's argument that the log-normal provides a better fit to the observed hazards in the data, but this does not validate the plausibility of the extrapolation. The ERG also acknowledges that the exponential still predicts that mortality drops below general population mortality (from year 31 as opposed to year 24), and does not fully overcome the issue.

It can be noted that the clinical expert response to technical engagement supported the idea that children who manage to wean off PS can expect to achieve normal survival outcomes. This would suggest that a survival benefit for teduglutide is plausible, and that those who remain on PS would continue to experience an excess morality risk compared to the general population. The omission of a potential survival benefit for teduglutide is conservative with respect to estimated QALY gains but may also underestimate the incremental cost.

Given the uncertainty relating to the potential for type 3 SBS-IF patients to achieve long-term survival in line with the general population, the ERG proposes some further scenarios whereby extrapolated mortality is not allowed to fall below general population mortality uplifted by fixed mortality ratios (1.2 through to 2). A similar approach is often applied in cancer appraisals where there is uncertainty surrounding the plausibility of a cure. The ERG

provides a further exploratory analysis whereby the mortality hazard of those who achieve PS independence in the teduglutide arm is reduced by increasing percentages (5% to 15%) compared to those who remain on PS.

4. Modelling of complications (Intestinal failure related liver disease and chronic kidney disease)

The ERG expressed concerns with respect to the company's approach to modelling serious long-term complications (CKD and IFALD) as a proportion of the surviving cohort, with no structural link to reflect the increased risks of morality in those affected by these complications.

In their response, the company further clarify that their approach was necessary because they used data on all-cause mortality which includes deaths from IFALD and CKD. Separately accounting for death in the proportion with IFLAD and CKD would therefore introduce double counting. They also note, based on advice from clinical experts, that deaths from IFALD and CKD in patients with SBS-IF are very rare and this is reflected in the data from Salazar et al. 2021.[6] Therefore, they argue that the bias is likely to be small. They note that the under their revised base case, the ICER is £13,943 when effectively removing these complications from the model. The ERG finds it useful that the company have provided this scenario as reassurance, and note that it is potentially less important in the context of the companies revised based case.

The clinical expert response also provided some further insight into the potential for teduglutide to provide a survival benefit compared to standard care, noting that by improving the ability to wean patients off PS, teduglutide would reduce the incidence of complications that can reduce life expectancy. They also note that patients who experience such complications may have their line removed and undergo intestinal transplant, which incurs high lifetime medical costs and a poorer survival outlook compared to someone who manages to wean off PS.

5. Modelling of adverse events

The ERG noted that the reduced adverse event rates applied for teduglutide after 6 months of treatment (based on data from the open label extension (STEPS-2)), resulted in an improved safety profile compared to standard care (informed by 6 months of safety data from the placebo arm of STEPS carried forwards). The ERG was concerned because there is no standard care safety data beyond 6 months to validate this effect, and it is a modest driver of cost-effectiveness. Further, the ERG felt that derivation of the applied event rates

had not been transparently presented in the company submission, and asked the company clarify their approach, and better justify their case that teduglutide has a more favourable safety profile compared to standard care in the longer term.

In their response the company have clarified their approach to calculating event rates, and the ERG are satisfied with this. They have also set out arguments which they believe justify the improved safety profile versus standards care (see company response). They note in particular that adverse events due to teduglutide treatment, and PS use, would be expected to reduce over time in the teduglutide arm, but not in the standard care arm. They further expect that some adverse events due to the underlying condition (SBS-IF) would also be expected to reduce in the teduglutide arm due to improvement in general wellbeing (e.g. increased muscle mass) as a result of treatment. Taken together, these arguments do illustrate a plausible mechanism for the modelled effect, as patients on teduglutide better tolerate it and reduce their PS requirements.

However, the counterfactual rate of adverse events for standard care beyond six months remains uncertain. It is possible, for example, that blinding influenced the frequency of adverse events in the placebo arm of STEPS through the mechanisms the company argue are responsible for the 'inappropriate' weaning that was observed. Thus, had comparative data been available for standard care following the 6-month blinded phase of STEPS, we might also have seen a reduction in adverse events.

Health state costs (specialist visits for people who reached independence from parenteral support and costs related to line sepsis)

The ERG queried the company's assumption that adult patients would have 3 gastroenterologist visits per year when receiving PS (4 for children receiving PS) and 0 visits per year when PS independent. The ERGs clinical advice suggested that all SBS-IF patients typically receive 3–4 clinic visits per years regardless of their PS requirements, and so the ERG applied this assumption in its base case. The company have accepted this change in their revised base case. However, the clinical expert response to technical engagement noted that patients who wean off PS no longer need the specialist intestinal failure rehabilitation service and can be followed up by a simpler gastroenterology nutrition service. This suggests that the follow-up resource intensity might be lower in those who wean off PS, even if follow-up frequency remains unchanged. The clinical expert also noted a further aspect of resource use in children which may not be included in the model; the need for admission to hospital for at least 48 hours whenever a child develops a fever (to treat it as a possible catheter related bloodstream infection (CRBSI), even if it is not). The model

includes only the cost of treating true CRBSI. Inclusion of hospitalisation costs for possible CRBSI would favour teduglutide. In this respect the health state costs could be considered conservative.

The ERG also queried whether it was reasonable to assume that line sepsis rates are correlated with the number of days of PS a patient requires per week. The company response focusses on the biological plausibility of this assumption, noting that infection can be introduced at the point of line insertion, and also during line use, and so it stands to reason that more days of PS per week will incur a higher infection risk. The ERG's clinical expert agreed with this assumption, as did the clinical expert who responded to technical engagement. However, clinical expert advice provided in the resource use study used to inform the model appeared to contradict this. The company noted that they could not identify literature that examined a connection between days per week of PS and the incidence of line sepsis. They suggest that most of the literature on line sepsis in PS reports the rate as a number of events 'per 1000 catheter days' (as opposed to 'per patient year'), which they say standardises the rate by the number of days per week a catheter is used for parenteral support. However, the ERGs understanding is that 'catheter days' is generally used to mean the number of days a patient has a central venous catheter inserted for access, and not the number of days it is used for parenteral support over a period of time. There are a few studies that appear to report rates using the actual number of PN days as the time at risk,[7] but then others define this denominator, or some variation of it, as time in days since a patient was initiated on parenteral nutrition (similar to catheter days). Ross et al., for example, using data from a US registry, counted PN days as the time patients were receiving HPN and followed in the Sustain registry.[8] In doing so, they were able to compare rates in patients receiving daily HPN to those receiving HPN fewer times per week, and noted no statistically significant difference. However, another study by Bozzetti et al. found a significant relationship between HPN days and the line sepsis rate based on data from 447 European patients commencing HPN between 1995 and 2000.[9] Another study by Buchman et al., supported an association between HPN frequency and CRBSI in children but not adults.[10] Thus, evidence to support or refute a relationship between PS frequency and line sepsis risk appears limited and provides mixed findings. Whilst the ERG supports the biological plausibility of a relationship, it may also be relevant to consider a scenario where the line sepsis risk is held constant across the PS health states (1-7 days) for the purpose of estimating expected health state costs.

Additional issue Ondansetron dosing

In response to a further query raised by the ERG, the company have confirmed their assumption around the dose of Ondansetron used by patients on PS. The ERG acknowledges and accepts this clarification.

ERG additional scenario analyses

In the following tables (1 and 2), the ERG provides some further scenario analysis as justified in the discussion above, around the company's revised base case. It can be noted that the ICER in the adults is most sensitive to applying a mortality benefit for those who achieve PS independence on teduglutide (scenarios 8-10), equalising adverse event rates between teduglutide and standard care beyond 6 months (scenarios 12 and 13), and simultaneously reducing the range in patient's utility and carer disutility between the PS7 and PS0 (or high and zero PS requirement) health states (scenarios 14-20). In the paediatric population, teduglutide remains dominant in all but one of the scenarios tested. Results using the confidential prices for components of parenteral support are provided in a separate confidential appendix.

Table 1. Additional ERG scenario analysis conducted upon the company base case post technical engagement – Adult population

#	Scenario	Incremental		ICER
		Cost	QALYs	
Company base case post technical engagement		[redacted]	[redacted]	**£9,691**
1	STEPS/STEPS-2 data only for health state transitions censored for 12-month stopping rule	[redacted]	[redacted]	£13,174
2	Exponential extrapolation of OS (Salazar 2021)	[redacted]	[redacted]	£12,918
3	No Complications (IFALD/Stage V CKD)	[redacted]	[redacted]	£13,943
4	10% increase in the annual risk of mortality compared to the general population	[redacted]	[redacted]	£9,794
5	20% increase in the annual risk of mortality compared to the general population	[redacted]	[redacted]	£9,898
6	50% increase in the annual risk of mortality compared to the general population	[redacted]	[redacted]	£10,198
7	100% increase in the annual risk of mortality compared to the general population	[redacted]	[redacted]	£10,679
8	PN independent patients HR of 0.95 against disease specific mortality	[redacted]	[redacted]	£17,178
9	PN independent patients HR of 0.90 against disease specific mortality	[redacted]	[redacted]	£24,379
10	PN independent patients HR of 0.85 against disease specific mortality	[redacted]	[redacted]	£31,318
11	Rate of sepsis equal to 0.44 for all patients receiving PN	[redacted]	[redacted]	£10,505
12	Equalise post 6-month adverse event rates to the teduglutide arm	[redacted]	[redacted]	£20,218
13	Equalise post 6-month adverse event rates to the standard care arm	[redacted]	[redacted]	£13,678
14	Reduction in range of health state utilities by 10% (patients and carers)	[redacted]	[redacted]	£10,676
15	Reduction in range of health state utilities by 20% (patients and carers)	[redacted]	[redacted]	£11,885
16	Reduction in range of health state utilities by 30% (patients and carers)	[redacted]	[redacted]	£13,402

17	Reduction in range of health state utilities by 70% (patients and carers)	[redacted]	[redacted]	£27,385
18	Reduction in range of health state utilities by 80% (patients and carers)	[redacted]	[redacted]	£37,049
19	Reduction in range of health state utilities by 90% (patients and carers)	[redacted]	[redacted]	£57,251
20	Reduction in range of health state utilities by 100% (patients and carers)	[redacted]	[redacted]	£125,910
21	Scenario 4 + Scenario 8	[redacted]	[redacted]	£17,215
22	Scenario 5 + Scenario 8	[redacted]	[redacted]	£17,267

Table 2. Additional ERG scenario analysis conducted upon the company base case post technical engagement – Paediatric population

#	Scenario	Incremental		ICER
		Cost	QALYs	
Company base case post technical engagement		[redacted]	[redacted]	**Dominates**
1	STEPS/STEPS-2 data only for health state transitions censored for 12-month stopping rule	[redacted]	[redacted]	Dominates
2	No Complications (IFALD/Stage V CKD)	[redacted]	[redacted]	Dominates
3	10% increase in the annual risk of mortality compared to the general population	[redacted]	[redacted]	Dominates
4	20% increase in the annual risk of mortality compared to the general population	[redacted]	[redacted]	Dominates
5	50% increase in the annual risk of mortality compared to the general population	[redacted]	[redacted]	Dominates
6	100% increase in the annual risk of mortality compared to the general population	[redacted]	[redacted]	Dominates
7	PN independent patients HR of 0.95 against disease specific mortality	[redacted]	[redacted]	Dominates
8	PN independent patients HR of 0.90 against disease specific mortality	[redacted]	[redacted]	Dominates
9	PN independent patients HR of 0.85 against disease specific mortality	[redacted]	[redacted]	£5,001
10	Rate of sepsis equal to 0.44 for all patients receiving PN	[redacted]	[redacted]	Dominates

11	Equalise post 6-month adverse event rates to the teduglutide arm	[redacted]	[redacted]	Dominates
12	Equalise post 6-month adverse event rates to the standard care arm	[redacted]	[redacted]	Dominates
13	Reduction in range of health state utilities by 10% (patients and carers)	[redacted]	[redacted]	Dominates
14	Reduction in range of health state utilities by 20% (patients and carers)	[redacted]	[redacted]	Dominates
15	Reduction in range of health state utilities by 30% (patients and carers)	[redacted]	[redacted]	Dominates
16	Reduction in range of health state utilities by 70% (patients and carers)	[redacted]	[redacted]	Dominates
17	Reduction in range of health state utilities by 80% (patients and carers)	[redacted]	[redacted]	Dominates
18	Reduction in range of health state utilities by 90% (patients and carers)	[redacted]	[redacted]	Dominates
19	Reduction in range of health state utilities by 100% (patients and carers)	[redacted]	[redacted]	Dominates
20	Scenario 3 + Scenario 7	[redacted]	[redacted]	Dominates
21	Scenario 4 + Scenario 7	[redacted]	[redacted]	Dominates

References

1. Jeppesen P, Pertkiewicz M, Messing B, Iyer K, Seidner D, O'Keefe S, et al. Teduglutide reduces need for parenteral support among patients with short bowel syndrome with intestinal failure. Gastroenterology. 2012;143(6):1473-81.
2. Schwartz LK, O'Keefe SJ, Fujioka K, Gabe SM, Lamprecht G, Pape UF, et al. Long-Term Teduglutide for the Treatment of Patients With Intestinal Failure Associated With Short Bowel Syndrome. Clin Transl Gastroenterol. 2016;7(2):e142.
3. EPAR Summary of Product Characteristics; Revestive | European Medicines Agency (europa.eu)
4. Wilburn J, McKenna SP, Heaney A, Rouse M, Taylor M, Culkin A, et al. Development and validation of the Parenteral Nutrition Impact Questionnaire (PNIQ), a patient-centric outcome measure for Home Parenteral Nutrition. Clin Nutr. 2018;37(3):978-83.
5. Burden ST, Jones DJ, Gittins M, Ablett J, Taylor M, Mountford C, et al. Needs-based quality of life in adults dependent on home parenteral nutrition. Clin Nutr. 2019;38(3):1433-8
6. Salazar E, Clermont-Dejean NM, Schwenger KJP, Noelting J, Lu Z, Lou W, et al. Patients With Severe Gastrointestinal Dysmotility Disorders Receiving Home Parenteral Nutrition Have Similar Survival As Those With Short-Bowel Syndrome: A Prospective Cohort Study. JPEN J Parenter Enteral Nutr. 2021;45(3):530-7
7. Dreesen M, Foulon V, Spriet I, Goossens GA, Hiele M, De Pourcq L, Willems L. Epidemiology of catheter-related infections in adult patients receiving home parenteral nutrition: a systematic review. Clin Nutr. 2013 Feb;32(1):16-26.
8. Ross VM, Guenter P, Corrigan ML, Kovacevich D, Winkler MF, Resnick HE, Norris TL, Robinson L, Steiger E. Central venous catheter infections in home parenteral nutrition patients: Outcomes from Sustain: American Society for Parenteral and Enteral Nutrition's National Patient Registry for Nutrition Care. Am J Infect Control. 2016 Dec 1;44(12):1462-1468.
9. Bozzetti F, Mariani L, Bertinet DB, Chiavenna G, Crose N, De Cicco M, Gigli G, Micklewright A, Moreno Villares JM, Orban A, Pertkiewicz M, Pironi L, Vilas MP, Prins F, Thul P. Central venous catheter complications in 447 patients on home parenteral nutrition: an analysis of over 100.000 catheter days. Clin Nutr. 2002 Dec;21(6):475-85.
10. Buchman AL, Opilla M, Kwasny M, Diamantidis TG, Okamoto R. Risk factors for the development of catheter-related bloodstream infections in patients receiving home parenteral nutrition. JPEN J Parenter Enteral Nutr. 2014 Aug;38(6):744-9.

Further questions from NICE

1. Does resource use related to delivering PS seem reasonable? - **yes**
2. Does resource use related to associated medication seem reasonable, considering:
   - Would all patients on PS receive all these classes of medications on a daily basis, and at the same dose/frequency regardless of frequency of PS needed**? Not in children. Doses would be adjusted according to age and weight. The medications would only be given if needed (please see comments in table)**
   - Would no patients who are PS-independent need any of these medications? **Some patients would need these medications when they first wean off PS, but would be expected to wean off after several weeks/months off PS**
   - Would PPIs and codeine phosphate be given exclusively by IV infusion? **If a patient is off PS they would be given orally/enterally**
   - Are daily doses correct? **Not applicable to children who have an age and weight adjusted dose**

Resource use related to PS delivery

Cost item	Units	No PS	PS1	PS2	PS3	PS4	PS5	PS6	PS7	Comments
PS bag (≥8 ingredients) band A	day/ week	0	1	2	3	4	5	6	7	
Delivery	delivery/ month	0	2	2	2	2	2	2	2	In children A small minority of patients will have weekly deliveries i.e. 4 per month
Nurse time (distinct from training costs)	hour/ week	0	0.8	1.6	2.4	3.2	4.0	4.8	5.6	In children - the nurse time would usually be formally trained parents - A few centres use nurses for some patients
Taurolock	day/ week	0	1	2	3	4	5	6	7	In children - Many centres would only use taurolock in children who have had catheter related bloodstream infections (CRBSI) i.e probably about 50% of cases

Associated medication

Cost item	Unit	No PS	PS1-7	Dose per unit (i.e. daily dose)	Comments
Proton pump inhibitors	day	0	1	omeprazole IV 40mg vial @80mg (2 vials) per day OR pantoprazole IV 40 mg vial @80mg (2 vials) per day Average cost of both drugs used in the model (implies expected equal use of 2 drugs in clinical practice)	In children: - A PPI would be used far less often in a patient weaned off PS. - The PPI would almost always be given iv in the patient on PS. It is used in about 50% of cases - The PPI would not be given iv, but orally/enterally when off PS - PPI treatment would eventually be stopped in most patients off PS
Antimotility agents	day	0	1	loperamide 2mg capsules and tablets, at dose of 32mg per day OR codeine phosphate 60mg/ml (ampule) at a dose of 240mg per day Average cost of 2 drugs used in the model (implies expected equal use of 2 drugs in clinical practice)	In children - Loperamide capsules or tablets would be used at lower doses according to body weight - Codeine would be avoided if at all possible (many centres do not use it at all) - Loperamide may be needed after PS is stopped in a minority of cases - In most cases loperamide is not used after the PS is stopped - Loperamide can often be stopped after several months (if needed after PN is stopped)
Fragmin	day	0	1	5,000units/day (0.2mL syringe)	In children - Only used if evidence of pulmonary emboli or if an underlying thrombotic condition
Ondansetron	day	0	1	16mg/day (2 * 8mg/4ml injections)	In children - Not normally required in SBS

1. Does resource use related to delivering PS seem reasonable? **YES**
2. Does resource use related to associated medication seem reasonable, considering:
   - Would all patients on PS receive all these classes of medications on a daily basis, and at the same dose/frequency regardless of frequency of PS needed? **NO – NOT ALL PATIENTS HAVE NURSING OR TAUROLOCK. DELIVERY FREQUENCY CAN VARY ALSO ACCORDING TO STABILITY**
   - Would no patients who are PS-independent need any of these medications? **NOT SURE I UNDERSTAND THE QUESTION. PS INDEPENDENT PATIENTS CAN STILL NEED THE MEDICATIONS**
   - Would PPIs and codeine phosphate be given exclusively by IV infusion? **NO, PPIs CAN BE ORAL OR IV, CODEINE PHOSPHATE IS ORAL**
   - Are daily doses correct? **I DO NOT THINK THAT FRAGMIN SHOULD BE INCLUDED IN THIS, DOSES ARE OTHERWISE CORRECT (ALTHOUGH THESE ARE MAXIMUM DOSES AND LOWER DOSES ARE OFTEN USED)**

Resource use related to PS delivery

Cost item	Units	No PS	PS1	PS2	PS3	PS4	PS5	PS6	PS7	Comments
PS bag (≥8 ingredients) band A	day/ week	0	1	2	3	4	5	6	7	
Delivery	delivery/ month	0	2	2	2	2	2	2	2	
Nurse time (distinct from training costs)	hour/ week	0	0.8	1.6	2.4	3.2	4.0	4.8	5.6	
Taurolock	day/ week	0	1	2	3	4	5	6	7	

Associated medication

Cost item	Unit	No PS	PS1-7	Dose per unit (i.e. daily dose)	Comments
Proton pump inhibitors	day	0	1	omeprazole IV 40mg vial @80mg (2 vials) per day OR pantoprazole IV 40 mg vial @80mg (2 vials) per day Average cost of both drugs used in the model (implies expected equal use of 2 drugs in clinical practice)	
Antimotility agents	day	0	1	loperamide 2mg capsules and tablets, at dose of 32mg per day OR codeine phosphate 60mg/ml (ampule) at a dose of 240mg per day	

				Average cost of 2 drugs used in the model (implies expected equal use of 2 drugs in clinical practice)	
Fragmin	day	0	1	5,000units/day (0.2mL syringe)	
Ondansetron	day	0	1	16mg/day (2 * 8mg/4ml injections)	

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Teduglutide for treating short bowel syndrome [ID3937]

Addendum to the ERG response to technical engagement

Produced by Aberdeen HTA group

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1 Overview

This document updates the ERG preferred base case and all analyses conducted as part of the ERG response to technical engagement document. This document also provides further scenarios which explore the uncertainty surrounding the company's assumptions for concomitant medication for home Parenteral Nutrition (PN).

The unit costs of concomitant medications reported by the company in table 40, page 128 of the original submission lack transparency in terms of their dosage, preparation, and administration. Therefore, the ERG and NICE have sought additional clinical consultation. The consultation finds that several of the assumptions indicated by the unit costs used by the company are not representative of clinical practice for home PN patients in England. Table 1 summarises the assumptions for both populations that are consistent with the costs of concomitant medications applied in the company submission.

Table 1. Concomitant medication assumptions used in the company base case

Medications	Preparation	Dose per day	PN independent patients receive?	Cost per day
PPIs	IV	80mg	No	£9.70
Antimotility agents				£11.68
Loperamide	Oral	32mg	No	
Codeine phosphate	IV	240mg	No	
Fragmin (dalteparin)	Syringe	5000 units	No	£2.82
Ondansetron	IV	16mg	No	£23.98

Clinical advice was sourced for both populations in the model. The ERG clinical expert, who works with adult patients, advocated for the use of these high doses for oral preparations as absorption in this patient population is compromised. The ERG clinical expert was supportive of the use of daily fragmin. The paediatric clinical expert provided insights which suggest that paediatric patients would be managed differently to adults in standard care. The clinical expert supported the use of IV preparations for

PPIs in children, however, suggested that the medication would only be given in 50% of cases and age and weight adjusted doses would be given. Furthermore, the use of antimotility agents would be restricted to the use of loperamide at an age and weight adjusted dose. For simplicity, we assume half the adult daily doses (40mg for PPIs and 16mg for loperamide) in the ERG preferred base case. The clinical expert does not support the use of codeine phosphate, fragmin or ondansetron in children. Analyses using paediatric specific costs revert to adult costs from age 18 in the model.

Therefore, the ERG has recalculated the daily unit cost of PPIs, antimotility agents and ondansetron as oral preparations, as indicated in table 2, 3 and 4 below for adults. For adults, the ERG calculated the average cost per day of tablets and capsules across each of the drugs. Additionally, given there are multiple PPIs available in the oral preparation, the average was taken across omeprazole, pantoprazole, esomeprazole and rabeprazole to generate the cost per day based on an 80mg dose. The use of capsules or tablets leads to a substantial reduction in the daily cost of PPIs, antimotility agents and ondansetron. The updated cost per day of concomitant medications is found within table 2, 3 and 4, these assume the daily dosages described within table 1. The BNF drug tariff prices are used, these assumes the medications are provided through primary care. A scenario using secondary care prices using the eMIT database is provided in scenario analysis. The eMIT average prices are provided within the appendix of this document. The summary of the ERG preferred assumptions is provided in table 4 and 5.

Table 2. Updated BNF unit costs of proton pump inhibitors (PPIs) and daily costs assuming adult doses

Drug	BNF					Average cost per day	
	Preparation	Pack size	mg	Drug tariff	Cost per day	Tablets /Capsules	Oral/ IV
Omeprazole	Capsule	7	40	£0.80	£0.23	£1.03	£0.41
Omeprazole	Tablet	7	40	£6.41	£1.83		
Pantoprazole	Tablet	28	40	£1.56	£0.11	£0.11	
Esomeprazole	Capsule	28	40	£2.95	£0.21	£0.27	
Esomeprazole	Tablet	28	40	£4.51	£0.32		
Rabeprazole sodium	Tablet	28	20	£1.62	£0.23	£0.23	
Omeprazole*	Powder solution for injection	5	40	£26.00	£10.40		£9.70

Pantoprazole*	Powder solution for injection	5	40	£22.50	£9.00		

*Paediatric analyses use IV PPIs but at half the adult daily dose

Table 3. Updated BNF unit costs of antimotility agents and daily costs assuming adult doses.

Drug	BNF					Average
	Preparation	Pack size	mg	Drug tariff	Cost per day	Tablets /Capsules
Loperamide*	Capsule	30	2	£1.32	£0.70	£0.92
Loperamide*	Tablet	30	2	£2.12	£1.13	
Codeine phosphate	Tablets	28	60	£2.03	£0.29	
Codeine phosphate	Solution for injection ampoules	10	60	£27.20	£10.88	
			Cost per day with oral codeine			£1.21
			Cost per day with IV codeine			£11.80

*Paediatric analyses use loperamide at half the adult daily dose

Table 4. Updated BNF unit costs of ondansetron and daily costs assuming 16mg per day

Drug	BNF					Average cost per day
	Preparation	Pack size	mg	Drug tariff	Cost per day	
Ondansetron	Tablet	10	4	£0.95	£0.38	£0.35
Ondansetron	Tablet	10	8	£1.55	£0.31	
Ondansetron	Solution for injection ampoules	5	8	£59.95	£23.98	£23.98

Additional scenarios were explored to account for additional advice provided by clinical experts regarding medication for PN independent patients. PN independent patients are assumed to no longer require the use of PPIs or antimotility agents in the model. However, the ERG clinical expert is skeptical of this assumption as these medications are used to manage the symptoms of living with SBS-IF. Therefore, scenarios where 25%, 50% and 75% of PN independent patients continue to use these medications are explored.

The paediatric clinical expert provided further insights which are explored through scenario analysis. Taurolock is assumed to be equal to the days of PN in the company model. The clinical expert advises that, in children, taurolock is used in those who have had catheter related bloodstream infections and estimates this to be approximately 50% of cases. Furthermore, the majority of parents are typically

trained in the administration of PN. Therefore, we also explore the scenario where home nurse time is removed from the paediatric analysis.

Finally, the ERG clinical expert finds that the dosages used in the company model are the maximum possible dosages for adults. Therefore, we explore the lower dose of 40mg per day of PPIs, 180mg per day of codeine phosphate and 12mg per day of ondansetron in scenario analysis. We also explore the use of the oral preparation of ondansetron in the model instead of the use of IV. The ERG clinical expert does not support the regular use of ondansetron, nor do they see its regular use in their practice. Therefore, we include a scenario where the daily use of ondansetron is removed from the adult model.

2 ERG preferred base case

The ERG has updated its preferred base case to incorporate the alternative pricing of PPIs and antimotility agents to account for the oral preparations of these medications. The ERG preferred base case ICER is £18,421 for the adult population. Teduglutide is found to dominate standard care in the paediatric population. Table 4 and 5 show the resulting cumulative ICER of these changes.

Table 5. ERG preferred base case assumptions – adult population

#	Scenario	Incremental		Cumulative ICER
		Cost	QALYs	
Company base case post technical engagement		[redacted]	[redacted]	**£9,691**
1	PPIs costed as oral preparations (80mg per day)	[redacted]	[redacted]	£13,742
2	Antimotility agents costed as oral preparations	[redacted]	[redacted]	£18,421
ERG preferred base case post technical engagement		[redacted]	[redacted]	**£18,421**

Table 6. ERG preferred base case assumptions – paediatric population

#	Scenario	Incremental		Cumulative ICER
		Cost	QALYs	
Company base case post technical engagement		[redacted]	[redacted]	**Dominates**

1	ERG preferred adult dosing assumptions applied from age 18	[redacted]	[redacted]	Dominates
2	50% paediatric patients receive PPIs IV	[redacted]	[redacted]	Dominates
3	40mg per day of PPIs for paediatric patients	[redacted]	[redacted]	Dominates
4	16mg per day of loperamide (half adult dose) for paediatric patients	[redacted]	[redacted]	Dominates
5	Removal of codeine phosphate for paediatric patients	[redacted]	[redacted]	Dominates
6	Removal of fragmin for paediatric patients	[redacted]	[redacted]	Dominates
7	Removal of ondansetron for paediatric patients	[redacted]	[redacted]	Dominates
ERG preferred base case post technical engagement		[redacted]	[redacted]	**Dominates**

3 Scenario analyses

The results of the scenario analysis from the ERG technical engagement response document to account for the ERG preferred base case assumptions around concomitant medications are provided in tables 7 and 8 below. Table 9 and 10 display the results of the additional scenarios described within section 1 of this document. For adults, the removal of daily ondansetron treatment has the greatest impact on the ICER (£29,015). In paediatric patients, the removal of home nurse requirements results in an ICER of £17,311, a substantial increase from dominance in the ERG base case.

Table 7. ERG scenario analyses – adult population (reproduced from table 1 of the ERG critique of company's response to technical engagement document)

#	Scenario	Incremental		ICER
		Cost	QALYs	
ERG preferred base case post technical engagement		[redacted]	[redacted]	**£18,421**
1	STEPS/STEPS-2 data only for health state transitions censored for 12-month stopping rule	[redacted]	[redacted]	£21,736
2	Exponential extrapolation of OS (Salazar 2021)	[redacted]	[redacted]	£21,594
3	No Complications (IFALD/Stage V CKD)	[redacted]	[redacted]	£22,797
4	10% increase in the annual risk of mortality compared to the general population	[redacted]	[redacted]	£18,523
5	20% increase in the annual risk of mortality compared to the general population	[redacted]	[redacted]	£18,625

6	50% increase in the annual risk of mortality compared to the general population	[redacted]	[redacted]	£18,921
7	100% increase in the annual risk of mortality compared to the general population	[redacted]	[redacted]	£19,396
8	PN independent patients HR of 0.95 against disease specific mortality	[redacted]	[redacted]	£25,223
9	PN independent patients HR of 0.90 against disease specific mortality	[redacted]	[redacted]	£31,766
10	PN independent patients HR of 0.85 against disease specific mortality	[redacted]	[redacted]	£38,071
11	Rate of sepsis equal to 0.44 for all patients receiving PN	[redacted]	[redacted]	£19,235
12	Equalise post 6-month adverse event rates to the standard care arm	[redacted]	[redacted]	£22,819
13	Equalise post 6-month adverse event rates to pre 6-month rates in the teduglutide arm	[redacted]	[redacted]	£29,534
14	Reduction in range of health state utilities by 10% (patients and carers)	[redacted]	[redacted]	£20,294
15	Reduction in range of health state utilities by 20% (patients and carers)	[redacted]	[redacted]	£22,592
16	Reduction in range of health state utilities by 30% (patients and carers)	[redacted]	[redacted]	£25,475
17	Reduction in range of health state utilities by 70% (patients and carers)	[redacted]	[redacted]	£52,055
18	Reduction in range of health state utilities by 80% (patients and carers)	[redacted]	[redacted]	£70,424
19	Reduction in range of health state utilities by 90% (patients and carers)	[redacted]	[redacted]	£108,826
20	Reduction in range of health state utilities by 100% (patients and carers)	[redacted]	[redacted]	£239,336
21	Scenario 4 + Scenario 8	[redacted]	[redacted]	£25,265
22	Scenario 5 + Scenario 8	[redacted]	[redacted]	£25,320

Table 8. ERG scenario analyses – paediatric population (reproduced from table 2 of the ERG critique of company's response to technical engagement document)

#	Scenario	Incremental	ICER

		Cost	QALYs	
ERG preferred base case		[redacted]	[redacted]	**Dominates**
1	STEPS/STEPS-2 data only for health state transitions censored for 12-month stopping rule	[redacted]	[redacted]	£1,616
2	No Complications (IFALD/Stage V CKD)	[redacted]	[redacted]	£4,176
3	10% increase in the annual risk of mortality compared to the general population	[redacted]	[redacted]	Dominates
4	20% increase in the annual risk of mortality compared to the general population	[redacted]	[redacted]	Dominates
5	50% increase in the annual risk of mortality compared to the general population	[redacted]	[redacted]	Dominates
6	100% increase in the annual risk of mortality compared to the general population	[redacted]	[redacted]	Dominates
7	PN independent patients HR of 0.95 against disease specific mortality	[redacted]	[redacted]	£4,765
8	PN independent patients HR of 0.90 against disease specific mortality	[redacted]	[redacted]	£10,150
9	PN independent patients HR of 0.85 against disease specific mortality	[redacted]	[redacted]	£15,470
10	Rate of sepsis equal to 0.44 for all patients receiving PN	[redacted]	[redacted]	Dominates
11	Equalise post 6-month adverse event rates to the standard care arm	[redacted]	[redacted]	£2,285
12	Equalise post 6-month adverse event rates to pre 6-month rates in the teduglutide arm	[redacted]	[redacted]	£7,639
13	Reduction in range of health state utilities by 10% (patients and carers)	[redacted]	[redacted]	Dominates
14	Reduction in range of health state utilities by 20% (patients and carers)	[redacted]	[redacted]	Dominates
15	Reduction in range of health state utilities by 30% (patients and carers)	[redacted]	[redacted]	Dominates
16	Reduction in range of health state utilities by 70% (patients and carers)	[redacted]	[redacted]	Dominates
17	Reduction in range of health state utilities by 80% (patients and carers)	[redacted]	[redacted]	Dominates

18	Reduction in range of health state utilities by 90% (patients and carers)	[redacted]	[redacted]	Dominates
19	Reduction in range of health state utilities by 100% (patients and carers)	[redacted]	[redacted]	Dominates
20	Scenario 4 + Scenario 8	[redacted]	[redacted]	£4,764
21	Scenario 5 + Scenario 8	[redacted]	[redacted]	£4,764

Table 9. Additional ERG scenario analyses – adult population

#	Scenario	Incremental		ICER
		Cost	QALYs	
ERG preferred base case post technical engagement		[redacted]	[redacted]	**£18,421**
Using eMIT prices for PPIs and antimotility agents		[redacted]	[redacted]	£18,833
Using eMIT prices for PPIs, antimotility agents and ondansetron		[redacted]	[redacted]	£29,196
1	50% of patients receive taurolock	[redacted]	[redacted]	£20,966
2	40mg per day of PPIs	[redacted]	[redacted]	£18,512
3	80mg PPIs as IV preparation	[redacted]	[redacted]	£14,317
4	25% of PN independent patients continue to receive PPIs and antimotility agents	[redacted]	[redacted]	£18,600
5	50% of PN independent patients continue to receive PPIs and antimotility agents	[redacted]	[redacted]	£18,778
6	75% of PN independent patients continue to receive PPIs and antimotility agents	[redacted]	[redacted]	£18,957
7	180mg oral codeine phosphate	[redacted]	[redacted]	£18,453
8	Removal of ondansetron	[redacted]	[redacted]	£29,015
9	12mg per day of ondansetron (IV)	[redacted]	[redacted]	£21,070
10	Ondansetron as oral preparation (16mg per day)	[redacted]	[redacted]	£28,863

Table 10. Additional ERG scenario analyses – paediatric population

#	Scenario	Incremental		ICER
		Cost	QALYs	
ERG preferred base case post technical engagement		[redacted]	[redacted]	**Dominates**
Using eMIT prices for PPIs and antimotility agents		[redacted]	[redacted]	3.91
Using eMIT prices for PPIs, antimotility agents and ondansetron		[redacted]	[redacted]	£5,073

1	Removal of home nurse requirements for home PN for paediatric patients	[redacted]	[redacted]	£17,735
2	80mg per day of PPIs (IV) for paediatric patients	[redacted]	[redacted]	Dominates
3	50% patients receive taurolock for paediatric patients	[redacted]	[redacted]	£360
4	25% of PN independent patients continue to receive PPIs and antimotility agents	[redacted]	[redacted]	Dominates
5	50% of PN independent patients continue to receive PPIs and antimotility agents	[redacted]	[redacted]	Dominates
6	75% of PN independent patients continue to receive PPIs and antimotility agents	[redacted]	[redacted]	£277

Appendix

Table A1. Updated eMIT unit costs of proton pump inhibitors (PPIs) and daily costs assuming adult doses

Drug	eMIT					Average
	Preparation	Pack size	mg	Average price	Cost per day	
Omeprazole	Capsules	28	40	£0.11	£0.01	£0.10
Pantoprazole	Tablets	28	20	£0.82	£0.12	
Esomeprazole	Capsules	28	40	£2.29	£0.16	
Rabeprazole sodium	Tablets	28	20	£0.90	£0.13	
Omeprazole*	Powder solution for injection	5	40	£5.48	£2.19	£2.10
Pantoprazole*	Powder solution for injectiom	5	40	£5.02	£2.01	

*Paediatric analyses use IV PPIs but at half the adult daily dose

Table A2. Updated eMIT unit costs of antimotility agents and daily costs assuming adult doses.

Drug	eMIT				
	Preparation	Pack size	mg	Average price	Cost per day
Loperamide*	Capsules	30	2	£0.83	£0.44
Codeine phosphate	Tablets	28	60	£0.97	£0.14
Codeine phosphate	Solution for injection ampoules	10	60	£24.87	£9.95
		Cost per day with oral codeine			£0.58

Cost per day with IV codeine	£10.39

*Paediatric analyses use loperamide at half the adult daily dose

Table A3. Updated eMIT unit costs of ondansetron and daily costs assuming 16mg per day

Drug	eMIT					Average cost per day
	Preparation	Pack size	mg	Average cost	Cost per day	
Ondansetron	Tablet	30	4	£0.95	£0.13	£0.16
Ondansetron	Tablet	10	8	£0.93	£0.19	
Ondansetron	Solution for injection ampoules	5	8	£1.31	£0.52	£0.52