NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Teduglutide for treating short bowel syndrome [ID3937]

Committee Papers

NICE National Institute for Health and Care Excellence

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:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Comments on the Appraisal Consultation Document** from Takeda

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   a. Patients On Intravenous & Nasogastric Nutrition Therapy (PINNT)

4. **Comments on the Appraisal Consultation Document from experts:**
   a. Dr Simon Gabe, Consultant in Gastroenterology & Intestinal Rehabilitation, clinical expert nominated by
   Dr Susan Hill, Paediatric Gastroenterology Consultant, clinical expert nominated by Takeda

5. **Comments on the Appraisal Consultation Document received through the NICE website**

6. **Evidence Review Group critique of company comments on the ACD**

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

Teduglutide for treating short bowel syndrome [ID3937]

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE 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 submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Company	Takeda	**Summary of response** We, as Takeda, are grateful for the time and effort dedicated to this appraisal. We are pleased to see the proposal to recommend teduglutide for initiation in children with SBS-IF, but are disappointed that adults with SBS-IF are not yet guaranteed access. We hope that our response can address the committee's remaining uncertainty sufficiently to enable access for the full licensed population. We have taken on board all the committee's feedback from the previous appraisal meeting, and have updated our model to produce a new base case ICER. The new base case has three differences compared to the previous base case: • Updated assumptions on co-medication use. These now reflect the committee's preferred assumptions (described in comment 3) • Updated PS costs • Updated PAS discount, [redacted] The revised base case ICER is £24,718 per QALY; further detail with regards this are provided in comment 2 below. To address additional uncertainties noted by the committee in section 3.22 of the Appraisal Consultation Document (ACD), we have provided further clarification for our interpretation of the results from STEPS (comment 4) and provided justification for the number of carers assumed per adult patient (comment 6). We have also, at the committee's request, explored the impact of reducing the starting age in the adult model (comment 5). Lastly, we have highlighted our equity concerns with the present decision in comment 7 and the ability of teduglutide to help address inequality in current access to PS. In short, we believe that making teduglutide only available for initiation in children and not adults is not equitable, and compounds upon significant inequity that patients with SBS-IF already face. We would also like to re-iterate that SBS-IF is an ultra-rare condition, and given such rarity it is likely that uncertainty will remain, despite our best efforts to address this. We note that the new NICE methods guide (The Manual, 2022) makes specific allowance for greater uncertainty in the case of rare diseases. We ask that the committee be mindful of this in their decision making.	Thank you for your comment. The committee considered it during their decision making. Teduglutide is now recommended in both children and adults with SBS.

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
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Please respond to each comment</th></tr>
<tr><td>2</td><td>Company</td><td>Takeda</td><td>
Revised base case

Taking on board the committee's feedback, we have produced a new base case ICER. The updated base case has three differences from our previous base case:
• Updated assumptions on co-medication use. These now reflect the committee's preferred assumptions, described in full in comment 3
• Updated PS costs. We hope that this new estimate better reflects the true mean cost of PS. However, as the actual costs are confidential to the NHS and we do not know the breakdown of the component parts, these costs are still an estimate:
o Previous assumed total average PS cost was [redacted], constituting:
o PS bags: [redacted]
o Delivery: [redacted]
o Nurse time: [redacted]
o Taurolock: [redacted]
o New assumed total average PS cost is [redacted], constituting:
o PS bags: [redacted]
o Delivery: [redacted]
o Nurse time: [redacted]
o Taurolock: [redacted] (reflects 50% usage as specified in the first committee meeting, see also comment 3)
• Updated PAS discount, [redacted]

The ICER for our updated base case is £24,718 per QALY, and further detailed in Table 1 below:

Table 1: Results for new base case
<table>
<tr><th>Option</th><th>Total costs</th><th>Total QALYs</th><th>Incremental costs</th><th>Incremental QALYs</th><th>ICER</th></tr>
<tr><td>Teduglutide</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td><td>£24,718</td></tr>
<tr><td>Standard care</td><td>[redacted]</td><td>[redacted]</td><td></td><td></td><td></td></tr>
<tr><td colspan="6">Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year</td></tr>
</table>
In addition, we have provided a range of scenario analyses to help the committee further explore the uncertainty associated with this new base case. These are outlined in Table 2 below:

Table 2: Scenario analyses for updated base case
<table>
<tr><th>Model component</th><th>Base case</th><th>Scenario</th><th>ICER</th></tr>
<tr><td colspan="3">Base case</td><td>£24,718</td></tr>
<tr><td>Transitions in standard care arm</td><td>No effect for standard care</td><td>Six month of transitions based on STEPS placebo data</td><td>£25,617</td></tr>
<tr><td>Co-medications</td><td>Committee-preferred assumptions from first meeting</td><td>Zero comedications</td><td>£26,323</td></tr>
</table>
</td><td>Thank you for providing this updated analysis as requested by the Committee. It was helpful in aiding their decision making. Conclusions relating to the cost-effectiveness of teduglutide can be found in section 3.23 of the FAD. Teduglutide is now recommended in both children and adults with SBS.</td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment

PS costs	[redacted] total	- 20%	£48,221
PS costs	[redacted] total	-10%	£36,469
PS costs	[redacted] total	+10%	£12,966
PS costs	[redacted] total	+20%	£1,215
Carers per adult	1	0.8	£26,228
Data source	STEPS/STEPS-2 + PSP (for first 12 months)	STEPS/STEPS-2 only	£29,578
Starting age	Age 50 with survival based on Salazar et al.	Age 45 with survival based on Salazar et al.	£23,728
Starting age & adjustment to survival	Age 50 with survival based on Salazar et al.	Age 45 with general population mortality rates until age 50, followed by Salazar et al. thereafter.	£19,694
Starting age	Age 50 with survival based on Salazar et al.	Age 40 with survival based on Salazar et al.	£22,954
Starting age & adjustment to survival	Age 50 with survival based on Salazar et al.	Age 40 with general population mortality rates until age 50, followed by Salazar et al. thereafter.	£16,234
Abbreviations: ICER, incremental cost-effectiveness ratio			

We would like to highlight that there are a number of benefits of teduglutide treatment in adults that are not captured in this base case:

- **Avoidance of intestinal transplant:** intestinal transplant is a critical, life-saving surgery for both adults and children with SBS-IF who lose line access for PS or have intestinal failure-associated liver disease (IFALD) evolving to liver failure[1]. However, it is a procedure that is costly, risky and represents a lifelong burden for patients. Due to the risks involved and limited supply of organs, it is therefore a procedure of last resort. Of particular note:
    - While mortality and patient quality of life have improved in recent years, graft rejection remains a significant and unpredictable concern; it has been described as '*insidious and subclinical until a late stage*'[2]. The prospect of graft rejection is likely to be a constant psychological burden on patients who have received a transplant. Patients who have undergone intestinal transplant have a high incidence of psychosocial problems[2].
    - As acknowledged in the ACD, it is likely that teduglutide will reduce the likelihood of patients needing intestinal transplant. By allowing patients to reduce PS, teduglutide reduces the likelihood of occluded catheter access, and reduces the incidence of IFALD – both complications that may result in intestinal transplant. However, this benefit to both adults and children with SBS-IF is not captured by our model
- **Reduction of PS volume but not days:** our model only attributes utility gain when patients reduce a day per week of PS. Patients who reduce their weekly PS volume, but not days, are assumed to

The committee discussed the additional benefits of teduglutide that are not captured in the cost-effectiveness analysis (see section 3.24 of the FAD).

<table>
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<tr><td></td><td></td><td></td><td>receive no benefit. This is not likely to be the case. Patients typically receive PS for 10–14 hours; as such, whilst PS is usually referred to as being given ‘overnight’, the reality is that being ‘hooked up’ to PS immobilises patients from early evening, overnight and into the morning[3]. Patients who can reduce the number of hours per night they receive PS have more flexibility: they can opt to have more hours of less disturbed sleep, or more time in the evening or morning for usual activities. These options improve quality of life but are not captured within our model.
• Service pressure: PS delivery within the NHS is currently under serious pressure; supply is constrained globally and this will not likely be resolved soon[4]. This is not simply a result of global supply crises following COVID-19, the supply of PS was designated an ‘emergency incident at the highest level’ in August 2019[5]. Whilst action has been taken to try to improve the situation, scarcity of compounded PS remains. Consequently, there are patients receiving more expensive multi-chamber bags with additional infusions, sub-optimal formulations of PS or not receiving PS at all – there is at least one patient currently unable to be discharged from hospital as they cannot access PS at home.
o By enabling patients to reduce their PS requirements and even to gain independence from PS, teduglutide will ease the pressure on PS supply. This will allow more patients who need compounded PS to receive it, and ultimately relieve pressure on hospital beds.</td><td></td></tr>
<tr><td>3</td><td>Company</td><td>Takeda</td><td>Co-medication costs

In line with the committee’s preferred assumptions, we have adjusted the use of co-medications in our model as described in Table 3.

To simplify the changes made, we have only altered the costs of co-medications rather than figures relating to usage (e.g. if feedback was that 50% of patients receive a given medicine and we had previously assumed 100%, we have reduced the price of that medicine to 50% of the original).

Table 3: Adjustments to co-medications in revised adult base case
<table>
<tr><th></th><th>Feedback</th><th>Original cost per unit</th><th>New cost per unit</th><th>Rationale</th></tr>
<tr><td>Taurolock</td><td>We had assumed all patients receive 1x taurolock per day of PS. Feedback was that 50% of patients receive taurolock</td><td>£10.00</td><td>£5.00</td><td>New cost = 10.00*0.5</td></tr>
<tr><td>Proton pump inhibitors</td><td>We had assumed all patients would receive IV proton pump inhibitors. Feedback was that only 20% of patients receive them IV, and 80% receive them orally</td><td>£9.70</td><td>£2.27</td><td>New cost = (9.70*0.2) + (0.41*0.8). Cost of oral proton pump inhibitors taken from the ERG addendum</td></tr>
<tr><td>Antimotility agents</td><td>We had assumed that all patients receive IV antimotility agents.</td><td>£11.80</td><td>£1.21</td><td>Cost of oral antimotility agents taken from the</td></tr>
</table></td><td>Thank you for updating this analysis as requested by the Committee. It was helpful in aiding their decision making. Conclusions relating to concomitant medication use can be found in section 3.21 of the FAD.</td></tr>
</table>

<table>
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<tr><td></td><td></td><td></td><td>
<table>
<tr><td></td><td>Feedback was that patients receive antimotility agents orally</td><td></td><td></td><td>ERG addendum</td></tr>
<tr><td>Fragmin</td><td>We had assumed that all patients receive fragmin; feedback was that 5% of patients receive fragmin</td><td>£2.82</td><td>£0.14</td><td>New cost = 2.82*0.05</td></tr>
<tr><td>Ondansetron</td><td>We had assumed that all patients receive ondansetron IV. Feedback was that 5% of patients receive ondansetron and they receive it orally</td><td>£23.98</td><td>£0.02</td><td>New cost = 0.35*0.05. Cost of oral ondansetron taken from the ERG addendum</td></tr>
<tr><td colspan="5">Abbreviations: ERG, evidence review group; IV, intravenous; PS, parenteral support</td></tr>
</table>

Combined with the changes to PS costs and PAS in our revised base case, this gives a new ICER of £24,718 per QALY. We have also provided a scenario where we have assumed zero co-medication costs. While conservative and implausible, we believe that this gives a clear idea of the upper bound of uncertainty. This scenario has an ICER of £26,323 per QALY, still comfortably within the bounds of cost-effectiveness.

We believe that the co-medication costs and use outlined in Table 3 above are plausible, but may lean towards being conservative:
• It is likely that use of teduglutide will reduce the use of co-medications relative to standard care, something we have not currently modelled and which would reduce our ICER. The teduglutide SmPC notes that 'there is potential for increased absorption of concomitant medicinal products'[6]. The STEPS study report further elaborates that 'Based on the mechanism of action, teduglutide could potentially increase absorption of orally administered drugs (e.g., motility medication, coumadin, psychotropics, metronidazole, digoxin), so consideration was given to modifying oral concomitant medication regimens'[7]. As a result of increased intestinal absorption, patients receiving teduglutide may have their oral dose of co-medications reduced, or may be able to switch from IV formulations to oral. Modelling these would reduce our ICER.
• Glucagon-like peptide 2 (GLP-2) inhibits gastric acid secretion[8], and teduglutide (as an analogue of GLP-2) has a similar effect[6, 9]. Proton pump inhibitors are prescribed to reduce gastric acid output[10], and so patients receiving teduglutide may have reduced need for proton pump inhibitors. Again, modelling lower proton pump inhibitor use in patients receiving teduglutide would lower our ICER.
British Society of Gastroenterology guidelines suggest that patients with <50 cm of small bowel remaining may need to receive IV proton pump inhibitors, rather than oral[10] due to highly limited intestinal absorption. In STEPS, 45% (n=39/86) of patients had <50 cm of small bowel remaining. Our revised base case assumes 20% of patients would receive IV proton pump inhibitors; this is lower than may be expected based on the proportion of the STEPS population with ultra-short bowel. Greater IV use of proton pump inhibitors would improve our ICER</td><td></td></tr>
<tr><td>4</td><td>Company</td><td>Takeda</td><td>Generalisability of results from STEPS

Two areas of outstanding uncertainty were identified in the ACD (section 3.22):

• The generalisability of clinical-effectiveness results of both the teduglutide and placebo arms of</td><td>Thank you for your comment. The committee considered this evidence during their decision making (please see sections 3.8</td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			STEPS • The company's approach to estimating health-state transition probabilities for both the teduglutide and standard care arm In particular, the committee concluded that our use of STEPS, STEPS-2 and the Patient Support Programme (PSP) data to model health state transitions is uncertain and may bias results in favour of teduglutide (section 3.11). This is linked to the committee's conclusion that the true relative treatment effect of teduglutide compared to placebo in STEPS was uncertain (section 3.8). We disagree that our model may be biased in favour of teduglutide, and would instead suggest that our heavy reliance on STEPS/STEPS-2 data means that our model is more likely to be biased in favour of standard care. For clarity, our position is fully laid out below. *STEPS weaning algorithm* The STEPS clinical trial is unusual in that its efficacy endpoints relate to the prescription of another medication (PS). To standardise this prescribing decision between trial sites, a weaning algorithm was used; this was necessary to enable a robust comparison of the clinical efficacy of teduglutide and placebo (a point specifically noted in the teduglutide EPAR: '*…in order to make the results reliable, stringent, objective algorithms [and adherence to these] for investigator decision on when and how to reduce/increase PS volume is critical*'[11]). To reduce PS, the requirements were as follows: *If 48-hour urine output is increased by at least 10% over baseline, reduce PS by at least 10% of optimised baseline level up to a clinically appropriate amount (maximum of 30%)* *Considerations to reduce PS will be made at all planned visits (weeks 2, 4, 8, 12, 16, 20, 24)* Several notable features of this algorithm do not reflect real-world practice: • The reliance solely on urine volume as criteria for making PS reductions does not reflect clinical reality. While increased urine volumes *could* indicate a patients PS consumption is too high, clinicians conduct a more holistic review of patient's nutritional and hydrational status prior to PS weaning in the real-world. o Furthermore, the wording used above is the wording that was provided to clinicians in the STEPS study. It is notable that clinicians are directed to reduce PS if the urine volume criteria is met; there was little room for clinical judgement. Clinicians in the real-world take a more flexible approach • The timing of study visits (at which PS could be reduced) was restrictive. In the real-world, clinicians can choose to adjust a patient's PS more frequently than every 4 weeks. • The magnitude of potential PS reduction feasible at each study visit was moderate-to-low (10–30%). Indeed, 72% of all PS reductions in the teduglutide arm of STEPS were between 0 and 10% of baseline PS volume; this illustrates the conservative approach encouraged by the algorithm. Clinical	and 3.11 of the FAD). Teduglutide is now recommended in both children and adults with SBS.

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			feedback suggests that patients can and do have their PS reduced by greater amounts in a single step in the real world. These differences affect how we interpret both the placebo and the teduglutide arms of STEPS, relative to what we would expect from standard care and teduglutide in the real world. *Placebo arm of STEPS* In the placebo arm, the sole reliance on urine volume as a marker for weaning (and directive nature of the algorithm) led to reductions in PS that would not be attempted with standard care in the real world. Professor Palle Jeppesen, international expert in the management of SBS-IF and lead investigator of the STEPS study has pointed out that [redacted]. Consequently, relying solely on urine volume as a weaning criteria in STEPS meant that patients could have their PS reduced without their intestinal absorption improving (and therefore, PS needs decreasing). Evidence that inappropriate weaning occurred in the placebo arm is supported by data from the study; patients in the placebo arm significantly increased oral fluid intake and lost weight by week 24 of STEPS[12, 13]. [redacted]. In the real-world, the decision to wean patients off PS is based on a holistic assessment of nutritional and hydrational balance, rather than looking at urine volume alone (in fact, urine volume data are not often available). As part of this holistic assessment, maintenance of weight and stable oral fluid intake are key requirements for PS weaning. Furthermore, as Dr Gabe emphasised at the first committee meeting, clinicians very rarely attempt to reduce PS for optimised patients who are stable and not receiving a treatment that improves their intestinal absorption. It should also be noted that the placebo response cannot be attributed to optimisation of care or improved adherence to prescribed medicines during STEPS. This is because 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*'[12] before they started treatment. The optimisation and stabilisation period was designed specifically to avoid optimisation of care or improved adherence contributing to observed PS reductions. In conclusion, the reliance of the weaning algorithm on urine volume alone to reduce PS, alongside [redacted] likely accounted for the placebo response seen in STEPS. Data on oral fluid intake and patient weight suggests that within 6 months, patients receiving placebo in STEPS were beginning to get into trouble on account of inappropriate PS weaning. Their PS reductions were unlikely to have been sustainable. In the real-world, weaning is not attempted in patients who are optimised and stable on PS. *Teduglutide arm of STEPS*	

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			In the teduglutide arm, the conservative timing of study visits and conservative range of permitted PS reductions appears to have resulted in smaller reductions in PS volume than would be attempted with teduglutide in the real-world. Evidence for this comes from real-world data which, compared to STEPS, show more rapid rates and higher proportions of patients achieving PS independence. This is likely to be a consequence of clinicians having more frequent opportunities to adjust PS prescriptions and/or being willing to make greater PS reductions. Before discussing real-world evidence, we should be clear that the mechanisms which led to a placebo effect in STEPS did not lead to an overestimation of teduglutide effect. Importantly, and in contrast to the placebo arm, the teduglutide arm did not have increased oral fluid intake at week 24, and on average patients gained weight. [redacted]. Reflective of this, data shows that greater reductions in PS are achieved in the real-world. We identified all published sources of real-world evidence for teduglutide from our systematic literature review (n=8 studies) and meta-analysed these data. We compared the pooled real-world proportion of patients gaining independence from PS to the proportion observed in STEPS/STEPS-2. This endpoint is a key driver of cost-effectiveness in our model (due to patients attaining almost normal utility and greatly reducing PS costs), and a life-changing milestone for patients on treatment. The analysis showed that [redacted] **Figure 1:** Meta-analysis results of STEPS/STEPS-2 vs pooled real-world data *A) Month 6*	

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			 *B) Month 12*	

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			 The meta-analysis provides strong evidence that the real-world absolute treatment effect of teduglutide is better than the efficacy observed in STEPS. It is striking also that this trend is so clearly evident in the raw data, which is shown in **Figure 2**. **Figure 2**: Percentage of patients gaining independence from PS in real-world studies and STEPS/STEPS-2	

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			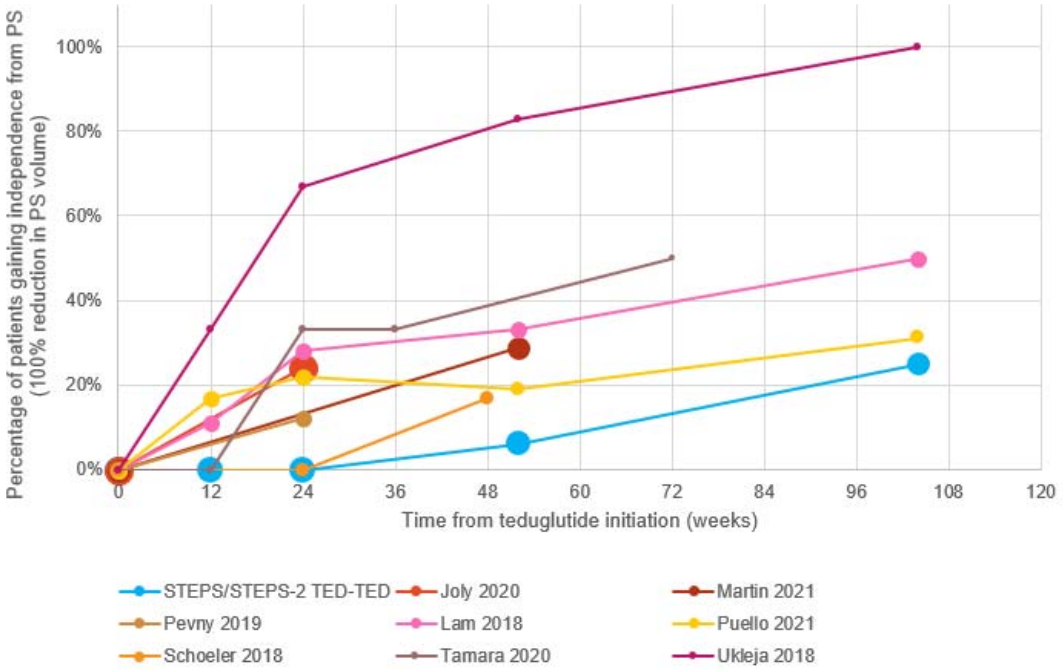 Abbreviations: PS, parenteral support; TED-TED, the subgroup of patients from STEPS-2 who were previously treated with teduglutide in STEPS For full discussion of **Figure 1**, see Document B, B.2.6.4.1, p 63 and B.2.8, p 71 Source: STEPS primary publication[12]; STEPS CSR[7]; STEPS-2 primary publication[14]; STEPS-2 CSR[15]; real-world study publications[16-23] It is particularly notable that not a single real-world evidence publication reports a lower rate of patients gaining independence from PS than STEPS/STEPS-2. This is despite the eight studies representing a range of countries (USA, France, Spain, Germany), a large number of patients for this ultra-rare disease (a total of >120 patients), a range of approaches to standard care, and a range of disease aetiologies and clinical features. Regardless of the real-world setting, teduglutide consistently shows a greater absolute treatment effect in the real-world than was seen in STEPS. None of the eight studies had a control group, and therefore relative treatment effect cannot be estimated. However, it is unlikely that patients in these cohorts could have reduced PS without teduglutide. The mean time on PS prior to teduglutide in these 8 studies ranged from 3.0 to 9.8 years, making it highly unlikely that patients were still undergoing any process of natural adaptation. Furthermore, clinical feedback received at	

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			the first committee meeting was clear that patients who are stable on PS would not be expected to achieve PS reductions. Further to the eight real-world publications identified above, a ninth real-world evidence study has been published since we conducted our systematic literature review. In this study, 69% (n=9/13) patients achieved PS independence within 24 weeks[24]. In the context of STEPS, where 0% of patients achieved independence within 24 weeks, this result is quite remarkable. It continues to reinforce the conclusion of our meta-analysis that more patients are able to gain independence from PS in the real-world than was seen in STEPS. As a final point, the authors of real-world publications have independently recognised the discrepancy between the clinical trial and real-world results, and highlight this in their papers: Joly 2020: *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*[16] Puello 2021: *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*[20] Harpain 2022: *We believe that a proactive and more aggressive dietetic adaptation of oral fluid and energy intake represents a crucial factor in enabling early and persistent teduglutide-induced reduction of PS volumes. The fast reduction in PN volumes, leading to PN-independency in >50% of patients after only 8 weeks and 92% after 72 weeks, is striking*[24] *Approach to modelling* To conclude, the placebo effect observed in STEPS led to patients increasing oral fluid intake and losing weight. These PS reductions would not have been attempted in the real-world. We acknowledge that this interpretation of the placebo results drives uncertainty – it calls into question whether the same could have occurred in the teduglutide arm and lead those results to be exaggerated. However, the fact that weaning with teduglutide in STEPS did not require increased fluid intake, enabled weight gain, and was significantly lower than real-world outcomes provides assurance that this is not the case. We therefore chose our modelling approach with the aim of best reflecting real-world practice. To reflect the implausibility of the placebo effect (patients stable on PS would be expected to remain stable on PS), we have not applied transitions for standard care in our base case. Assuming a placebo effect could apply to standard care (or subtracting a placebo effect from the teduglutide arm, which has the same impact) inhibits the generalisability of our model to the real-world. At the committee's request, we have provided a scenario where standard care experiences transitions for 6 months based on the placebo effect in STEPS and then reverts to baseline (ICER: £25,617 per QALY vs updated base case ICER: £24,718 per QALY). We don't	

<table>
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Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>believe that scenarios applying a placebo effect for longer than 6 months are warranted as the placebo response seen in STEPS is unlikely to have been sustainable given the observations of increased oral fluid intake and weight loss.

To reflect the better results experienced with teduglutide in the real-world, we have pooled data from STEPS/STEPS-2 with real-world data from our Patient Support Programme in Australia. This approach is still conservative; the PSP data provide data for [redacted] (compared to STEPS/STEPS-2 n=42) and are only used to inform transitions for 12 months (compared to STEPS/STEPS-2 for 30 months). Furthermore, our meta-analysis showed that, [redacted]

Although we acknowledge the PSP data lacks a control arm, we would hope the committee may be willing to accept a greater uncertainty for an ultra-rare condition such as SBS-IF. As both the previous Guide to Methods of Technology Appraisal (2013) and the latest NICE Manual (2022) acknowledge, evidence generation for rare diseases is ‘particularly difficult’[25], and ‘the evidence base will necessarily be weaker for some technologies, such as technologies used to treat patients with very rare diseases’ [26]. We note that ‘in these specific circumstances, the committee may be able to make recommendations accepting a higher degree of uncertainty’[25].

While uncertainty remains in the true treatment effect of teduglutide – which is to be expected for an ultra-rare condition – we are confident that our modelling approach errs on the side of being conservative but remains robust. Our model base case, with an ICER of £24,718 per QALY is comfortably cost-effective.</td><td></td></tr>
<tr><td>5</td><td>Company</td><td>Takeda</td><td>Starting age in model

The committee commented that it was unsure whether the starting age of the adult population in our model (50 years) reflected the real world. We chose 50 years as the mean age of patients at baseline in STEPS was 50.3 years. Table 3 shows the average age of adult teduglutide patients included in real-world evidence identified by our clinical systematic literature review. As can be seen, patients in these studies similarly cluster around an age of initiation of 50 years old (range 46–54 years; weighted average 51 years). On this basis, there appears to be little justification to lower the starting age of the adult model.

Table 3: Mean age of real-world teduglutide patients
<table>
<tr><th>Study</th><th>Minimum age for inclusion</th><th>N</th><th>Mean age of population at initiation of teduglutide</th></tr>
<tr><td>Joly 2020</td><td>≥18 years</td><td>54</td><td>52.3</td></tr>
<tr><td>Lam 2018</td><td>≥18 years</td><td>18</td><td>47 (median)</td></tr>
<tr><td>Martin 2021</td><td>≥18 years</td><td>31</td><td>51 (median)</td></tr>
</table></td><td>Thank you for providing this additional analysis as requested by the Committee. It was helpful in aiding their decision making. Conclusions relating to starting age in the model can be found in section 3.13 of the FAD.</td></tr>
</table>

<table>
<tr><th>Comment number</th><th>Type of stakeholder</th><th>Organisation name</th><th>Stakeholder comment
Please insert each new comment in a new row</th><th>NICE Response
Please respond to each comment</th></tr>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>Pevny 2019</td><td>≥18 years</td><td>27</td><td>51</td></tr>
<tr><td>Puello 2021</td><td>≥18 years</td><td>18</td><td>54.4 (median)</td></tr>
<tr><td>Schoeler 2018</td><td>Not specified (but all patients were ≥18)</td><td>14</td><td>49.1</td></tr>
<tr><td>Tamara 2020</td><td>≥18 years</td><td>4</td><td>53</td></tr>
<tr><td>Ukleja 2018</td><td>≥18 years</td><td>6</td><td>46.3</td></tr>
</table>

Despite this, at the request of the committee, we investigated how much changing the starting age affects our ICER. Lowering the starting age of the model (and making no other changes) improves the ICER, as it provides a longer time for cost savings and QALYs to accrue:

• Starting age 50 (base case): ICER £24,718 per QALY
• Starting age 45: ICER £23,728 per QALY
• Starting age 40: ICER £22,954 per QALY

It is notable that the ICER is not particularly sensitive to changes in starting age (see Figure 3, blue line). This is largely because our model uses extrapolated survival data from Salazar et al. 2021 (where the mean age at baseline was 53 years) and the change to starting age represented by the blue line in Figure 3 does not change the use of the Salazar data. This means that even with a starting age of 18, the model assumes a starting mortality rate equivalent to a 53-year old cohort.

In the interest of fully exploring the issue, we can adjust for this, however the method is crude. The green line in Figure 3 shows the ICER if we assume general population mortality applies until age 50, and after 50, mortality data are applied from Salazar et al. This is clearly implausible, however, the green line in Figure 3 does provide a ‘lower bound’ ICER driven by reducing starting age, in contrast to the ‘upper bound’ ICER shown by the blue line in Figure 3. The true ICER for lower starting ages will sit between these two lines.

Figure 3: ICER by adult starting age with and without adjustment to mortality</td><td></td></tr>
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			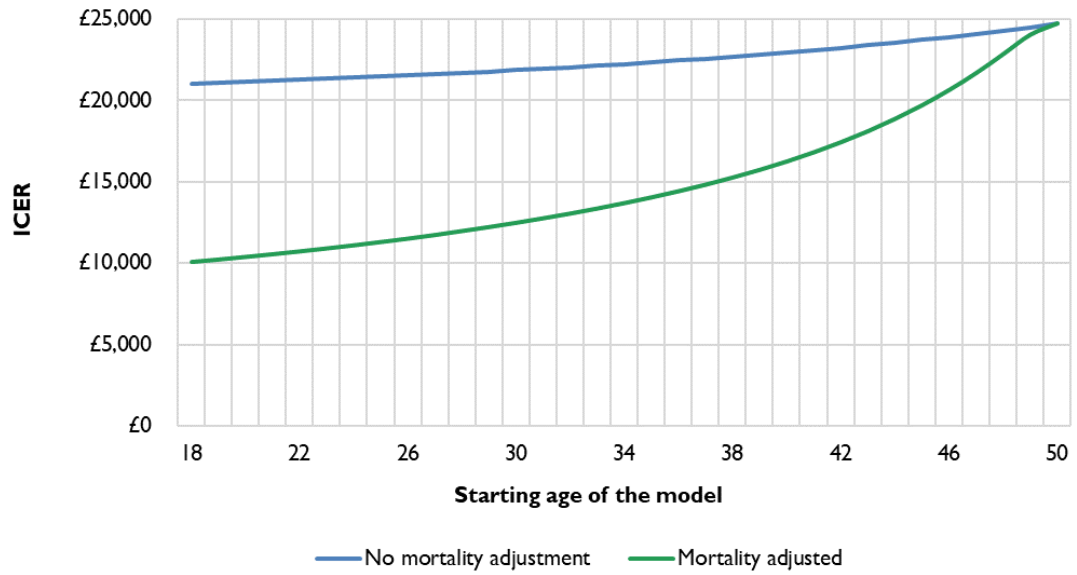 Abbreviations: ICER, incremental cost-effectiveness ratio Given our strong preference that, regardless of age (within license), SBS-IF patients receive equitable access to teduglutide (see comment 7), we also think it is merited to consider the overall cost-effectiveness of teduglutide in the population as a whole. Assuming [redacted] of teduglutide patients are paediatric (based on internal Takeda data), a weighted ICER for the whole population of patients with SBS-IF would be [redacted] per QALY based on a base case ICER of £24,718 per QALY in adults and £2,396 per QALY in children (the ICER in children is similarly calculated using the committee's preferred assumptions for co-medications, updated PS costs and updated PAS). Although we acknowledge that the committee may decide to not recommend a technology in a particular subgroup, even if the technology is clinically and cost effective in the whole population[25], we hope the committee will keep this comfortably cost-effective weighted ICER in-mind when considering the degree of outstanding uncertainty and equity concerns.	
6	Company	Takeda	**Number of adult caregivers** The committee questioned whether it was appropriate to assume that all adults would have a caregiver.	Thank you for providing this additional analysis as requested by the

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			To be clear, we calculated that adult patients would have on average one caregiver each based on a multinational survey (including the UK) of 181 adult patients with SBS-IF. The survey did not explicitly ask how many caregivers each adult patient had. When asked about their living situations, [redacted]. We therefore assumed that: • 21% of patients have zero carers [redacted] o This is likely to underestimate the number of carers per adult patient since it assumes all caregivers live with patients, despite some patients having a carer who does not live with them. [redacted] • 17% of patients have two carers [redacted] o This is also likely to underestimate the number of carers per adult patient, as some patients who reported having 'more than one' carer may have more than two carers • 62% (the remainder) have one carer This results in a weighted average of 0.96 carers per adult patient (at a minimum, considering how the calculation likely underestimates carers per patient), and so on this basis we assumed one caregiver per adult patient. To address the committee's uncertainty that an average of 1 carer per patient might be an overestimate, we have provided a scenario with 0.8 carers per adult patient. This scenario has an ICER of £26,228 per QALY (vs our base case of £24,718 per QALY), and is therefore still comfortably cost-effective. Finally, we would like to echo comments heard during the first committee meeting and captured in the ACD about the extraordinary burden that carers face in this setting. There are several aspects to this, but particularly notable are the degree of medical care and skill needed, and the constant emotional labour that stems from having another person's life in your hands. Caregivers are never afforded the time to forget their carer responsibilities. The following quotes from a very recent publication looking at carers of paediatric patients receiving PS illustrates these points: *"[W]ell, every morning, you have to unhook them, you've gotta give them their medicine, you've gotta make sure their lines and everything are taken care of and well managed. You've got to maintain any activities, everything is safe for them and for their body and what they're doing. You have to do all the prep for the [PS], you have to prep the lines, you've gotta do, again usually evening medication, medications during the day, etc. So, there's just a lot of medical work that's involved."*[28] *"I feel like we need to be flawless. I feel like we don't accept mistakes from ourselves or anybody else. But we put a lot of pressure on ourselves because we realize very much the stakes of us not being perfect."*[28]	Committee. It was helpful in aiding their decision making. Conclusions relating to the number of adult caregivers can be found in section 3.19 of the FAD.

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7	Company	Takeda	**Equity** The decision to issue an optimised recommendation for initiation of teduglutide in children only is not equitable. There is no difference in clinical need for teduglutide between an SBS-IF patient aged 17 and an SBS-IF patient aged 18, however by the present proposed recommendation, one will be allowed to receive teduglutide and one will not. Clinicians will be placed in the unenviable position of having to tell patients they cannot receive teduglutide – a treatment that could remove the constraint of PS from their life – because their bowel was resected too late. Moreover, once paediatric patients transition into adult care there will be a palpable, within-waiting room inequity between adult patients, potentially even of the same age – one who benefits from teduglutide and the other who cannot. This is an ultra-rare condition, a small and well-connected patient population, treated in a small number of highly specialist intestinal failure centres. This inequity will not go unnoticed. Furthermore, this equity issue compounds equity issues already faced by the SBS-IF patient population which teduglutide could help to address. The need for PS in England outstrips the available supply, particularly for compounded PS bags. The equity issue here is stark: who misses out when supply is poor? By reducing patients' days per week of PS and ultimately enabling some patients to wean off PS entirely, teduglutide is a technology which could ease PS supply burden. In turn, this would directly address inequality and unfairness in the existing distribution of PS. NICE's Health Technology Evaluations: The Manual (2022)[25] states that '*If considering excluding a subgroup, the committee must be convinced the harm to the NHS of including it is great enough to justify this decision'.* We hope that with this ACD response, we have been able to demonstrate that the NHS will not be harmed by the approval of teduglutide for use in the very small number of adults with SBS-IF. We believe that this is true, given that the range of ICERs we have provided for teduglutide show it is comfortably cost-effective.	Thank you for your comment. The committee considered it during their decision making. Teduglutide is now recommended in both children and adults with SBS.
8	Consultee	PINNT	Gravely disappointed that adults who stated the following will be severely disillusioned that their hopes have been thwarted with the decision not to provide access to teduglutide for adults, over 17 years of age: Member 2: …'I have been very disappointed and amazed that in almost 30 years there has been no drug, treatment or therapy offered to me which could address my underlying gut motility disorder, alleviate my symptoms or decrease my reliance on PN to any degree at all. Now, at last, there may be a drug or treatment available that could improve my condition, alleviate some of my symptoms and hopefully reduce or remove the need for PN. It would be devastating if this treatment or something similar was not made available, especially when it is available to other patients in other countries.' Member 3: … 'The only hope for some relief from this burden until now has been a transplant; suitable or not I've decided it's not for me, I would be replacing one set of problems for another. The concept of such an enormous operation with great risks that I currently face is not for me. A treatment that could avoid surgery and have the potential to reduce my nights on PN therefore reducing the number of times my CVC is	Thank you for your comment. The views of clinical experts and patient/carer representatives were considered by the Committee when formulating its recommendations. Teduglutide is now recommended in both children and adults with SBS.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			accessed which reduces the risk of infection/sepsis is the only hope on the horizon for people like me. The burden of SBS/IF and PN is not an easy one to bear, I've adjusted, I cope most of the time, but I hide the fear for my future.' Impact of no treatment for people 17 years of age plus: devastating. Benefit of teduglutide for people 17 years of age plus: viable medication option prior to surgical route, transplant if suitable.	
9	Consultee	PINNT	We are deeply concerned that while the committee initially acknowledged the 'impact of parenteral support on people with SBS and their carers was high' this has not resulted in equitable access to teduglutide for people aged 17 years and over.	Thank you for your comment. The views of clinical experts and patient/carer representatives were considered by the Committee when formulating its recommendations. Teduglutide is now recommended in both children and adults with SBS.
10	Consultee	PINNT	Recommendation: when it is started in children and young people aged 1 to 17 If started prior to the age of 17, this is permitted to be continued into adulthood whereas 17 years plus will not have access to the medication. This will create a strong feeling of inequity and potentially raise concerns that the lives of those 17 years and over are not equally valued thus increasing the burden that patients and carers already endure.	Thank you for your comment. The views of clinical experts and patient/carer representatives were considered by the Committee when formulating its recommendations. Teduglutide is now recommended in both children and adults with SBS.
11	Consultee	PINNT	Deeply concerned that within the close community of patients and carers who live with, and support people with short bowel syndrome and parenteral nutrition, people will rightly share the good news of access to the medication which will affect people being deprived of the treatment. The SBS and PN community stretches beyond hospitals, wards and waiting rooms; we're connected via social media platforms where people have access to information about treatment options which they too would like to benefit from for themselves or their loved ones.	Thank you for your comment. The views of clinical experts and patient/carer representatives were considered by the Committee when formulating its recommendations. Teduglutide is now

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				recommended in both children and adults with SBS.
12	Consultee	PINNT	Fearful for the impact on those who do not welcome nor accept parenteral nutrition, finding out that a medication has been denied to them which could eliminate or reduce what they see as a tremendous burden may have serious consequences.	Thank you for your comment. The views of clinical experts and patient/carer representatives were considered by the Committee when formulating its recommendations. Teduglutide is now recommended in both children and adults with SBS.
13	Consultee	PINNT	Provision of home parenteral nutrition: this is under considerable strain which impacts directly on the patients and carers. Multiple infusions, increased infusion times, on and off contingency bags (not knowing what kind of nutritional support will be available and when) additional procedures to perform which all contribute to a reduce quality of life and an increase in mental health issues. The potential to reduce or stop parenteral nutrition should be welcomed by all. There will be cost savings, reduced risks and complications in addition to relieving the pressure on a fragile home parenteral nutrition service.	Thank you for your comment. The views of clinical experts and patient/carer representatives were considered by the Committee when formulating its recommendations. Teduglutide is now recommended in both children and adults with SBS.
14	Consultee	PINNT	3.26 – There were no equality issues identified for teduglutide. The committee's decision not to make a recommendation for teduglutide in adults will cause significant equality issues.	Thank you for your comment. The views of clinical experts and patient/carer representatives were considered by the Committee when formulating its recommendations. Teduglutide is now recommended in both children and adults with SBS.
15	Consultee	PINNT	We are aware of the submission by Dr Simon Gabe and fellow signatories and wish to record our support for	Thank you for your

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			their submission.	comment. The views of clinical experts and patient/carer representatives were considered by the Committee when formulating its recommendations. Teduglutide is now recommended in both children and adults with SBS.
16	Clinical expert	[Insert organisation name]	We read the NICE appraisal consultation document assessment regarding teduglutide with some surprise. Our primary concern relates to discrimination against adults in England, for example: - Adult patients in Scotland will be able to have access to this medication whereas they will not in England. - A 17-year-old patient with short bowel who starts this medication will be able to continue to have this in adulthood whereas a young adult with short bowel would not be able to start this medication. - Many other countries in Europe, America, Asia, Australia and New Zealand have access to this medication for patients with short bowel. We believe that this is an effective treatment and our patients in England are being deprived of this potential treatment. Although the committee did acknowledge the enormous burden experienced by patients with short bowel and that new treatments are needed and would be welcomed, it feels that this is simply a token acknowledgement. If the cost effectiveness of the drug assessed by complex modelling is marginal or uncertain then the committee should decide in the favour of acting for the patients. The acknowledgement of the burden is there at the beginning of the appraisal document but totally lacking in the final conclusions. This decision goes against both clinical and patient advice.	Thank you for your comment. The views of clinical experts and patient/carer representatives were considered by the Committee when formulating its recommendations. Teduglutide is now recommended in both children and adults with SBS.
17	Clinical expert	[Insert organisation name]	*Page 4: "Clinical trial evidence shows that teduglutide reduces the number of days a week people with SBS need parenteral support compared with placebo. However, how much it reduces this is uncertain because the trial design may not reflect NHS practice."* This statement is not evidence-based. Furthermore, centres in England participated in the randomised controlled studies. We also do not think that this is a true statement regarding NHS practice in the management of short bowel syndrome. All clinical trials differ in some respect from the day-to-day clinical practice in all countries. The way the patients are managed in the NHS does not differ from other countries in Europe. We can be sure about this as we communicate regularly with our colleagues in Europe and some of these colleagues have come to view our clinical practice at our hospitals and taken back elements to enhance their practice of managing these patients. Therefore, we suggest that the real-world and trial evidence of the efficacy of teduglutide that is available from other countries is applicable to the same patient group in the	Thank you for your comment. The views of clinical experts and patient/carer representatives were considered by the Committee when formulating its recommendations. The generalisability of the trial evidence is discussed in section 3.8 of the FAD.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			NHS.	Teduglutide is now recommended in both children and adults with SBS.
18	Clinical expert	[Insert organisation name]	*Page 4: Because of the uncertainties in the clinical evidence, the cost-effectiveness estimates are uncertain.* We presume this relates to data quality? There is a significant amount of data demonstrating that teduglutide is effective in decreasing parenteral nutrition requirements in patients with short bowel, as agreed by the committee. This is not just from the clinical trial data but also from 8 non-interventional real-world studies. However, the data relating to the real world studies was not included in the modelling. This data was presented to the committee and originates from a number of different countries and consistently shows a similar degree of benefit (approximately 30% reduction in parenteral nutrition requirements). We are not sure that appropriate weight is given to this information due to the methodology that is used by NICE.	Thank you for your comment. The views of clinical experts and patient/carer representatives were considered by the Committee when formulating its recommendations. The clinical evidence considered during the appraisal is discussed in section 3.5 of the FAD. Teduglutide is now recommended in both children and adults with SBS.
19	Clinical expert	[Insert organisation name]	*Page 17: The cost-effectiveness results for children are much more favourable than for adults. The ERG clarified that this is because of the younger starting age and longer time horizon in the model for children. Teduglutide also reduces the costs associated with parenteral support (see section 3.11),* *and these 2 attributing factors mean that QALYs and cost benefits accrue for longer in the model. The committee concluded that the difference seen between the ICERs for adults and children are feasible.* One reason that the modelling comes out more cost-effective for children than for adults is that children have a longer lifespan and therefore the number of complications that can occur over time is greater than for adults. One of the problems that we have with this is that within the adult population there is considerable variability in the frequency of complications. There are plenty of patients who develop frequent and repeated central venous catheter infections, for example. For some patients this can happen 3 or 4 times a year and this is very resource intensive, with patients sometimes requiring intensive care support. In such patients we are sure that teduglutide would work out as being much more cost-effective, if this was included the model. We appreciate that when undertaking modelling, average numbers or frequencies needs to be used but as a result, incorrect conclusions have been drawn.	Thank you for your comment. The views of clinical experts and patient/carer representatives were considered by the Committee when formulating its recommendations. Complications relating to SBS and adverse events of teduglutide are discussed in sections 3.15, 3.16 and 3.17 of the FAD. Teduglutide is now recommended in both children and adults with SBS.
20	Clinical expert	[Insert organisation name]	*Page 23: The ERG provided ICERs using the lowest cost HPN provider, highest cost HPN provider and the mean price of all HPN providers to explore uncertainties around the true price of HPN in the NHS. When doing this, the ICERs ranged from cost-saving to cost-ineffective. … The committee considered the cost of parenteral support to be highly uncertain and noted the large impact on the cost-effectiveness results. It concluded that using the mean price of HPN was likely to be most appropriate for decision making because it is unlikely that the lowest HPN price would be accessed by the entire population with SBS. It also concluded*	Thank you for your comment. The views of clinical experts and patient/carer representatives were considered by the

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			that it would consider the highest and lowest cost HPN providers in scenario analyses We appreciate that this is a difficult area. At the moment there are particular issues with the provision of home parenteral nutrition using compounded parenteral nutrition in England. Ultimately there are not enough compounding slots for the number of patients that we have. As a result, the prescriptions for home parenteral nutrition are becoming increasingly complicated, requiring multiple infusions every night. Not only has the burden increased for patients but also complications may be more frequent and the resultant cost of HPN provision is increasing and likely to continue to do so. We are using multi-chamber bags (MCB) with additional infusions of IV fluids and sometimes also additional IV vitamins and micronutrients. This is much more costly than the standard compounded home parenteral nutrition. Although we do not have the costs, we are unsure that this has been taken into account when asking NHS England for the costs of home parenteral nutrition. Equally, an average cost may not be appropriate if the range is skewed. As these issues have only developed over the past 1-2 years the data that you may have received may either be out of date or more skewed than has been appreciated. Furthermore, the fact that we now have to ration compounded home parenteral nutrition for patients in England means that any treatment which would enable patients to reduce or come off parenteral nutrition should be welcomed; not only from a patient quality perspective, but also in order to reduce the national burden aseptic pharmacy services in compounding PN. Indeed, NHSE & I recognise the lack of aseptic pharmacy capacity as a major risk in the UK, not least because it has resulted in delayed hospital discharges throughout the country. This is a recent and evolving issue and therefore has not been considered by the committee. Clearly any medication that can reduce PN requirements will be of clinical and ultimately likely cost benefit to this stressed system. In addition, around 30% of patients on home parenteral nutrition are now receiving additional specialist nursing care and there are also not enough specialist nurses to provide the service in the country. This issue is also increasing the length of stay for new patients being discharged on home parenteral nutrition, adding both burden and cost to the NHS overall. While these issues cannot be modelled for, we strongly recommend that the committee takes them into account.	Committee when formulating its recommendations. The discussions relating to HPN resource use and costs are summarised in section 3.20 of the FAD. Teduglutide is now recommended in both children and adults with SBS.
21	Clinical expert	[Insert organisation name]	*Page 26: NICE's guide to the methods of technology appraisal notes that judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICERs. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented.* Following this statement, the document mentions that the committee noted uncertainties in 6 different elements and yet it goes on to state that for the committee to recommend teduglutide, the ICER would have to be comfortably within the range of cost effectiveness. This is likely to be the core of any disagreement. It seems to be appreciated that there is uncertainty around the ICER and yet more emphasis is placed upon a calculation that shows clear cost effectiveness (see section 3.24). Surely if there is a lack of certainty then this method of relying on the ICER should be discarded (in the same way that some clinical data has been discarded by the committee).	Thank you for your comment. The views of clinical experts and patient/carer representatives were considered by the Committee when formulating its recommendations. The committee's discussions around the cost effectiveness of teduglutide are summarised in section 3.22 and 3.23 of the FAD.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
				Teduglutide is now recommended in both children and adults with SBS.
22	Clinical expert	[Insert organisation name]	*Page 28: 3.26 There were no equality issues identified for teduglutide.* As described above, we believe that this final decision would cause significant equality issues in this patient group (based on age), within the UK (as it is available in Scotland and within Europe and the rest of the world).	Thank you for your comment. The views of clinical experts and patient/carer representatives were considered by the Committee when formulating its recommendations. Teduglutide is now recommended in both children and adults with SBS.
23	Clinical expert	Intestinal failure rehabilitation service, Gastroenterology Department, Great Ormond Street Hospital for Children, NHS Foundation Trust, London WC1N 3JH	I am delighted that the committee is prepared to recommend funding the use of teduglutide in children with SBS associated intestinal failure. In addition to transforming the life of many children with short bowel syndrome the benefits of teduglutide should improve life for siblings and parents.	Thank you for your comment.
24	Clinical expert	Intestinal failure rehabilitation service, Gastroenterology Department, Great Ormond Street Hospital for Children, NHS Foundation Trust, London WC1N 3JH	I am concerned that a young person presenting in their 20's or 30's with short bowel syndrome and intestinal failure would not be able to benefit from teduglutide. The young adult still has a long life-expectancy and at the same time needs the best possible health to develop their career/establish their working life + may have the added burden of caring for small children. Even a night or two off PN each week (and if one night off can be managed then it is immediately possible to have two nights/week off) would make a huge difference to their ability to keep a fulltime job and support a young family.	Thank you for your comment. The views of clinical experts and patient/carer representatives were considered by the Committee when formulating its recommendations. Teduglutide is now recommended in both children and adults with SBS.

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25	Clinical expert	Intestinal failure rehabilitation service, Gastroenterology Department, Great Ormond Street Hospital for Children, NHS Foundation Trust, London WC1N 3JH	I am concerned that the committee were not made aware of the increased demand for home PN in England. Bespoke Home parenteral nutrition (PN) formulations tailored to the individual patient's needs are a limited resource. As a result, some adults with intestinal failure have not had access to individualised formulations and have had to make do with standard preparations which could result in impaired health and more complex infusions.	Thank you for your comment. The views of clinical experts and patient/carer representatives were considered by the Committee when formulating its recommendations. The discussions relating to HPN resource use and costs are summarised in section 3.20 of the FAD. Teduglutide is now recommended in both children and adults with SBS.
26	Clinical expert	Intestinal failure rehabilitation service, Gastroenterology Department, Great Ormond Street Hospital for Children, NHS Foundation Trust, London WC1N 3JH	I am concerned that this recommendation will impede the care given by adult intestinal failure rehabilitation centres in England which up to now has been to the highest standard on a worldwide basis. Teduglutide is most effective when the patient's care is managed by a specialist multidisciplinary intestinal failure rehabilitation service. There is the best possible framework already in place for ensuring appropriate use of teduglutide in adults with national clinical meetings to discuss individual cases and two national reference centres, St Marks, London and Manchester.	Thank you for your comment. The views of clinical experts and patient/carer representatives were considered by the Committee when formulating its recommendations. Teduglutide is now recommended in both children and adults with SBS.
27	Clinical expert	Intestinal failure rehabilitation service, Gastroenterology Department, Great Ormond Street Hospital for Children, NHS Foundation Trust, London WC1N 3JH	I am concerned that the committee will not be aware of our recently publication on the cost of short bowel syndrome associated intestinal failure to the specialist centre (which is not the full cost since emergency admissions with catheter -related bloodstream infections and other complications that could be managed in the local hospital were not dealt with in the specialist centre). Although this is a paediatric paper adult services will have some similar costs that may not have been taken into account: Jones BC, O'Sullivan B, Amin SP, et al. Patient-level costing analysis of paediatric short bowel syndrome care in a specialist tertiary centre. Pediatric Surgery International. 2022 Apr;38(4):533-539. DOI: 10.1007/s00383-022-05074-6. PMID: 35211770; PMCID: PMC8913464.	Thank you for your comment. The views of clinical experts and patient/carer representatives were considered by the Committee when formulating its recommendations. Teduglutide is now recommended in both children and adults with SBS.
28	Web		I believe that much of the evidence collected demonstrates the awesome burden PS places on patients and	Thank you for your

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			carers. Death from Intestinal Failure may be rare - however as recently as last month we have witnessed a friend's child needing a liver transplant due to TPN. His parents feel lucky but realise he will now need life long medication. The child of another family we know had to have a bowel transplant due of lost line sites. Yesterday a 3 year old was 'blue lighted' to hospital because his line had split and caused a serious loss bleed! These are the issues faced by families on PS	comment. The views of clinical experts and patient/carer representatives were considered by the Committee when formulating its recommendations. Teduglutide is now recommended in both children and adults with SBS.
29	Web		The summaries of clinical and cost effectiveness do seem reasonable for use in children and young people. I understand that NICE need more up to date review of the cost of concomitant medications for use with adults by the Company - but would expect that all patients with SBS -Intestinal Failure are given access to Teduglutide if needed.	Thank you for your comment.
30	Web		I believe the recommendations for use with children and young people are a suitable basis on which to provide guidance to the NHS.	Thank you for your comment.
31	Web		I am minded to suggest that setting the limit for provision of Teduglutide at 17 may prove discriminatory on the grounds of age?	Thank you for your comment. The views of clinical experts and patient/carer representatives were considered by the Committee when formulating its recommendations. Teduglutide is now recommended in both children and adults with SBS.
32	Web		I am pleased that NICE has recommended Teduglutide for use with children and young people and that once started it will continue to be provided as long as needed regardless of age,	Thank you for your comment. The views of clinical experts and patient/carer representatives were considered by the Committee when formulating its recommendations. Teduglutide is now recommended in both

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
				children and adults with SBS.
33	Web		People would welcome new treatment options for short bowel syndrome that reduce the number of days of parenteral support "I believe people would welcome the new treatment. Many have inquired about it having seen reports over time, particularly families struggling with PS long term 7 nights per week sometimes single handed because of a partner being disabled. This burden can, and does lead to depression! Also two families that have been on the trials have requested that their children be allowed continue treatment with Teduglutide."	Thank you for your comment. The views of clinical experts and patient/carer representatives were considered by the Committee when formulating its recommendations. Teduglutide is now recommended in both children and adults with SBS.
34	Web		The post-trial real world experience needs to be better considered, to reflect the better response rates.	Thank you for your comment.
35	Web		- The post-trial real world experience needs to be better considered, to reflect the better response rates. - In addition, patient value should be better considered. There is strong published evidence that QoL is better with fewer PN nights. Patients ask to reduce their PN nights when reviewed in clinic and this is a strong driver for requesting this drug; indeed this is evidence-based in published qualitative research. - The potential impact on IFALD needs to be better considered. Reduced PN and improved absorption leads to reduced liver injury. This could prevent the need for multivisceral transplantation.	Thank you for your comment.
36	Web		No - in view of my comments above.	Thank you for your comment.
37	Web		Age: this discriminates against those > 18 years old. Geography: this discriminates against people in England vs Scotland, or people who with IF who wish to move from Scotland to England. People: this discriminates against my patient who has ceased PN with Teduglutide. He will be forced back on PN if the drug is stopped.	Thank you for your comment. The views of clinical experts and patient/carer representatives were considered by the Committee when formulating its recommendations. Teduglutide is now recommended in both children and adults with SBS.

NICE National Institute for Health and Care Excellence

Teduglutide for treating short bowel syndrome [ID3937]

Consultation on the appraisal consultation document – deadline for comments end of day on **1 April 2022**. Please submit via NICE Docs.

Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Takeda UK Ltd
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	Not applicable
Name of commentator person completing form:	[redacted]

Comment number	Comments
1	**Summary of response** We, as Takeda, are grateful for the time and effort dedicated to this appraisal. We are pleased to see the proposal to recommend teduglutide for initiation in children with SBS-IF, but are disappointed that adults with SBS-IF are not yet guaranteed access. We hope that our response can address the committee's remaining uncertainty sufficiently to enable access for the full licensed population. We have taken on board all the committee's feedback from the previous appraisal meeting, and have updated our model to produce a new base case ICER. The new base case has three differences compared to the previous base case: • Updated assumptions on co-medication use. These now reflect the committee's preferred assumptions (described in comment 3) • Updated PS costs • Updated PAS discount, [redacted] The revised base case ICER is £24,718 per QALY; further detail with regards this are provided in comment 2 below. To address additional uncertainties noted by the committee in section 3.22 of the Appraisal Consultation Document (ACD), we have provided further clarification for our interpretation of the results from STEPS (comment 4) and provided justification for the number of carers assumed per adult patient (comment 6). We have also, at the committee's request, explored the impact of reducing the starting age in the adult model (comment 5). Lastly, we have highlighted our equity concerns with the present decision in comment 7 and the ability of teduglutide to help address inequality in current access to PS. In short, we believe that

making teduglutide only available for initiation in children and not adults is not equitable, and compounds upon significant inequity that patients with SBS-IF already face.

We would also like to re-iterate that SBS-IF is an ultra-rare condition, and given such rarity it is likely that uncertainty will remain, despite our best efforts to address this. We note that the new NICE methods guide (The Manual, 2022) makes specific allowance for greater uncertainty in the case of rare diseases. We ask that the committee be mindful of this in their decision making.

2

Revised base case

Taking on board the committee's feedback, we have produced a new base case ICER. The updated base case has three differences from our previous base case:

- Updated assumptions on co-medication use. These now reflect the committee's preferred assumptions, described in full in comment 3
- Updated PS costs. We hope that this new estimate better reflects the true mean cost of PS. However, as the actual costs are confidential to the NHS and we do not know the breakdown of the component parts, these costs are still an estimate:
  - Previous assumed total average PS cost was [redacted], constituting:
    - PS bags: [redacted]
    - Delivery: [redacted]
    - Nurse time: [redacted]
    - Taurolock: [redacted]
  - New assumed total average PS cost is [redacted], constituting:
    - PS bags: [redacted]
    - Delivery: [redacted]
    - Nurse time: [redacted]
    - Taurolock: [redacted] (reflects 50% usage as specified in the first committee meeting, see also comment 3)
- Updated PAS discount, [redacted]

The ICER for our updated base case is £24,718 per QALY, and further detailed in **Table 1** below:

Table 1: Results for new base case

Option	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Teduglutide	[redacted]	[redacted]	[redacted]	[redacted]	£24,718
Standard care	[redacted]	[redacted]			
Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year					

In addition, we have provided a range of scenario analyses to help the committee further explore the uncertainty associated with this new base case. These are outlined in **Table 2** below:

Table 2: Scenario analyses for updated base case

Model component	Base case	Scenario	ICER
Base case			£24,718
Transitions in standard care arm	No effect for standard care	Six month of transitions based on STEPS placebo data	£25,617
Co-medications	Committee-preferred assumptions from first meeting	Zero comedications	£26,323
PS costs	[redacted] total	- 20%	£48,221
PS costs	[redacted] total	-10%	£36,469
PS costs	[redacted] total	+10%	£12,966

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PS costs	[redacted] total	+20%	£1,215
Carers per adult	1	0.8	£26,228
Data source	STEPS/STEPS-2 + PSP (for first 12 months)	STEPS/STEPS-2 only	£29,578
Starting age	Age 50 with survival based on Salazar et al.	Age 45 with survival based on Salazar et al.	£23,728
Starting age & adjustment to survival	Age 50 with survival based on Salazar et al.	Age 45 with general population mortality rates until age 50, followed by Salazar et al. thereafter.	£19,694
Starting age	Age 50 with survival based on Salazar et al.	Age 40 with survival based on Salazar et al.	£22,954
Starting age & adjustment to survival	Age 50 with survival based on Salazar et al.	Age 40 with general population mortality rates until age 50, followed by Salazar et al. thereafter.	£16,234
Abbreviations: ICER, incremental cost-effectiveness ratio			

We would like to highlight that there are a number of benefits of teduglutide treatment in adults that are not captured in this base case:

- **Avoidance of intestinal transplant:** intestinal transplant is a critical, life-saving surgery for both adults and children with SBS-IF who lose line access for PS or have intestinal failure-associated liver disease (IFALD) evolving to liver failure[1]. However, it is a procedure that is costly, risky and represents a lifelong burden for patients. Due to the risks involved and limited supply of organs, it is therefore a procedure of last resort. Of particular note:
    - While mortality and patient quality of life have improved in recent years, graft rejection remains a significant and unpredictable concern; it has been described as '*insidious and subclinical until a late stage*'[2]. The prospect of graft rejection is likely to be a constant psychological burden on patients who have received a transplant. Patients who have undergone intestinal transplant have a high incidence of psychosocial problems[2].
    - As acknowledged in the ACD, it is likely that teduglutide will reduce the likelihood of patients needing intestinal transplant. By allowing patients to reduce PS, teduglutide reduces the likelihood of occluded catheter access, and reduces the incidence of IFALD – both complications that may result in intestinal transplant. However, this benefit to both adults and children with SBS-IF is not captured by our model
- **Reduction of PS volume but not days:** our model only attributes utility gain when patients reduce a day per week of PS. Patients who reduce their weekly PS volume, but not days, are assumed to receive no benefit. This is not likely to be the case. Patients typically receive PS for 10–14 hours; as such, whilst PS is usually referred to as being given 'overnight', the reality is that being 'hooked up' to PS immobilises patients from early evening, overnight and into the morning[3]. Patients who can reduce the number of hours per night they receive PS have more flexibility: they can opt to have more hours of less disturbed sleep, or more time in the evening or morning for usual activities. These options improve quality of life but are not captured within our model.
- **Service pressure:** PS delivery within the NHS is currently under serious pressure; supply is constrained globally and this will not likely be resolved soon[4]. This is not simply a result of global supply crises following COVID-19, the supply of PS was designated an 'emergency incident at the highest level' in August 2019[5]. Whilst action has been taken to try to improve the situation, scarcity of compounded PS remains. Consequently, there are patients receiving more expensive multi-chamber bags with additional infusions, sub-optimal

formulations of PS or not receiving PS at all – there is at least one patient currently unable to be discharged from hospital as they cannot access PS at home.

- By enabling patients to reduce their PS requirements and even to gain independence from PS, teduglutide will ease the pressure on PS supply. This will allow more patients who need compounded PS to receive it, and ultimately relieve pressure on hospital beds.

3

Co-medication costs

In line with the committee's preferred assumptions, we have adjusted the use of co-medications in our model as described in **Table 3**.

To simplify the changes made, we have only altered the costs of co-medications rather than figures relating to usage (e.g. if feedback was that 50% of patients receive a given medicine and we had previously assumed 100%, we have reduced the price of that medicine to 50% of the original).

Table 3: Adjustments to co-medications in revised adult base case

	Feedback	**Original cost per unit**	**New cost per unit**	**Rationale**
Taurolock	We had assumed all patients receive 1x taurolock per day of PS. Feedback was that 50% of patients receive taurolock	£10.00	£5.00	New cost = 10.00*0.5
Proton pump inhibitors	We had assumed all patients would receive IV proton pump inhibitors. Feedback was that only 20% of patients receive them IV, and 80% receive them orally	£9.70	£2.27	New cost = (9.70*0.2) + (0.41*0.8). Cost of oral proton pump inhibitors taken from the ERG addendum
Antimotility agents	We had assumed that all patients receive IV antimotility agents. Feedback was that patients receive antimotility agents orally	£11.80	£1.21	Cost of oral antimotility agents taken from the ERG addendum
Fragmin	We had assumed that all patients receive fragmin; feedback was that 5% of patients receive fragmin	£2.82	£0.14	New cost = 2.82*0.05
Ondansetron	We had assumed that all patients receive ondansetron IV. Feedback was that 5% of patients receive ondansetron and they receive it orally	£23.98	£0.02	New cost = 0.35*0.05. Cost of oral ondansetron taken from the ERG addendum
Abbreviations: ERG, evidence review group; IV, intravenous; PS, parenteral support				

Combined with the changes to PS costs and PAS in our revised base case, this gives a new ICER of £24,718 per QALY. We have also provided a scenario where we have assumed zero co-medication costs. While conservative and implausible, we believe that this gives a clear idea of the upper bound of uncertainty. This scenario has an ICER of £26,323 per QALY, still comfortably within the bounds of cost-effectiveness.

We believe that the co-medication costs and use outlined in **Table 3** above are plausible, but may lean towards being conservative:

- It is likely that use of teduglutide will reduce the use of co-medications relative to standard care, something we have not currently modelled and which would reduce our ICER. The teduglutide SmPC notes that '*there is potential for increased absorption of concomitant*

	medicinal products'[6]. The STEPS study report further elaborates that '*Based on the mechanism of action, teduglutide could potentially increase absorption of orally administered drugs (e.g., motility medication, coumadin, psychotropics, metronidazole, digoxin), so consideration was given to modifying oral concomitant medication regimens*'[7]. As a result of increased intestinal absorption, patients receiving teduglutide may have their oral dose of co-medications reduced, or may be able to switch from IV formulations to oral. Modelling these would reduce our ICER. • Glucagon-like peptide 2 (GLP-2) inhibits gastric acid secretion[8], and teduglutide (as an analogue of GLP-2) has a similar effect[6, 9]. Proton pump inhibitors are prescribed to reduce gastric acid output[10], and so patients receiving teduglutide may have reduced need for proton pump inhibitors. Again, modelling lower proton pump inhibitor use in patients receiving teduglutide would lower our ICER. • British Society of Gastroenterology guidelines suggest that patients with <50 cm of small bowel remaining may need to receive IV proton pump inhibitors, rather than oral[10] due to highly limited intestinal absorption. In STEPS, 45% (n=39/86) of patients had <50 cm of small bowel remaining. Our revised base case assumes 20% of patients would receive IV proton pump inhibitors; this is lower than may be expected based on the proportion of the STEPS population with ultra-short bowel. Greater IV use of proton pump inhibitors would improve our ICER
4	**Generalisability of results from STEPS** Two areas of outstanding uncertainty were identified in the ACD (section 3.22): • The generalisability of clinical-effectiveness results of both the teduglutide and placebo arms of STEPS • The company's approach to estimating health-state transition probabilities for both the teduglutide and standard care arm In particular, the committee concluded that our use of STEPS, STEPS-2 and the Patient Support Programme (PSP) data to model health state transitions is uncertain and may bias results in favour of teduglutide (section 3.11). This is linked to the committee's conclusion that the true relative treatment effect of teduglutide compared to placebo in STEPS was uncertain (section 3.8). We disagree that our model may be biased in favour of teduglutide, and would instead suggest that our heavy reliance on STEPS/STEPS-2 data means that our model is more likely to be biased in favour of standard care. For clarity, our position is fully laid out below. *STEPS weaning algorithm* The STEPS clinical trial is unusual in that its efficacy endpoints relate to the prescription of another medication (PS). To standardise this prescribing decision between trial sites, a weaning algorithm was used; this was necessary to enable a robust comparison of the clinical efficacy of teduglutide and placebo (a point specifically noted in the teduglutide EPAR: '*…in order to make the results reliable, stringent, objective algorithms [and adherence to these] for investigator decision on when and how to reduce/increase PS volume is critical*'[11]). To reduce PS, the requirements were as follows: *If 48-hour urine output is increased by at least 10% over baseline, reduce PS by at least 10% of optimised baseline level up to a clinically appropriate amount (maximum of 30%)* *Considerations to reduce PS will be made at all planned visits (weeks 2, 4, 8, 12, 16, 20, 24)* Several notable features of this algorithm do not reflect real-world practice:

- The reliance solely on urine volume as criteria for making PS reductions does not reflect clinical reality. While increased urine volumes *could* indicate a patients PS consumption is too high, clinicians conduct a more holistic review of patient's nutritional and hydrational status prior to PS weaning in the real-world.
    - Furthermore, the wording used above is the wording that was provided to clinicians in the STEPS study. It is notable that clinicians are directed to reduce PS if the urine volume criteria is met; there was little room for clinical judgement. Clinicians in the real-world take a more flexible approach
- The timing of study visits (at which PS could be reduced) was restrictive. In the real-world, clinicians can choose to adjust a patient's PS more frequently than every 4 weeks.
- The magnitude of potential PS reduction feasible at each study visit was moderate-to-low (10–30%). Indeed, 72% of all PS reductions in the teduglutide arm of STEPS were between 0 and 10% of baseline PS volume; this illustrates the conservative approach encouraged by the algorithm. Clinical feedback suggests that patients can and do have their PS reduced by greater amounts in a single step in the real world.

These differences affect how we interpret both the placebo and the teduglutide arms of STEPS, relative to what we would expect from standard care and teduglutide in the real world.

Placebo arm of STEPS

In the placebo arm, the sole reliance on urine volume as a marker for weaning (and directive nature of the algorithm) led to reductions in PS that would not be attempted with standard care in the real world. Professor Palle Jeppesen, international expert in the management of SBS-IF and lead investigator of the STEPS study has pointed out that [redacted]. Consequently, relying solely on urine volume as a weaning criteria in STEPS meant that patients could have their PS reduced without their intestinal absorption improving (and therefore, PS needs decreasing). Evidence that inappropriate weaning occurred in the placebo arm is supported by data from the study; patients in the placebo arm significantly increased oral fluid intake and lost weight by week 24 of STEPS[12, 13]. [redacted].

In the real-world, the decision to wean patients off PS is based on a holistic assessment of nutritional and hydrational balance, rather than looking at urine volume alone (in fact, urine volume data are not often available). As part of this holistic assessment, maintenance of weight and stable oral fluid intake are key requirements for PS weaning. Furthermore, as Dr Gabe emphasised at the first committee meeting, clinicians very rarely attempt to reduce PS for optimised patients who are stable and not receiving a treatment that improves their intestinal absorption.

It should also be noted that the placebo response cannot be attributed to optimisation of care or improved adherence to prescribed medicines during STEPS. This is because 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*'[12] before they started treatment. The optimisation and stabilisation period was designed specifically to avoid optimisation of care or improved adherence contributing to observed PS reductions.

In conclusion, the reliance of the weaning algorithm on urine volume alone to reduce PS, alongside [redacted] likely accounted for the placebo response seen in STEPS. Data on oral fluid intake and patient weight suggests that within 6 months, patients receiving placebo in STEPS were beginning to get into trouble on account of inappropriate PS weaning. Their PS reductions were unlikely to have been sustainable. In the real-world, weaning is not attempted in patients who are optimised and stable on PS.

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Teduglutide arm of STEPS

In the teduglutide arm, the conservative timing of study visits and conservative range of permitted PS reductions appears to have resulted in smaller reductions in PS volume than would be attempted with teduglutide in the real-world. Evidence for this comes from real-world data which, compared to STEPS, show more rapid rates and higher proportions of patients achieving PS independence. This is likely to be a consequence of clinicians having more frequent opportunities to adjust PS prescriptions and/or being willing to make greater PS reductions.

Before discussing real-world evidence, we should be clear that the mechanisms which led to a placebo effect in STEPS did not lead to an overestimation of teduglutide effect. Importantly, and in contrast to the placebo arm, the teduglutide arm did not have increased oral fluid intake at week 24, and on average patients gained weight. [redacted].

Reflective of this, data shows that greater reductions in PS are achieved in the real-world. We identified all published sources of real-world evidence for teduglutide from our systematic literature review (n=8 studies) and meta-analysed these data. We compared the pooled real-world proportion of patients gaining independence from PS to the proportion observed in STEPS/STEPS-2. This endpoint is a key driver of cost-effectiveness in our model (due to patients attaining almost normal utility and greatly reducing PS costs), and a life-changing milestone for patients on treatment.

The analysis showed that [redacted]

Figure 1: Meta-analysis results of STEPS/STEPS-2 vs pooled real-world data
A) Month 6

B) Month 12

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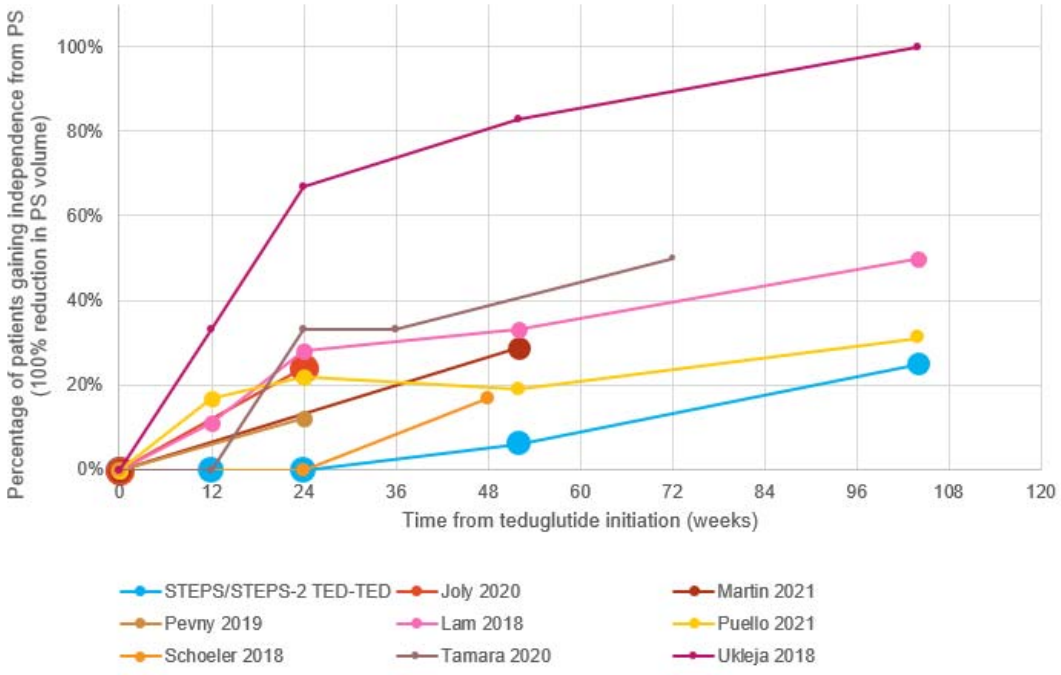
[redacted]

The meta-analysis provides strong evidence that the real-world absolute treatment effect of teduglutide is better than the efficacy observed in STEPS. It is striking also that this trend is so clearly evident in the raw data, which is shown in **Figure 2**.

Figure 2: Percentage of patients gaining independence from PS 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
For full discussion of **Figure 1**, see Document B, B.2.6.4.1, p 63 and B.2.8, p 71
Source: STEPS primary publication[12]; STEPS CSR[7]; STEPS-2 primary publication[15]; STEPS-2 CSR[15]; real-world study publications[17-24]

It is particularly notable that not a single real-world evidence publication reports a lower rate of patients gaining independence from PS than STEPS/STEPS-2. This is despite the eight studies

representing a range of countries (USA, France, Spain, Germany), a large number of patients for this ultra-rare disease (a total of >120 patients), a range of approaches to standard care, and a range of disease aetiologies and clinical features. Regardless of the real-world setting, teduglutide consistently shows a greater absolute treatment effect in the real-world than was seen in STEPS.

None of the eight studies had a control group, and therefore relative treatment effect cannot be estimated. However, it is unlikely that patients in these cohorts could have reduced PS without teduglutide. The mean time on PS prior to teduglutide in these 8 studies ranged from 3.0 to 9.8 years, making it highly unlikely that patients were still undergoing any process of natural adaptation. Furthermore, clinical feedback received at the first committee meeting was clear that patients who are stable on PS would not be expected to achieve PS reductions.

Further to the eight real-world publications identified above, a ninth real-world evidence study has been published since we conducted our systematic literature review. In this study, 69% (n=9/13) patients achieved PS independence within 24 weeks[24]. In the context of STEPS, where 0% of patients achieved independence within 24 weeks, this result is quite remarkable. It continues to reinforce the conclusion of our meta-analysis that more patients are able to gain independence from PS in the real-world than was seen in STEPS.

As a final point, the authors of real-world publications have independently recognised the discrepancy between the clinical trial and real-world results, and highlight this in their papers:

Joly 2020: *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*[17]

Puello 2021: *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*[20]

Harpain 2022: *We believe that a proactive and more aggressive dietetic adaptation of oral fluid and energy intake represents a crucial factor in enabling early and persistent teduglutide-induced reduction of PS volumes. The fast reduction in PN volumes, leading to PN-independency in >50% of patients after only 8 weeks and 92% after 72 weeks, is striking*[24]

Approach to modelling

To conclude, the placebo effect observed in STEPS led to patients increasing oral fluid intake and losing weight. These PS reductions would not have been attempted in the real-world. We acknowledge that this interpretation of the placebo results drives uncertainty – it calls into question whether the same could have occurred in the teduglutide arm and lead those results to be exaggerated. However, the fact that weaning with teduglutide in STEPS did not require increased fluid intake, enabled weight gain, and was significantly lower than real-world outcomes provides assurance that this is not the case.

We therefore chose our modelling approach with the aim of best reflecting real-world practice.

To reflect the implausibility of the placebo effect (patients stable on PS would be expected to remain stable on PS), we have not applied transitions for standard care in our base case. Assuming a placebo effect could apply to standard care (or subtracting a placebo effect from the teduglutide arm, which has the same impact) inhibits the generalisability of our model to the real-world. At the committee's request, we have provided a scenario where standard care experiences transitions for 6 months based on the placebo effect in STEPS and then reverts to baseline (ICER: £25,617 per QALY vs updated base case ICER: £24,718 per QALY). We don't believe that scenarios applying a placebo effect for longer than 6 months are warranted as the placebo response seen in STEPS is

unlikely to have been sustainable given the observations of increased oral fluid intake and weight loss.

To reflect the better results experienced with teduglutide in the real-world, we have pooled data from STEPS/STEPS-2 with real-world data from our Patient Support Programme in Australia. This approach is still conservative; the PSP data provide data for [redacted] (compared to STEPS/STEPS-2 n=42) and are only used to inform transitions for 12 months (compared to STEPS/STEPS-2 for 30 months). Furthermore, our meta-analysis showed that, [redacted]

Although we acknowledge the PSP data lacks a control arm, we would hope the committee may be willing to accept a greater uncertainty for an ultra-rare condition such as SBS-IF. As both the previous Guide to Methods of Technology Appraisal (2013) and the latest NICE Manual (2022) acknowledge, evidence generation for rare diseases is '*particularly difficult*'[25], and '*the evidence base will necessarily be weaker for some technologies, such as technologies used to treat patients with very rare diseases'* [26]. We note that *'in these specific circumstances, the committee may be able to make recommendations accepting a higher degree of uncertainty'*[25].

While uncertainty remains in the true treatment effect of teduglutide – which is to be expected for an ultra-rare condition – we are confident that our modelling approach errs on the side of being conservative but remains robust. Our model base case, with an ICER of £24,718 per QALY is comfortably cost-effective.

5 **Starting age in model**

The committee commented that it was unsure whether the starting age of the adult population in our model (50 years) reflected the real world. We chose 50 years as the mean age of patients at baseline in STEPS was 50.3 years. **Table 3** shows the average age of adult teduglutide patients included in real-world evidence identified by our clinical systematic literature review. As can be seen, patients in these studies similarly cluster around an age of initiation of 50 years old (range 46–54 years; weighted average 51 years). On this basis, there appears to be little justification to lower the starting age of the adult model.

Table 3: Mean age of real-world teduglutide patients

Study	Minimum age for inclusion	N	Mean age of population at initiation of teduglutide
Joly 2020	≥18 years	54	52.3
Lam 2018	≥18 years	18	47 (median)
Martin 2021	≥18 years	31	51 (median)
Pevny 2019	≥18 years	27	51
Puello 2021	≥18 years	18	54.4 (median)
Schoeler 2018	Not specified (but all patients were ≥18)	14	49.1
Tamara 2020	≥18 years	4	53
Ukleja 2018	≥18 years	6	46.3

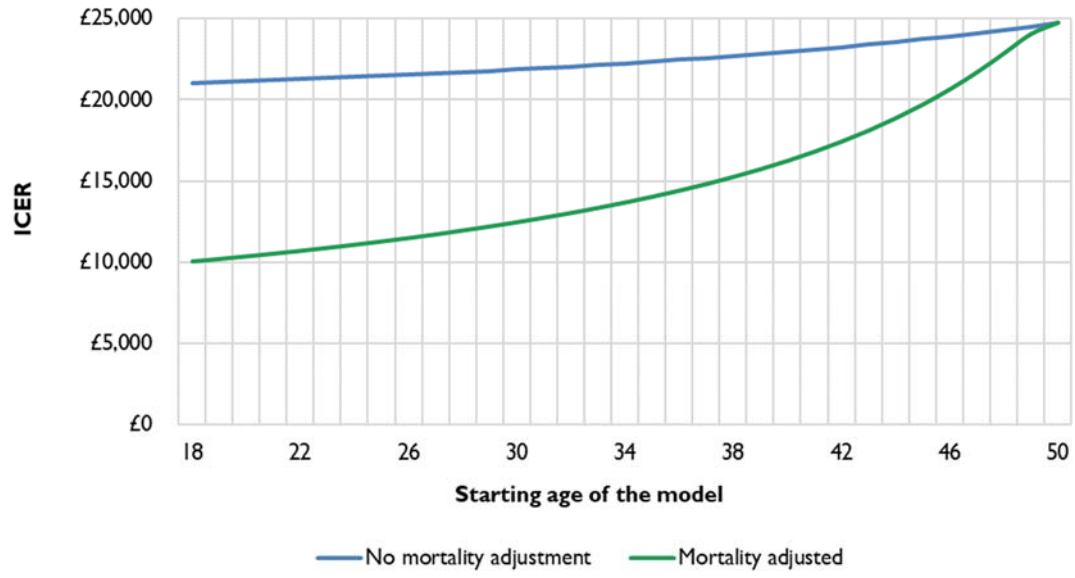
Despite this, at the request of the committee, we investigated how much changing the starting age affects our ICER. Lowering the starting age of the model (and making no other changes) improves the ICER, as it provides a longer time for cost savings and QALYs to accrue:

- Starting age 50 (base case): ICER £24,718 per QALY
- Starting age 45: ICER £23,728 per QALY
- Starting age 40: ICER £22,954 per QALY

It is notable that the ICER is not particularly sensitive to changes in starting age (see **Figure 3,** blue line). This is largely because our model uses extrapolated survival data from Salazar et al. 2021 (where the mean age at baseline was 53 years) and the change to starting age represented by the blue line in **Figure 3** does not change the use of the Salazar data. This means that even with a starting age of 18, the model assumes a starting mortality rate equivalent to a 53-year old cohort.

In the interest of fully exploring the issue, we can adjust for this, however the method is crude. The green line in **Figure 3** shows the ICER if we assume general population mortality applies until age 50, and after 50, mortality data are applied from Salazar et al. This is clearly implausible, however, the green line in **Figure 3** does provide a 'lower bound' ICER driven by reducing starting age, in contrast to the 'upper bound' ICER shown by the blue line in **Figure 3**. The true ICER for lower starting ages will sit between these two lines.

Figure 3: ICER by adult starting age with and without adjustment to mortality



Abbreviations: ICER, incremental cost-effectiveness ratio

Given our strong preference that, regardless of age (within license), SBS-IF patients receive equitable access to teduglutide (see comment 7), we also think it is merited to consider the overall cost-effectiveness of teduglutide in the population as a whole. Assuming [redacted] of teduglutide patients are paediatric (based on internal Takeda data), a weighted ICER for the whole population of patients with SBS-IF would be [redacted] per QALY based on a base case ICER of £24,718 per QALY in adults and £2,396 per QALY in children (the ICER in children is similarly calculated using the committee's preferred assumptions for co-medications, updated PS costs and updated PAS).

Although we acknowledge that the committee may decide to not recommend a technology in a particular subgroup, even if the technology is clinically and cost effective in the whole population[25], we hope the committee will keep this comfortably cost-effective weighted ICER in-mind when considering the degree of outstanding uncertainty and equity concerns.

Teduglutide for treating short bowel syndrome [ID3937]

Consultation on the appraisal consultation document – deadline for comments end of day on **1 April 2022**. Please submit via NICE Docs.

6	**Number of adult caregivers**
	
	The committee questioned whether it was appropriate to assume that all adults would have a caregiver.
	
	To be clear, we calculated that adult patients would have on average one caregiver each based on a multinational survey (including the UK) of 181 adult patients with SBS-IF. The survey did not explicitly ask how many caregivers each adult patient had. When asked about their living situations, [redacted]. We therefore assumed that:
	
	• 21% of patients have zero carers [redacted]
	  o This is likely to underestimate the number of carers per adult patient since it assumes all caregivers live with patients, despite some patients having a carer who does not live with them. [redacted]
	• 17% of patients have two carers [redacted]
	  o This is also likely to underestimate the number of carers per adult patient, as some patients who reported having 'more than one' carer may have more than two carers
	• 62% (the remainder) have one carer
	
	This results in a weighted average of 0.96 carers per adult patient (at a minimum, considering how the calculation likely underestimates carers per patient), and so on this basis we assumed one caregiver per adult patient. To address the committee's uncertainty that an average of 1 carer per patient might be an overestimate, we have provided a scenario with 0.8 carers per adult patient. This scenario has an ICER of £26,228 per QALY (vs our base case of £24,718 per QALY), and is therefore still comfortably cost-effective.
	
	Finally, we would like to echo comments heard during the first committee meeting and captured in the ACD about the extraordinary burden that carers face in this setting. There are several aspects to this, but particularly notable are the degree of medical care and skill needed, and the constant emotional labour that stems from having another person's life in your hands. Caregivers are never afforded the time to forget their carer responsibilities. The following quotes from a very recent publication looking at carers of paediatric patients receiving PS illustrates these points:
	
	"[W]ell, every morning, you have to unhook them, you've gotta give them their medicine, you've gotta make sure their lines and everything are taken care of and well managed. You've got to maintain any activities, everything is safe for them and for their body and what they're doing. You have to do all the prep for the [PS], you have to prep the lines, you've gotta do, again usually evening medication, medications during the day, etc. So, there's just a lot of medical work that's involved."[29]
	
	"I feel like we need to be flawless. I feel like we don't accept mistakes from ourselves or anybody else. But we put a lot of pressure on ourselves because we realize very much the stakes of us not being perfect."[29]

7	**Equity** The decision to issue an optimised recommendation for initiation of teduglutide in children only is not equitable. There is no difference in clinical need for teduglutide between an SBS-IF patient aged 17 and an SBS-IF patient aged 18, however by the present proposed recommendation, one will be allowed to receive teduglutide and one will not. Clinicians will be placed in the unenviable position of

	having to tell patients they cannot receive teduglutide – a treatment that could remove the constraint of PS from their life – because their bowel was resected too late. Moreover, once paediatric patients transition into adult care there will be a palpable, within-waiting room inequity between adult patients, potentially even of the same age – one who benefits from teduglutide and the other who cannot. This is an ultra-rare condition, a small and well-connected patient population, treated in a small number of highly specialist intestinal failure centres. This inequity will not go unnoticed. Furthermore, this equity issue compounds equity issues already faced by the SBS-IF patient population which teduglutide could help to address. The need for PS in England outstrips the available supply, particularly for compounded PS bags. The equity issue here is stark: who misses out when supply is poor? By reducing patients' days per week of PS and ultimately enabling some patients to wean off PS entirely, teduglutide is a technology which could ease PS supply burden. In turn, this would directly address inequality and unfairness in the existing distribution of PS. NICE's Health Technology Evaluations: The Manual (2022)[25] states that '*If considering excluding a subgroup, the committee must be convinced the harm to the NHS of including it is great enough to justify this decision'.* We hope that with this ACD response, we have been able to demonstrate that the NHS will not be harmed by the approval of teduglutide for use in the very small number of adults with SBS-IF. We believe that this is true, given that the range of ICERs we have provided for teduglutide show it is comfortably cost-effective.
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Teduglutide for treating short bowel syndrome [ID3937]

Consultation on the appraisal consultation document – deadline for comments end of day on **1 April 2022**. Please submit via NICE Docs.

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Teduglutide for treating short bowel syndrome [ID3937]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**Insert organisation name**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row.

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Teduglutide for treating short bowel syndrome [ID3937]

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Gravely disappointed that adults who stated the following will be severely disillusioned that their hopes have been thwarted with the decision not to provide access to teduglutide for adults, over 17 years of age: Member 2: …'I have been very disappointed and amazed that in almost 30 years there has been no drug, treatment or therapy offered to me which could address my underlying gut motility disorder, alleviate my symptoms or decrease my reliance on PN to any degree at all. Now, at last, there may be a drug or treatment available that could improve my condition, alleviate some of my symptoms and hopefully reduce or remove the need for PN. It would be devastating if this treatment or something similar was not made available, especially when it is available to other patients in other countries.' Member 3: … 'The only hope for some relief from this burden until now has been a transplant; suitable or not I've decided it's not for me, I would be replacing one set of problems for another. The concept of such an enormous operation with great risks that I currently face is not for me. A treatment that could avoid surgery and have the potential to reduce my nights on PN therefore reducing the number of times my CVC is accessed which reduces the risk of infection/sepsis is the only hope on the horizon for people like me. The burden of SBS/IF and PN is not an easy one to bear, I've adjusted, I cope most of the time, but I hide the fear for my future.' Impact of no treatment for people 17 years of age plus: devastating. Benefit of teduglutide for people 17 years of age plus: viable medication option prior to surgical route, transplant if suitable.
2	We are deeply concerned that while the committee initially acknowledged the 'impact of parenteral support on people with SBS and their carers was high' this has not resulted in equitable access to teduglutide for people aged 17 years and over.
3	Recommendation: when it is started in children and young people aged 1 to 17 If started prior to the age of 17, this is permitted to be continued into adulthood whereas 17 years plus will not have access to the medication. This will create a strong feeling of inequity and potentially raise concerns that the lives of those 17 years and over are not equally valued thus increasing the burden that patients and carers already endure.
4	Deeply concerned that within the close community of patients and carers who live with, and support people with short bowel syndrome and parenteral nutrition, people will rightly share the good news of access to the medication which will affect people being deprived of the treatment. The SBS and PN community stretches beyond hospitals, wards and waiting rooms; we're connected via social media platforms where people have access to information about treatment options which they too would like to benefit from for themselves or their loved ones.
5	Fearful for the impact on those who do not welcome nor accept parenteral nutrition, finding out that a medication has been denied to them which could eliminate or reduce what they see as a tremendous burden may have serious consequences.
6	Provision of home parenteral nutrition: this is under considerable strain which impacts directly on the patients and carers. Multiple infusions, increased infusion times, on and off contingency bags (not knowing what kind of nutritional support will be available and when) additional procedures to perform which all contribute to a reduce quality of life and an increase in mental health issues. The potential to reduce or stop parenteral nutrition should be welcomed by all. There will be cost savings, reduced risks and complications in addition to relieving the pressure on a fragile home parenteral nutrition service.
7	3.26 – There were no equality issues identified for teduglutide. The committee's decision not to make a recommendation for teduglutide in adults will cause significant equality issues.
8	We are aware of the submission by Dr Simon Gabe and fellow signatories and wish to record our support for their submission.

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Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, 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 our consultations 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.

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22 March 2022

Prof Jane Adam
Appraisal Committee Chair
National Institute for Health and Care Excellence

Re: Appraisal consultation document: teduglutide for treating short bowel syndrome

We read the NICE appraisal consultation document assessment regarding teduglutide with some surprise.

Our primary concern relates to discrimination against adults in England, for example:

- Adult patients in Scotland will be able to have access to this medication whereas they will not in England.
- A 17-year-old patient with short bowel who starts this medication will be able to continue to have this in adulthood whereas a young adult with short bowel would not be able to start this medication.
- Many other countries in Europe, America, Asia, Australia and New Zealand have access to this medication for patients with short bowel.

We believe that this is an effective treatment and our patients in England are being deprived of this potential treatment.

Although the committee did acknowledge the enormous burden experienced by patients with short bowel and that new treatments are needed and would be welcomed, it feels that this is simply a token acknowledgement. If the cost effectiveness of the drug assessed by complex modelling is marginal or uncertain then the committee should decide in the favour of acting for the patients. The acknowledgement of the burden is there at the beginning of the appraisal document but totally lacking in the final conclusions. This decision goes against both clinical and patient advice.

Other aspects from the consultation document include:

Page 4: "Clinical trial evidence shows that teduglutide reduces the number of days a week people with SBS need parenteral support compared with placebo. However, how much it reduces this is uncertain because the trial design may not reflect NHS practice."

This statement is not evidence-based. Furthermore, centres in England participated in the randomised controlled studies. We also do not think that this is a true statement regarding NHS practice in the management of short bowel syndrome. All clinical trials differ in some respect from the day-to-day clinical practice in all countries. The way the patients are managed in the NHS does not differ from other countries in Europe. We can be sure about this as we communicate regularly with our colleagues in Europe and some of these colleagues have come to view our clinical practice at our hospitals and taken back elements to enhance their practice of managing these patients. Therefore, we suggest that the real-world and trial evidence of the efficacy of teduglutide that is available from other countries is applicable to the same patient group in the NHS.

Page 4: Because of the uncertainties in the clinical evidence, the cost-effectiveness estimates are uncertain.

We presume this relates to data quality? There is a significant amount of data demonstrating that teduglutide is effective in decreasing parenteral nutrition requirements in patients with short bowel, as agreed by the committee. This is not just from the clinical trial data but also from 8 non-interventional real-world studies. However, the data relating to the real world studies was not included in the modelling. This data was presented to the committee and originates from a number of different countries and consistently shows a similar degree of benefit (approximately 30% reduction in parenteral nutrition requirements). We are not sure that appropriate weight is given to this information due to the methodology that is used by NICE.

Page 17: The cost-effectiveness results for children are much more favourable than for adults. The ERG clarified that this is because of the younger starting age and longer time horizon in the model for children. Teduglutide also reduces the costs associated with parenteral support (see section 3.11), and these 2 attributing factors mean that QALYs and cost benefits accrue for longer in the model. The committee concluded that the difference seen between the ICERs for adults and children are feasible.

One reason that the modelling comes out more cost-effective for children than for adults is that children have a longer lifespan and therefore the number of complications that can occur over time is greater than for adults. One of the problems that we have with this is that within the adult population there is considerable variability in the frequency of complications. There are plenty of patients who develop frequent and repeated central venous catheter infections, for example. For some patients this can happen 3 or 4 times a year and this is very resource intensive, with patients sometimes requiring intensive care support. In such patients we are sure that teduglutide would work out as being much more cost-effective, if this was included the model. We appreciate that when undertaking modelling, average numbers or frequencies needs to be used but as a result, incorrect conclusions have been drawn.

Page 23: The ERG provided ICERs using the lowest cost HPN provider, highest cost HPN provider and the mean price of all HPN providers to explore uncertainties around the true price of HPN in the NHS. When doing this, the ICERs ranged from cost-saving to cost-ineffective. … The committee considered the cost of parenteral support to be highly uncertain and noted the large impact on the cost-effectiveness results. It concluded that using the mean price of HPN was likely to be most appropriate for decision making because it is unlikely that the lowest HPN price would be accessed by the entire population with SBS. It also concluded that it would consider the highest and lowest cost HPN providers in scenario analyses

We appreciate that this is a difficult area. At the moment there are particular issues with the provision of home parenteral nutrition using compounded parenteral nutrition in England. Ultimately there are not enough compounding slots for the number of patients that we have. As a result, the prescriptions for home parenteral nutrition are becoming increasingly complicated, requiring multiple infusions every night. Not only has the burden increased for patients but also complications may be more frequent and the resultant cost of HPN provision is increasing and likely to continue to do so. We are using multi-chamber bags (MCB) with additional infusions of IV fluids and sometimes also additional IV vitamins and micronutrients. This is much more costly than the standard compounded home parenteral nutrition. Although we do not have the costs, we are unsure that this has been taken into account when asking NHS England for the costs of home parenteral nutrition. Equally, an average cost may not be appropriate if the range is skewed. As these issues have only developed over the past 1-2 years the data that you may have received may either be out of date or more skewed than has been appreciated.

Furthermore, the fact that we now have to ration compounded home parenteral nutrition for patients in England means that any treatment which would enable patients to reduce or come off parenteral nutrition should be welcomed; not only from a patient quality perspective, but also in order to reduce the national burden aseptic pharmacy services in compounding PN. Indeed, NHSE & I recognise the lack of aseptic pharmacy capacity as a major risk in the UK, not least because it has resulted in delayed hospital discharges throughout the country. This is a recent and evolving issue and therefore has not been considered by the committee. Clearly any medication that can reduce PN requirements will be of clinical and ultimately likely cost benefit to this stressed system. In addition, around 30% of patients on home parenteral nutrition are now receiving additional specialist nursing care and there are also not enough specialist nurses to provide the service in the country. This issue is also increasing the length of stay for new patients being discharged on home parenteral nutrition, adding both burden and cost to the NHS overall. While these issues cannot be modelled for, we strongly recommend that the committee takes them into account.

Page 26: NICE's guide to the methods of technology appraisal notes that judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICERs. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented.

Following this statement, the document mentions that the committee noted uncertainties in 6 different elements and yet it goes on to state that for the committee to recommend teduglutide, the ICER would have to be comfortably within the range of cost effectiveness. This is likely to be the core of any disagreement. It seems to be appreciated that there is uncertainty around the ICER and yet more emphasis is placed upon a calculation that shows clear cost effectiveness (see section 3.24). Surely if there is a lack of certainty then this method of relying on the ICER should be discarded (in the same way that some clinical data has been discarded by the committee).

Page 28: 3.26 There were no equality issues identified for teduglutide.

As described above, we believe that this final decision would cause significant equality issues in this patient group (based on age), within the UK (as it is available in Scotland and within Europe and the rest of the world).

Dr Simon Gabe, Director of the National Reference Centre for severe intestinal failure, St Mark's hospital, London

Professor Simon Lal, Director of the National Reference Centre for severe intestinal failure, Northern Care Alliance, Salford, Manchester

Dr Trevor Smith, BAPEN President & director of the severe intestinal failure Centre, University Hospital Southampton, Southampton

Dr Jeremy Nightingale, Chair of the British Intestinal Failure Alliance (BIFA) and emeritus consultant gastroenterologist, St Mark's hospital, London

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Teduglutide for treating short bowel syndrome [ID3937]

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Intestinal failure rehabilitation service,** **Gastroenterology Department,** **Great Ormond Street Hospital for Children, NHS Foundation Trust,** **London WC1N 3JH**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**no links with tobacco industry**]
Name of commentator person completing form:	Dr Susan Hill

Comment number	**Comments** Insert each comment in a new row.

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	I am delighted that the committee is prepared to recommend funding the use of teduglutide in children with SBS associated intestinal failure. In addition to transforming the life of many children with short bowel syndrome the benefits of teduglutide should improve life for siblings and parents.
2	I am concerned that a young person presenting in their 20's or 30's with short bowel syndrome and intestinal failure would not be able to benefit from teduglutide. The young adult still has a long life-expectancy and at the same time needs the best possible health to develop their career/establish their working life + may have the added burden of caring for small children. Even a night or two off PN each week (and if one night off can be managed then it is immediately possible to have two nights/week off) would make a huge difference to their ability to keep a fulltime job and support a young family.
3	I am concerned that the committee were not made aware of the increased demand for home PN in England. Bespoke Home parenteral nutrition (PN) formulations tailored to the individual patient's needs are a limited resource. As a result, some adults with intestinal failure have not had access to individualised formulations and have had to make do with standard preparations which could result in impaired health and more complex infusions.
4	I am concerned that this recommendation will impede the care given by adult intestinal failure rehabilitation centres in England which up to now has been to the highest standard on a worldwide basis. Teduglutide is most effective when the patient's care is managed by a specialist multidisciplinary intestinal failure rehabilitation service. There is the best possible framework already in place for ensuring appropriate use of teduglutide in adults with national clinical meetings to discuss individual cases and two national reference centres, St Marks, London and Manchester.
5	I am concerned that the committee will not be aware of our recently publication on the cost of short bowel syndrome associated intestinal failure to the specialist centre (which is not the full cost since emergency admissions with catheter -related bloodstream infections and other complications that could be managed in the local hospital were not dealt with in the specialist centre). Although this is a paediatric paper adult services will have some similar costs that may not have been taken into account: Jones BC, O'Sullivan B, Amin SP, et al. Patient-level costing analysis of paediatric short bowel syndrome care in a specialist tertiary centre. Pediatric Surgery International. 2022 Apr;38(4):533-539. DOI: 10.1007/s00383-022-05074-6. PMID: 35211770; PMCID: PMC8913464.
6	

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- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more

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Teduglutide for treating short bowel syndrome [ID3937]

Consultation on the appraisal consultation document – deadline for comments end of day on **1 April 2022**. Please submit via NICE Docs.

information.

- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, 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 our consultations 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.

Comments on the ACD received from the public through the NICE Website

Name	[redacted]
Role	
Other role	
Organisation	Short Bowel Survivor & Friends
Comments on the ACD:	
Has all of the relevant evidence been taken into account?	I believe that much of the evidence collected demonstrates the awesome burden PS places on patients and carers. Death from Intestinal Failure may be rare - however as recently as last month we have witnessed a friend's child needing a liver transplant due to TPN. His parents feel lucky but realise he will now need life long medication. The child of another family we know had to have a bowel transplant due of lost line sites. Yesterday a 3 year old was 'blue lighted' to hospital because his line had split and caused a serious loss bleed! These are the issues faced by families on PS
Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?	The summaries of clinical and cost effectiveness do seem reasonable for use in children and young people. I understand that NICE need more up to date review of the cost of concomitant medications for use with adults by the Company - but would expect that all patients with SBS - Intestinal Failure are given access to Teduglutide if needed.
Are the recommendations sound and a suitable basis for guidance to the NHS?	I believe the recommendations for use with children and young people are a suitable basis on which to provide guidance to the NHS.
Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	I am minded to suggest that setting the limit for provision of Teduglutide at 17 may prove discriminatory on the grounds of age?
	I am pleased that NICE has recommended Teduglutide for use with children and young people and that once started it will continue to be provided as long as needed regardless of age,

	People would welcome new treatment options for short bowel syndrome that reduce the number of days of parenteral support "I believe people would welcome the new treatment. Many have inquired about it having seen reports over time, particularly families struggling with PS long term 7 nights per week sometimes single handed because of a partner being disabled. This burden can, and does lead to depression! Also two families that have been on the trials have requested that their children be allowed continue treatment with Teduglutide."

Name	[redacted]
Role	
Other role	
Organisation	
Comments on the ACD:	
Has all of the relevant evidence been taken into account?	The post-trial real world experience needs to be better considered, to reflect the better response rates.
Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?	- The post-trial real world experience needs to be better considered, to reflect the better response rates. - In addition, patient value should be better considered. There is strong published evidence that QoL is better with fewer PN nights. Patients ask to reduce their PN nights when reviewed in clinic and this is a strong driver for requesting this drug; indeed this is evidence-based in published qualitative research. - The potential impact on IFALD needs to be better considered. Reduced PN and improved absorption leads to reduced liver injury. This could prevent the need for multivisceral transplantation.
Are the recommendations sound and a suitable basis for guidance to the NHS?	No - in view of my comments above.
Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	Age: this discriminates against those > 18 years old. Geography: this discriminates against people in England vs Scotland, or people who with IF who wish to move from Scotland to England. People: this discriminates against my patient who has ceased PN with Teduglitude. He will be forced back on PN if the drug is stopped.

Teduglutide for treating short bowel syndrome [ID3937]

ERG critique of the company response to the Appraisal Consultation Document (ACD)

Produced by: Aberdeen HTA Group

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Date completed: **7 April 2022**

Contains: [redacted]

Following the first committee meeting for this appraisal, the committee released an appraisal consultation document (ACD) indicating that they were minded not to recommend teduglutide for adults for routine commissioning, but that they would recommend teduglutide for patients who commence treatment before they are aged 18.

In their response to the ACD, the company provided a revised economic base case, updated PS costs, updated PAS discount and outlined further arguments to support their approach in relation to several assumptions which the committee expressed reservations about:

1. Generalisability of the results from STEPS/STEPS-2 trials
2. Starting age in the model
3. Number of adult caregivers

They urge the committee to reconsider the evidence to make teduglutide available for all patients with SBS-IF under routine commissioning. The company raises two key issues for the committee to take into account; (1) the inequity of recommending the treatment to only those who initiate treatment before the age of 18, and (2) the fact that SBS-IF is an ultra-rare condition in which decisions must be made under greater uncertainty.

In this document, the ERG provides a brief commentary/critique of the company's response and their revised economic modelling. It should be read in conjunction with the company's response to the ACD. The ERG will provide a further cPAS appendix that reproduces the company's revised analysis and the ERG's additional scenario analyses (table 1) using the confidential CMU prices available for co-medications which includes: oral ondansetron and intra-venous proton pump inhibitors (PPIs).

1. Revised base case and benefits not captured by economic model

The company have made several updates to their base case, utilising the preferred assumptions of the committee. These include preferred comedication costs, the mean cost of PS sourced from all companies within the HPN framework and an updated PAS discount ([redacted]). These combined changes result in an ICER of £24,718 per QALY (previously £9,691).

Table 2. Company base case post ACD

Scenario	Incr. cost	Incr. QALY	Cumulative ICER
Previous company base case	[redacted]	[redacted]	£9,691
Committee preferred comedication assumptions	[redacted]	[redacted]	£29,372
Mean PS costs	[redacted]	[redacted]	£40,174
Updated PAS discount	[redacted]	[redacted]	£24,718
Company base case post ACD	[redacted]	[redacted]	£24,718

Given the variety of prices available for HPN, the company have provided scenarios where the total cost of all HPN components (PS bags, delivery, nurse time and taurolock), based on mean prices, is adjusted by up to ±20%. It should be noted that a decrease of 10% results in an increase in the ICER over the cost-effectiveness threshold of £30,000 per QALY.

The company also highlights other benefits of teduglutide not currently captured in the economic model. These are:

a) Avoidance of intestinal transplant

The company note the discussions at the first committee meeting, and subsequently reiterated following the ACD, that the ability of teduglutide to reduce a patient's required days of PS would reduce the likelihood of complications that may result in the need for intestinal transplant.

The ERG agrees that this is a potential benefit of teduglutide, however acknowledges that there is insufficient data to back up these claims and the magnitude of benefit may be small given the rarity of the procedure in SBS-IF patients. Intestinal transplant should only be considered in a minority, select group of patients in which their condition cannot be managed with PS or have a high risk of death due to the underlying disease.[1,2]

b) Reduction of PS volume but not days

The model focusses upon the reduction of PS days required each week. However, the company states that hourly reductions in PS required per night, through reduced volume, would also represent a benefit for patients. Typically, patients receive 10-14 hours of PS per night which represents a substantial burden resulting in disrupted sleep and time taken out of their morning and evening activities.

Following comments made by patient and carer representatives at the first committee meeting and in the original company submission it is clear that any reduction in PS requirements does offer a substantial benefit to patients and carers. However, the ERG contends that this benefit is captured in the model. The model does not specify the number of hours a patient is on PN. Therefore, it can be assumed that, given the heterogeneity of the disease, that the HRQoL data for reductions in PS days captures the differences in PS volume required per night by patients. A global study of SBS-IF patients (N=181) found that on average patients receive [redacted] *of PS per night suggesting the variability observed between patients.*[3] *It should also be acknowledged, that the relationship between PS volume and quality of life has not been established, nor did any studies identified in the company's SLR report utility values by volume of PS received (section B 3.4.2 document B). Furthermore, the previously cited study* [redacted].

c) Service pressure

The ERG notes the company's argument that Teduglutide may help to relieve some of the pressure the NHS is currently under in its provision of home PN, and supply issues with PS. The company argues that the ability of teduglutide to reduce home PN requirements would alleviate some of this pressure.

The ERG agrees with the company that teduglutide may help alleviate pressure on the supply of PS through a reduction in home PN requirements, and that these benefits have not been explicitly captured in the model.

2. Co-medication costs

The company have applied the preferred assumptions for co-medication requirements of SBS-IF patients outlined within the ACD. These assumptions are listed on page 24 of the ACD document and summarised by the company within table 3 of their response.

The company argues that the revised resource use, in particular proportions receiving treatment under IV, may be conservative, but have accepted the committees' assumptions in

their revised base case. The ERG is agreeable to the company's amendments to their comedication assumptions. The ERG also acknowledges a comment by a clinical expert at the committee meeting that ondansetron and IV PPIs would be prescribed within the secondary care setting. Therefore, the use of eMIT prices is more representative. The eMIT price per day is £2.10 for IV PPIs and £0.16 for ondansetron which is a substantial reduction over the BNF prices used by the company (£9.70 and £0.35 per day respectively). The ERG includes the revised eMIT prices in its preferred base case analysis.

3. Generalisability of results from STEPS

The company presents several limitations of the STEPS trial in terms of its generalisability to standard SBS-IF care and its rationale for the modelling approach used in this appraisal. The company explains that the treatment effect in the standard of care arm is not representative of a patient's improvements in intestinal absorption but rather the effect of an inappropriate weaning algorithm used in the trial. The company therefore considered it appropriate to remove the placebo effect, assuming that patients retain their baseline value on standard care treatment.

Furthermore, the company argue that, given the restrictive nature of PS adjustment algorithms used in the trial, the magnitude of reductions in PS observed in the teduglutide arm was lower than what would be achievable in clinical practice. The company argue that both of these issues compound into an underestimation of the treatment effect of teduglutide. The company provides a detailed explanation with evidence from the trial to back up their claims within comment 4 of their response.

A meta-analysis which compares the proportion of patients who achieved PS independence in STEPS with 8 real world studies is presented to exemplify the lack of generalisability of the results. The results show that [redacted]

The company concludes that incorporating the placebo effect in their model inhibits the model's generalisability, citing that the reductions in PS seen in the standard of care arm would not be attempted in clinical practice. However, the company have provided an additional analysis which utilises the transitions observed in the placebo arm of STEPS before they revert to baseline after 6 months. This results in a small increase in the ICER to £25,617.

The ERG considers the company's explanation of the limitations of the STEPS trial to be reasonable and in concordance with the views of both the ERG's clinical expert and clinical

expert opinion from the committee meeting, that using urine output alone to determine whether to reduce a patient's PS is not representative of UK clinical practice. The ERG agrees that the trial effect may under-estimate the true relative effectiveness, and hence over-estimate the ICER for teduglutide vs. standard care.

However, the meta-analysis results should be interpreted with caution. Whilst they do suggest that a [redacted] *would achieve PS independence than that observed in the STEPS/STEPS-2 trials, the studies compared are observational with no comparator treatment. Therefore, the studies are more prone to methodological bias. Furthermore, the comparison of an RCT with observational studies adds substantial uncertainty of the relative effect size for teduglutide as the benefit of randomisation is lost.*

Similar to the criticisms of the meta-analysis, the use of the PSP data within the model leads to further uncertainty. These patients were not subjected to the weaning protocol of patients within the STEPS trials, therefore the reductions in PS observed are not directly comparable. The ERG has also considered whether the magnitude of PS reductions in the STEPS population could be greater in the long term over patients in the PSP study whose reductions in PS were not constrained by their baseline PS volume. However, as exemplified in figure 2 of the company's response, the proportion of patients gaining PS independence after 12 months was comparable to that seen in the STEPS population regardless of the significantly greater reductions in PS observed up to month 12 in the real-world observational studies.

The ERG provides additional scenario analyses that 1) use the STEPS data only rather than pooled data for the Teduglutide arm, 2) incorporate the placebo effect for the first 6 months in the standard care arm and 3) a combination of scenarios 1 and 2. It should be acknowledged that the third scenario represents a worst-case scenario for teduglutide and is likely an under-estimate of the true relative treatment effect of teduglutide.

4. Starting age in model

At the first committee meeting, it was found that a significant driver of cost-effectiveness in the paediatric population was the long-time horizon of the model in children (94 years) versus adults (50 years). This is because greater QALY benefits and cost savings accrue over the longer timeframe. Further discussions centred around the plausibility that the starting age of 50 used in the model was not representative of adult patients with SBS-IF in the real world. The starting age used was determined by the average age of patients within the STEPS trial at baseline (50.3 years).

The company presents data on age at initiation of teduglutide, sourced from several studies which exemplify that the starting age used in the model is in line with what is seen in the real world. However, in order to explore the uncertainty, the company presents several scenarios in table 2 their response where differing starting ages are used (age 45 and 50) with general population mortality adjustments made participants who are younger than the average age of patients within the mortality data used(53 years).[4] The implication of the mortality adjustment is clearly presented in figure 3 of the response, where applying the mortality risk of a 53-year-old to an 18-year-old results in an ICER which is insensitive to changes in starting age. The company argue that applying general population mortality before age 50 represents a "best case" scenario and applying the Salazar et al. data for the total model time horizon represents the "worst case" scenario, where the true ICER would lie somewhere in between.

Finally, the company presents analysis of the total population. The company's finds that the recommendation of teduglutide treatment for initiation in children only is inequitable, therefore the whole population should be considered in the determination of cost-effectiveness (discussed further in section 6 or comment 7 of the company's response). A weighted average ICER of both populations is calculated which assumes that [redacted] of patients are paediatric (based on internal teduglutide data). This results in an ICER of [redacted].

The ERG agrees with the company's choice of starting age in the model and considers it appropriate that the starting age reflects the trial population. The ERG presents further evidence of the average age of SBS-IF patients:

- *A cohort study of 53,040 US SBS patients hospitalised between 2005 and 2014 reported an average of 56.6 years.[5]*
- *UK HES data for 2019/20 of patients undergoing a hospital procedure associated with SBS (*Endoscopic extirpation of lesion of lower bowel using fibreoptic sigmoidoscope) *reports an average age of 60.2 years.[6]*

Given a slightly older age in the HES data, exploring a scenario with an older starting age may also be of interest. The ERG provides a scenario where a starting age of 60 is explored in section 7 of this document.

Scenario analyses that reduce / increase starting age in the model result in a moderate decrease /increase in the ICER, especially in scenarios where general population mortality is assumed before the age of 50. These scenarios illustrate the uncertainty surrounding the impact of starting age, but the ERG is satisfied that the company base case analysis is appropriate.

The ERG does not recommend the use of the total population ICER to be used in decision making. The ERG finds this analysis to be crude and not transparent in light of the significant uncertainties identified in the paediatric base case.

5. Number of adult caregivers

The company clarifies that the assumption of 1 caregiver per patient assumed in the model is based on a large multinational survey of patients and carers with SBS-IF.[3] The survey collected information on a patient's living situation and whether they had more than one caregiver, the survey results did not report how many caregivers each patient has. Therefore, using inferred information from the survey results, the company developed a weighted average of 0.96 caregivers per patient which was rounded to 1. To explore the uncertainty, the company provides a scenario of 0.8 caregivers per patient which results in a small increase in the ICER to £26,228.

The ERG finds the assumption of one caregiver per patient agreeable and acknowledges the company's comments with regard to the significant burden experienced by carers. These comments were also echoed by patient and carer groups within the first committee meeting. The ERG also notes an additional assumption within the model that patients would receive 0.8 hours of home nurse care per week for each day of PN they require. This value is based on a resource use study where it was reported that 30-50% of patients require 2 hours of home nurse care per day of PN.[7] To illustrate the impact of caregivers and home nurse requirements on the cost effectiveness results, the ERG presents a scenario of removing carer disutility's and home nurse costs from the model in section 7 of this document.

6. Equity

The company present arguments for why the recommendation for teduglutide only in patients who initiate treatment before the age of 18 is inequitable and note the supply issues within the HPN framework where clinicians are already having to make the determination of who will receive home parenteral support when supply is low.

The ERG agrees that the company's equity considerations have merit, particularly given that differing recommendations in adults and children would lead to a potential implication where two adult patients with equal clinical need may have different access to treatments, driven purely by whether they developed their condition as a child or as an adult.

7. ERG preferred base case and additional analyses

The tables below present the ERG's preferred base case and scenario analysis. The ERG prefers the use of secondary care prices for IV PPIs and Ondansetron following the advice from clinical experts during the first committee meeting. The ERG base case ICER is £25,393, representing a small increase over the company's base case ICER of £24,718.

The additional scenario analyses conducted by the ERG find that the use of STEPS/STEPS-2 data only in the model and applying the placebo transitions observed in STEPS up to 6 months in the model result in an ICER of £31,301. As stated previously, this represents a pessimistic scenario therefore it is likely the true ICER would be lower than this. The increase in starting age in the model moderately increases the ICER which is anticipated given the shorter time horizon in which cost and QALY benefits would accrue. The removal of carer disutilities and home nursing costs is a purely demonstrative scenario. The scenario shows the QALY and cost implications of care for these patients and their effect on the cost-effectiveness results.

Table 2. ERG preferred base case post ACD

Scenario	Incr. cost	Incr. QALY	ICER
Company base case post ACD	[redacted]	[redacted]	£24,718
eMIT prices used for IV PPIs and oral ondansetron	[redacted]	[redacted]	£25,393
ERG base case	[redacted]	[redacted]	£25,393

Table 3. Additional scenario analyses conducted by the ERG

Scenario	Incr. cost	Incr. QALY	ICER
ERG base case post ACD	[redacted]	[redacted]	£25,393
1. STEPS/STEPS-2 data for teduglutide arm	[redacted]	[redacted]	£30,285
2. Apply placebo transitions to standard of care arm up to 6-months	[redacted]	[redacted]	£26,296
3. 2+3	[redacted]	[redacted]	£31,301
4. Starting age of 60	[redacted]	[redacted]	£28,417
5. Removal of carer disutilities and home nursing costs	[redacted]	[redacted]	£98,556

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