Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende teduglutid til behandling af korttarmssyndrom

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. teduglutid
2. Forhandlingsnotat fra Amgros vedr. teduglutid
3. Ansøgers endelige ansøgning vedr. teduglutid

Kommentarer fra Takeda Pharmaceuticals A/S på Medicinrådets udkast til anbefaling vedr. teduglutid til behandling af korttarmssyndrom

Side 4

"Dog ophørte 26 % af patienterne behandlingen med teduglutid pga. uønskede hændelser i opfølgningsstudiet"

Det er vi ikke enige i. 23% stoppede pga. en AE (16+4/88). Se venligst nedenstående tekst taget direkte fra STEPS-2 publikationen:

> *"Of the 88 patients enrolled in STEPS-2, 65 (74%) completed the study (n=30/37 TED/TED; n=29/39 PBO/TED; n=6/12 NT/TED). In the TED/TED subgroup, seven patients discontinued because of AEs (n=4; three were TEAEs, described below, and one was an ongoing event (nontreatment-emergent AE) that originated during the initial placebo-controlled study), patient decision (n=2), and death (n=1; case of catheter-related sepsis described below). In the combined NT/TED and PBO/TED subgroups, 16 patients discontinued because of AEs (n=12), patient decision (n=2), or investigator decision (n=2)."*

Side 32

"Medicinrådet vurderer, at ansøgers analyser af opfølgningsstudierne, 005, STEPS-2 og STEPS-3 ikke er retvisende. Ingen af disse studier indeholder en kontrolgruppe, og ansøger antager, at de observerede effekter i studierne fuldt ud kan tilskrives teduglutid. Medicinrådet er uenige i denne antagelse og fremhæver, at SBS er en heterogen og ofte dynamisk tilstand, hvor patienterne kan opleve ændringer i deres behov for HPS."

På intet tidspunkt antyder Takeda, at "*de observerede effekter i studierne fuldt ud kan tilskrives teduglutid*". Desuden blev opfølgningsstudierne først inkluderet i den komparative analyse under valideringsfasen på direkte opfordring af medicinrådet.

Side 39

"Medicinrådet vurderer, at der ikke er dokumenteret forskelle mellem teduglutid og placebo eller SOC ift. andelen af patienter, der bliver fri for HPS."

Her mener Takeda at Medicinrådet bør tilføje … *ikke er dokumenteret forskelle mellem teduglutid og placebo eller SOC ift. andelen af patienter, der bliver fri for HPS* ***indenfor 6 måneder****.*

Side 40

*"… I studie-004 blev patienternes livskvalitet vurderet ved 3 forskellige ikke-sygdomsspecifikke spørgeskemaer (****IBDQ****, EQ5D og SF36) ved …"*

IBDQ er sygdomsspecifik. Blot ikke for SBS-IF.

Side 40

Tabel 9 indeholder upublicerede data fra Appendix R, som skal blændes.

Side 42

"Størrelsen af teduglutids effekt overfor placebo kan ikke vurderes ud fra de tilgængelige data."

Takeda forstår ikke, hvorfor dette er tilfældet. Vil I være venlige at uddybe.

Side 45

"Desuden blev der rapporteret om tre tilfælde af udvikling af cancer hos patienter behandlet med teduglutid i STEPS2 (hhv. ikke-småcellet lungecancer, planocellulær lungecarcinom og adenocarcinom af ukendt oprindelse), ***hvoraf de to tilfælde ikke kunne udelukkes at have forbindelse til teduglutid****."*

I artiklen skriver forfatterne at de 2 tilfælde vurderes til *ikke* at være forbundet til teduglutid:

> *"A 64-year-old man in the PBO/TED subgroup was diagnosed with non-small-cell lung cancer 3 months after starting teduglutide. This patient had an extensive smoking history (about 30 cigarettes per day for about 30 years). In addition, during his career as a technician, the patient had been exposed to asbestos for an unknown period of time. Teduglutide was discontinued upon diagnosis (5 months before death), and the event was considered unrelated to the study drug. A third patient was diagnosed with cancer during STEPS-2. A 74-yearoldman in the TED/TED subgroup with a history of smoking (10 cigarettes per day for 5 years and stopped approximately 25 years ago) was diagnosed with lung squamous cell carcinoma more than 1 year after starting teduglutide and withdrew from the study. The event was not considered related to teduglutide and was ongoing as of last follow-up."*

Takeda mener at dette bør reflekteres i ordlyden i rapporten.

Side 45

"… hvilket ikke indikerer en ***væsentlig*** *øget samlet forekomst… "*

Ud fra konteksten mener Takeda, at dette bør ændres til *… hvilket ikke indikerer en* ***signifikant*** *øget samlet forekomst…*

Side 47

"Ingen af studierne har tilstrækkelig styrke til sikkert at kunne detektere forskelle mellem interventionen og komparatoren."

Det er ikke korrekt, at de placebokontrollerede registreringsstudier ikke har styrke til at detektere forskelle imellem intervention og komparator.

I publikationen for STEPS står der blandt andet følgende i afsnittet *Statistical Analysis*:

> *"Eighty-six patients were randomized in a 1:1 ratio to detect differences in responder rates between teduglutide 0.05 mg/kg/d and placebo groups of 35% vs 6%, respectively, based on the response rates reported in the earlier phase 3 study (α = .05, 2-sided test and power = 90%)."*

Og for 004 publikationen står der følgende i *Statistical Analysis* afsnittet:

> *"All statistical tests were two-sided with a level of 0.05. A sample size of 80 randomised subjects (32 subjects in each of the two teduglutide treatment groups and 16 subjects in the*

placebo group) was required to provide at least 90% power to detect an increase in the percentage of subjects who had the protocol defined minimum response defined as a parenteral volume decrease of 20% for week 20 and maintained at week 24 which, on average, was estimated to correspond to one day off. parenteral support (from 5% in the placebo treatment group to 50% in the teduglutide treatment groups in the study). The power calculations were based on two-sided tests of significance using the Fisher exact test."

Side 68

"Medicinrådet vælger derfor kun at inkludere serious adverse events, som defineres som hændelser, som er livstruende, kræver hospitalisering eller resulterer i død."

Denne definition af serious adverse events er ikke korrekt. Se definitionen af serious adverse events samt definitionen af intensiteten af et adverse event (mild, moderate og severe), som Takeda har delt med Medicinrådet under valideringsfasen.

Andet

SBS-Registry (eksempelvis s. 28)
Der skal generelt gøres opmærksom på hvilket data-cut der præsenteres/henvises til i rapporten. Vi gør opmærksom på, at seneste data cut endnu ikke er publiceret, og derfor skal resultater derfra blændes.

Høringssvar fra Takeda Pharmaceuticals A/S på Medicinrådets udkast til anbefaling vedr. teduglutid til behandling af korttarmssyndrom

Takeda appreciate the opportunity to comment on the draft evaluation report for teduglutide and to provide clarity on a few misperceptions and disagreements.

As recognized by the Danish Medicines Council (DMC), Short-Bowel Syndrome with Intestinal Failure (SBS-IF) is a rare and heterogenous condition, which makes generating high quality evidence and performing accurate economic evaluations challenging. Takeda aimed to make the most of the available evidence in our application to the DMC while being transparent and honest about the limitations of the submitted evidence. Further to this, Takeda has proposed to address any remaining uncertainties in an outcomes-based agreement.

Teduglutide has been available in other countries to treat SBS-IF in adults since 2012 and in children since 2016. Consequently, there is a wealth of **Real-World Evidence (RWE)** available to support the findings of the registration studies. Having this amount of data available on real-world effectiveness at the time of a DMC evaluation is unique, and especially so for a rare disease. However, in their assessment, the DMC only accept placebo-controlled **Randomized Controlled Trials (RCTs)** as clinical documentation and the DMC put very little weight on other evidence, including RWE. This is a significant limitation in the evaluation of teduglutide because the full benefits of teduglutide are not expected to be realised during the first 6 months of treatment i.e., within the duration of the placebo controlled RCTs. Takeda believes that broadening the scope of evidence considered for the evaluation of treatments targeting rare diseases beyond placebo controlled RCTs would lead to better and more informed decisions.

Modelling assumptions in rare conditions are inherently uncertain. Takeda has based our assumptions on RCTs, RWE, consultations with clinical experts, and dialogue with the DMC and investigated the impact of these assumptions in sensitivity analyses. Unfortunately, on several accounts the draft evaluation report does not acknowledge the nuances of preliminary dialogues with the DMC, discussions in the application and input from clinical experts. Further to this, based on the tone and conclusions of the report, Takeda is concerned that not all key issues have been fully represented by the DMC in discussions with the expert committee. Takeda has prioritized selected points below that require clarification or rectification.

Analysis of extension studies (transition probabilities for teduglutide)

The DMC disagrees with Takeda's analyses of the extension studies (005, STEPS-2 and STEPS-3). Takeda would like to clarify that the extension studies were not initially included in the comparative analysis but were added during the validation phase on specific request from the DMC.

The DMC argues that data from the extension studies cannot be used as clinical documentation for the effect of teduglutide beyond week 24 and, consequently, that there is no clinical documentation for the effect of teduglutide beyond 24 weeks. This animates the DMC to present the following 2 main scenarios:

1) **Include STEPS-2 data**; assuming an effect of teduglutide beyond 24 weeks, and
2) **Exclude STEPS-2 data**; assuming no additional effect of teduglutide beyond 24 weeks.

Excluding STEPS-2 represents a clinically implausible scenario. All available evidence suggests that the effect of teduglutide continues beyond week 24. Further to this, the parenteral support (PS) weaning algorithms of the 004 and STEPS studies did not realistically allow patients to wean off PS completely within 24 weeks,

which means that the exclusion of STEPS-2 is also, essentially, assuming that teduglutide cannot lead to complete wean off. Scenario 2 causes the QALY gain to be cut in half (from 0.8 to 0.4) and the ICER to increase by a factor of 2.4 (from 8.9 to 21.5 mio. DKK/QALY gained) vs scenario 1.

Testimony of Global Key Opinion Leader and Principal Investigator is not reflected in the draft evaluation report (transition probabilities for SOC)

Takeda finds it surprising that the DMC goes directly against a testimony from a global clinical expert in SBS-IF without acknowledging it and without assessing the impact of the assumption in a scenario analysis in their draft evaluation report.

In a detailed written testimony (Appendix S), Global Key Opinion Leader and Principal Investigator of the STEPS study, Prof. Palle Bekker Jeppesen states that the high placebo response in STEPS was caused by a protocol violation and would not be sustainable. Takeda included the artificially high placebo response from STEPS in the first 24 weeks of the model, leading to a bias in favour of SOC. However, Takeda did not extrapolate the artificially high and unsustainable placebo response beyond the 24-week duration of the STEPS study in our base case model. The impact of this assumption was tested in a scenario analysis. Conversely, the DMC assumes without any documentation that the placebo response from the STEPS study can be sustained for the rest of the patients' lives. Takeda does not find this assumption realistic. Further, the assumption is changed without mentioning the expert testimony (Appendix S) and without investigating the impact of the assumption in a sensitivity analysis.

HRQoL values

Takeda applies literature based HRQoL values from a peer reviewed UK vignette study in their base case analysis. In a scenario analysis, Takeda applies HRQoL values from an unpublished (abstract only) Canadian vignette study. Takeda argues that the UK HRQoL values are most relevant because 1) other HRQoL values applied in the model are also based on UK preference weights, and 2) they are the only HRQoL values available that have been peer reviewed. Despite the above argumentation, the DMC chose to apply the Canadian HRQoL values, because, in their opinion, the UK HRQoL values are too high. Takeda disagrees with this approach and find that it is not sufficiently documented.

Lifetime treatment

The DMC argues that treatment with teduglutide would most likely be stopped following a stable period, but then fail to adjust for the reduced cost in the health economic model. Given that the price of teduglutide is the main cost driver, Takeda believes that the DMC should have attempted to quantify the impact on the ICER of assuming that teduglutide is not a lifetime treatment for all patients in a number of sensitivity analyses.

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

16-05-2022
MGK/CAF

Forhandlingsnotat

Dato for behandling i Medicinrådet	15.06.2022
Leverandør	Takeda
Lægemiddel	Revestive (teduglutid)
Ansøgt indikation	Korttarmssyndrom

Forhandlingsresultat

Amgros har opnået følgende pris på Revestive (teduglutid):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Nuværende SAIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Revestive (teduglutid)	5mg*	28 stk.	121.998,27	[redacted]	[redacted]	[redacted]
Revestive (teduglutid)	1,25mg**	28 stk.	55.474,62	[redacted]	[redacted]	[redacted]

[redacted]

Informationer fra forhandlingen

Amgros har ikke forhandlet med leverandøren, da Revestive (teduglutid) har været i udbud.

[redacted]

Konkurrencesituationen

Der er på nuværende tidspunkt ingen lægemidler i direkte konkurrence. Tabel 2 nedenfor, viser de årlige lægemiddelpriser for behandling med Revestive (teduglutid).

Tabel 2: Årlige lægemiddelpriser

Lægemiddel	Dosis	Pakningsstørrelse	Pakningspris SAIP (DKK)	Antal pakninger/år	Årlig lægemiddelpris SAIP pr. år (DKK)
Revestive (teduglutid)	5mg	28 stk.	[redacted]	[redacted]	[redacted]
Revestive (teduglutid)	1,25mg	28 stk.	[redacted]	[redacted]	[redacted]

*Det antages at patienterne ikke gemmer eller deler hætteglas.

Status fra andre lande

Norge: Under evaluering[1].
Sverige: Ikke anbefalet[2]
England: Under evaluering[3].

Konklusion

Det er Amgros vurdering, at det ikke er muligt at opnå en lavere pris på Revestive (teduglutid).

[1] https://nyemetoder.no/metoder/teduglutid-revestive
[2] https://janusinfo.se/nationelltinforandeavlakemedel/produktinfo/revestiveteduglutid.4.1dfa69ad1630328ad7c38c20.html
[3] https://www.nice.org.uk/guidance/indevelopment/gid-ta10842

Medicinrådet

Application for the assessment of Revestive® (teduglutide) for the treatment of patients aged 1 year and above with Short Bowel Syndrome

08.02.2022

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

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1. Basic information

Contact information	
Name	**Christian Bæk Hvid**
Title	Value Demonstration Lead
Phone number	(+45) 27 77 97 58
E-mail	christian.hvid@takeda.com
Name	**Mads Carstensen**
Title	Medical Advisor
Phone number	(+45) 2932 9499
E-mail	mads.carstensen@takeda.com

Overview of the pharmaceutical	
Proprietary name	Revestive®
Generic name	Teduglutide
Marketing authorization holder in Denmark	Shire Pharmaceuticals Ireland Ltd (Takeda)
ATC code	A16AX08
Pharmacotherapeutic group	Group 4
Active substance(s)	Teduglutide
Pharmaceutical form(s)	Powder and solvent for solution for injection. The powder is white and the solvent is clear and colorless. Vials are available as 1.25 mg strength for pediatric use (patients with a body weight <20 kg) and as 5 mg strength for adult use (patients with a body weight ≥20).
Mechanism of action	Revestive® (teduglutide) is a glucagon-like peptide-2 (GLP-2) analogue produced in Escherichia coli cells by recombinant DNA technology. The naturally occurring human glucagon-like peptide-2 (GLP-2) is a peptide secreted by L cells of the intestine which is known to increase intestinal and portal blood flow, inhibit gastric acid secretion, and decrease intestinal motility. Teduglutide is an analogue of GLP-2. In several nonclinical studies, teduglutide has been shown to preserve mucosal integrity by promoting repair and normal growth of the intestine through an increase of villus height and crypt depth. These effects translate into an increased absorption of nutrients from the intestine.

Overview of the pharmaceutical	
Dosage regimen	The recommended dose of Revestive is 0.05 mg/kg body weight once daily. The recommended dose of Revestive in children and adolescents (aged 1 to 17 years) is the same as for adults.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Revestive is indicated for the treatment of patients aged 1 year and above with Short Bowel Syndrome (SBS). Patients should be stable following a period of intestinal adaptation after surgery.
Other approved therapeutic indications	No.
Will dispensing be restricted to hospitals?	Yes.
Combination therapy and/or co-medication	No. However, patient who are living with SBS-IF require parenteral support, i.e. parenteral nutrition and/or intravenous fluids.
Packaging – types, sizes/number of units, and concentrations	Revestive is available as 1.25 mg and 5 mg strengths per vial. One package contains 28 vials. After reconstitution, each vial contains respectively 1.25 or 5 mg teduglutide in 0.5 ml of solution, corresponding to a concentration of 2.5 mg/ml or 10 mg/ml.
Orphan drug designation	Yes

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2. Abbreviations

AE	Adverse Event
AIC	Akaike Information Criterion
ARGIS	Autologous gastrointestinal reconstructive surgery
BIC	Bayesian Information Criterion
CIF	Chronic intestinal failure
CLABSI	Central line-associated blood stream infections
DMC	Danish Medicines Council
DRG	Diagnose Relaterede Grupper
EPAR	European Public Assessment Report
EN	Enteral nutrition
EOT	End of treatment
EQ-5D	EuroQol five dimensions
GLP-2	Glucagon like peptide 2
HEN	Home enteral nutrition
HRQoL	Health Related Quality-of-Life
HSUV	Health State Utility Value
IBD	Inflammatory bowel disease
IPD	Individual Patient Data
IV	Intravenous
KM	Kaplan-Meyer
LFT	Liver function test
NICE	National Institute for Health and Excellence
PBO	Placebo
PICO	Population, Intervention, Comparator, Outcome
PNALD	Parenteral nutrition-associated liver disease
PS	Parenteral Support
QALY	Quality-Adjusted Life Year
QoL	Quality of life (QoL)
RCT	Randomized controlled trial
SAE	Serious Adverse Event
SBS	Short Bowel Syndrome
SBS-IF	Short Bowel Syndrome with Intestinal failure
SBS-QoL	Short Bowel Syndrome quality of life
SC	Standard Care
SF-36	36 item short form questionnaire
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SOC	Standard of Care
TED	Teduglutide
TEAE	Treatment Emergent Adverse Event
TESAE	Treatment Emergent Serious Adverse Event
TTO	Time trade-off
VAS	Visual Analogue Scale

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3. Tables and Figures

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Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

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Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

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4. Summary

This submission covers the full marketing authorization for Revestive® (teduglutide). Teduglutide is indicated for the treatment of patients aged 1 year and above with Short Bowel Syndrome (SBS) who are clinically stable following a period of intestinal adaptation after surgery. Teduglutide is an add-on treatment to standard care, and teduglutide treatment is consequently compared to placebo or standard care without teduglutide treatment.

Patients with SBS will die without life-sustaining parenteral support (PS), which is a complex, sophisticated treatment that involves intravenous delivery of nutrients and fluids administered for an average of 10–14 hours overnight for 2–7 nights a week. Due to being 'hooked up' to an IV line overnight or in daytime, PS can have a large disruptive effect on patients' sleep, relationships, work, and social lives; as well as the lives of their families and/or caregivers. Thus, reducing dependence on PS as much as possible is a critical treatment goal for patients. Further to this, PS is associated with significant serious and occasionally fatal complications; a number of these are related to the use of a catheter to administer PS. These complications include catheter-related bloodstream infections and sepsis, which may result in prolonged antibiotic treatment, repeated hospitalization, replacement of a catheter device, and death if not sufficiently treated. PS is also associated with metabolic complications. Key among these is decreased kidney function, which may progress to chronic kidney disease and intestinal failure-associated liver disease, which may progress to advanced liver disease and, in some cases end-stage liver failure. Chronic kidney disease and liver failure are both potentially fatal.

The above complications (particularly catheter-related infections, central venous thrombosis and liver disease) are even more common in children with SBS-IF than adults. In addition, children receiving PS experience growth retardation, which can manifest as gaining excess weight without gaining height and gaining fat mass rather than lean mass. Attainment of bone mass is also a concern in children, who are at increased risk of developing metabolic bone disease. Summarily, PS is not conducive to healthy physical growth in children.
In the context of the above, reducing the quality-of-life burden of PS and minimizing associated complications are therefore key treatment goals for both adults and children.

Teduglutide is a modified analogue of the naturally occurring human glucagon-like peptide 2 (GLP-2), a peptide produced by enteroendocrine L cells mainly in the ileum and colon. GLP-2 is a key mediator of intestinal adaptation, with a number of intestinotrophic effects that include increasing intestinal and portal blood flow, stimulating growth of the gastrointestinal epithelium, inhibiting gastric acid secretion, and decreasing intestinal motility. All of these effects translate into an improved absorption of fluids and nutrients in the intestines which allows partial or complete weaning from parenteral support.

The most consistently reported endpoints across randomized clinical trials and real-world studies of teduglutide are:

- Percentage of patients achieving clinical response (≥20% reduction in PS volume from baseline),
- Number and percentage of subjects who achieved at least a 1-day reduction in weekly PS, and
- Percentage of patients gaining independence from PS (100% reduction in PS volume from baseline).

These three endpoints are used in the comparative analysis, where teduglutide treatment consistently demonstrates a highly clinically meaningful effect across all of these endpoints and across different study designs and baseline disease characteristics.

Under normal circumstances, an application would rely on data from the registration studies only. However, because teduglutide was approved by EMA in 2012 (adults) and 2016 (pediatrics), a strength of the present application is the

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

ability to leverage real world data based on several years of experience with teduglutide treatment in real-world clinical settings in neighboring- and European countries.

To compare the efficacy of teduglutide based on clinical trials and the effectiveness of teduglutide based on real-world evidence, pooled estimates were calculated by synthesizing different sources of published evidence, encompassing 5 clinical trials and 8 real world evidence publications covering more than 300 teduglutide treated patients. As illustrated in Table 12 in section **7.1.4**, the baseline characteristics of the clinical trials and the real-world study populations are comparable, making a comparison of results between studies appropriate.

Table 1 below shows the number teduglutide treated adult patients in France, Germany and Spain, and the size of the populations covered by published real-world evidence studies in each country. Almost 30% of these patients are covered by the published real-world evidence studies, which corresponds to 18.5 % of the total adult teduglutide treated population in all of Europe and the United Kingdom combined.

Table 1 Teduglutide treated patients vs. real-world evidence patient numbers

	Adult teduglutide treated patients per August 2021 (n)	Adult teduglutide treated patients described in RWE (n)	Proportion teduglutide treated patients covered by RWE (%)	*RWE source*
France	135	85	63.0%	*Martin 2021 (n=31), Joly 2020 (n=54)*
Germany	232	33	14.2%	*Schoeler 2018 (n=14), Pevny 2019b (n=19)*
Spain	41	4	9.8%	*Tamara 2020 (n=4)*
Total	**408**	**122**	**29.9%**	
EU + UK total	***659***	***122***	***18.5%***	*Takeda Pharma EUCAN Patient Metrics*

Sources: Takeda Pharma EUCAN Patient Metrics, Martin 2021[1] (n=31), Joly 2020[2] (n=54), Schoeler 2018[3] (n=14), Pevny 2019b[4] (n=19), Tamara 2020[5] (n=4). **Key**: EU; European Union, UK; United Kingdom, RWE; Real-World Evidence

[redacted]

The effect estimate of teduglutide from the STEPS studies is conservative in nature due to an artificially high placebo response which has been addressed by the principal investigator Prof. Palle Jeppesen, who in an expert statement, describes the placebo response rate as 'artificially high' and that it represents 'a protocol violation'. Prof Jeppesen argues that the PS weaning in the placebo arm of STEPS was driven by natural fluctuations in urine volume combined with the weaning algorithm and led to patients increasing their oral fluid intake to try to avoid dehydration, and loss of weight which will not be healthy or sustainable. In the teduglutide arm, PS weaning was driven by enhanced intestinal absorption; patients did not have to increase their oral fluid intake to make up for decreased PS and were able to gain weight.

[redacted]

Regarding measuring health outcomes in the clinical trials, it must be acknowledged that the quality-of-life tools used in this trial were either not specific for patients with SBS, or unvalidated disease specific instruments lacking the required sensitivity for capturing quality of life impacts of treatment. Consequently, no improvements in health-related quality of life (HR-QoL) in relation to teduglutide treatment could be demonstrated when employing generic measures such as the SF-36, EQ-5D and IBDQ tools. However, since there is large heterogeneity in the symptoms of patients with SBS, it is likely that the benefits perceived in relation to teduglutide treatments could translate into heterogeneous outcomes not specifically captured by the tools employed. In addition, the study was likely to be underpowered to detect clinically meaningful changes, and the small number of subjects in this study hindered meaningful subgroup analyses. Owing to the large heterogeneity of patients with SBS with intestinal failure, it is difficult to evaluate the clinical meaningfulness of the suggested benefits of teduglutide at present.

Regarding the safety of teduglutide, integrated safety analysis in both adults and pediatrics show that the spectrum of gastrointestinal adverse events (AEs) in teduglutide-treated patients was generally comparable to that occurring in patients in the placebo or standard care arms. The comparative analysis showed consistently with this, that there was no statistically significant difference between the occurrence of adverse and serious adverse events between teduglutide and placebo/standard care.

[redacted]

Compared to baseline, teduglutide significantly improved the SBS-QoL total score and for 9 of the 17 single items of the SBS-QoL, a statistically significant reduction in the item score, from baseline to week 24, was found in the teduglutide group. This was only observed for only one item (diarrhea/stomal output) in the placebo group. Changes in the total sum score for SBS-QoL were however not statistically significant compared to placebo nor greater than the pre-defined MCID of 18.4. However, the model itself and the threshold for the minimally clinically important

difference (MCID) at 18.4 for the SBS-QoL score is however subject to debate. The first published MCID (18.4) was determined by an approach combining the measured error and experts' opinions and was not anchored on a clinical change that is meaningful to patients, which is the preferred methodology recommended by the FDA. As of today, no clinical consensus has been reached on what the MCID is, and the benchmark is developing as more research is conducted on the QoL of patients with SBS.[6] [redacted]

Given the nature of SBS-IF as an ultra-rare disease and teduglutide as a life-long treatment, there is inherent uncertainty within the clinical data and therefore the economic analyses as well. Every effort has been made to obtain as much relevant evidence as possible to mitigate the uncertainties in the analysis. The cost-effectiveness model was developed using a Markov cohort methodology, using mutually exclusive Markovian health states to capture the benefits associated with reduced PS-dependency, including costs and health-related quality of life (HRQoL).

The model consists of nine unique, core health states (including death) that patients can transition between over time, alongside two concurrent, separately modeled complications. A health state represents patients at a similar course of their disease who incur the same costs and have the same quality of life.

The STEPS studies were used for clinical input to the model, including baseline characteristics, time varying transition probabilities and adverse events. The cycle length was set to 28 days, aligning with the follow-up schedule of the STEPS studies.

Costs were mainly sourced from DRG tariffs[7] and the Danish Medicines Council's cost catalogue[8]. Due to the lack of Danish estimates, we relied on UK resource use estimates for some of the PS related costs from a previous NICE submission, supported by Danish clinical expert. We originally aimed to elicit resource use estimates via a Danish Delphi panel, but, due to the rarity of the disease, the clinical experts were not able to provide accurate resource use estimates.

To overcome the limitations with measuring HRQoL in STEPS, the cost-effectiveness model employs literature-based utility values from a published UK based vignette study in the base case scenario. When generic preference-based measures and other standardized approaches are not feasible, vignette-based methods are often used to estimate utilities for use in cost-utility analyses (CUA). A health state vignette is a description of the impact of a medical condition that is valued in a preference elicitation task to obtain a utility estimate. Vignette-based utilities are often published and used in CUAs that are conducted to inform decision making about healthcare resource allocation. An alternative scenario using utility values derived from STEPS is also included in the application.

Adult and pediatric populations are, as described elsewhere, different in several aspects that are important to the treatment of teduglutide and are thus consequently modeled separately. Unfortunately, the data from the pediatric trials are not suitable for cost-effectiveness modeling, due to the lack of randomization and the low number of patients included. Instead, we have based our pediatric model on the adult model, with the following adjustments for the pediatric indication:

- Baseline age (Adults: 50 years, Pediatrics: 6 years),
- Time horizon (Adults: 40 years, Pediatrics: 94 years),
- Costs, and
- Survival.

The transition probabilities in the pediatric, as for the adult model, are from the STEPS studies, i.e., sourced from an adult population. While this assumption is crude and limiting, it is also conservative in favor of the comparator, because we would expect a higher efficacy in children compared to adults based on results from the pediatric trials, and because children have a higher potential for intestinal adaptation, and thus a higher potential for treatment response. The limitations of this approach for modeling the pediatric indication were discussed and accepted by clinical experts during a dialogue meeting related to the present submission.[9]

The base case incremental cost-effectiveness ratio (ICER), based on the list price of teduglutide, was 2.507.713,23 kr. per quality-adjusted life year (QALY) gained for adults, and 1.894.267,81 kr./QALY gained for pediatrics, which is not considered to be cost-effective use of resources based on standard ICER thresholds. However, alternative pricing scenarios are provided in **8.7.1** and in **Appendix N**, showing that teduglutide treatment is potentially cost-effective.

In our analysis of the budget impact of recommending teduglutide treatment in **section 9**, we have assumed that 100 adult patients and 15 pediatric patients are prevalent with SBS-IF and eligible for teduglutide treatment, and that 10 adult and 3 pediatric patients each year are incident with SBS-IF and eligible for treatment with teduglutide. We have assumed, based on dialogue with Danish clinical experts and Danish incidence and prevalence numbers, that 10 of the prevalent and eligible adults in year 1 initiate treatment, and that all incident and eligible adult patients each year initiates treatment as well, leading to 20 adult patients initiating treatment in year 1, and 10 adult patients initiating treatment in each of the following 4 years. Analogously for the pediatric indication, we have assumed that 3 of the prevalent and eligible pediatric patients initiates treatment in year 1, and that all incident and eligible patients each year initiates treatment, leading to 6 pediatric patients initiating treatment in year 1, and 3 pediatric patients initiating treatment in each of the following 4 years. The budget impact is derived directly and dynamically from the cost-effectiveness model.

The results of the clinical data and health economic analyses presented demonstrates that treatment with teduglutide for patients with short bowel syndrome and intestinal failure (SBS-IF) represents a clinically relevant effect and that teduglutide treatment is potentially cost effective.

5. The patient population, the intervention and choice of comparator(s)

5.1 The medical condition and patient population

5.1.1 Patient populations relevant for this application

Patients aged 1 year and above with Short Bowel Syndrome (SBS). Patients should be stable following a period of intestinal adaptation after surgery. Please see Appendix U for new information on infant indication.

Short bowel syndrome (SBS) is a rare gastrointestinal condition characterised by a clinically significant reduction in intestinal absorptive capacity as a consequence of surgical resection of large portions of the intestine, commonly due to disease, trauma, complications of surgery or congenital abnormalities.[10,11] It is characterised by malabsorption of nutrients, diarrhoea, weight loss, dehydration, and malnutrition.[12] If intestinal adaptation is inadequate following

resection, the absorptive capacity of the residual intestine becomes insufficient to meet the nutritional, fluid and electrolyte needs to sustain life which constitutes intestinal failure (IF), which again constitutes major organ failure.[13] IF associated with SBS (SBS-IF) is an ultra-rare condition but can occur in both adults and paediatric patients due to a variety of underlying causes.[14,15]

Patients with SBS have impaired quality of life (QoL).[16] SBS-IF patients depend on parenteral support (PS) with parenteral nutrition (PN)/intravenous (IV) fluids and require lifelong follow-up. Those on PN require frequent monitoring of serum chemistries; liver function tests; and vitamin, mineral, and trace element levels. Although PS is a life-sustaining therapy, it is potentially associated with life-threatening complications such as catheter related blood stream infections or sepsis, central vein thromboses as well as liver or kidney damage.[17] Complications of the liver and biliary system are among the most common and serious problems associated with PS. Symptoms of parenteral nutrition-associated liver disease (PNALD) range from transient elevations in liver function tests (LFTs) to fibrosis, cirrhosis, and irreversible hepatic failure.[18] Other complications to parenteral nutrition are inflammation of the gallbladder (cholecystitis) and bone disease (osteoporosis).

Furthermore, patients are greatly inconvenienced by the need to 'hook up' to the catheter for up to 16 hours per day, restricting their mobility and spontaneity. While liberating the patients during the daytime, night-time infusions exacerbate the need for nocturnal urination and disturb sleep. The pumps used for infusions are not 100% silent and hence spouses sleep is also affected by night-time infusions.

Due to symptoms of malabsorption and burden of PS, most SBS-IF patients have a high physical and psychosocial strain, feel incapacitated, and are restricted in their leisure activities, social, family, and sexual life.[19] Patients often suffer from chronic fatigue, which negatively affects their working capability, overall economic situation or even precludes working completely.[16] Therefore, treatments reducing the symptoms related to large stomal or faecal losses and the consequent reduction of the need for PS by improving intestinal absorption can benefit the QoL of SBS-IF patients. Paediatric patients with SBS-IF receive some of the most complex medical care. The care of paediatric patients with SBS-IF is complex, expensive and requires long-term commitment by trained individuals and, unlike in adults, is associated with a higher rate of liver injury and difficulty in maintaining vascular access.[20] Thus, there is a significant burden for carers of, especially paediatric, SBS-IF patients.

The symptoms and severity of SBS-IF depend on the **length**, **anatomy**, and **functional capacity** of the remaining bowel.[13,21]

5.1.1.1 Length of remaining bowel

There is a lack of consensus in the literature regarding the definition of SBS-IF, with some definitions based on anatomy and others based on function.[14] Evidence suggests that patients with <200 cm small intestine are likely to develop IF and, as such, SBS-IF is often defined as the condition associated with a remaining small intestine <200 cm in length.[13,22] However, factors such as the function of the remaining intestine and conservation of the large intestine also contribute to clinical outcomes, meaning that such definitions have limited use in clinical practice.[14] In paediatric patients, the use of remaining intestinal length to define SBS is further complicated by the fact that many paediatric patients are premature neonates in whom normal intestinal length is difficult to establish, and unlike adult patients, paediatric patients experience small bowel growth over time, particularly during the first 18 months of life.[23]

5.1.1.2 Anatomy of remaining bowel

SBS can be categorised into three groups, which are defined depending on the anatomy of the remaining bowel following resection:

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A. **Jejunoileal anastomosis** with both the ileo-caecal valve and the entire colon in continuity
B. **Jejunocolic anastomosis** with no ileo-caecal valve in continuity
C. **End-jejunostomy** with no colon in continuity

5.1.1.3 Functional capacity of remaining bowel

The prognosis of SBS varies depending on the extent of resection, and anatomy and function of the remaining intestine.[21] However, SBS-IF occurs when the degree of malabsorption is such that a patient is dependent on parenteral support to maintain health and/or growth. PS comprises parenteral nutrition (PN) and intravenous (IV) fluids, which provide energy and nutrients, and fluids and electrolytes, respectively. IF may be an acute or chronic issue and can be classified as Type I–III according to onset, metabolic status, and expected outcome criteria:[13]

- **Type I;** Acute, short-term, and usually self-limiting condition, which is common in the perioperative setting or in association with critical illness
- **Type II;** Prolonged acute condition, often in metabolically unstable patients, requiring complex multi-disciplinary care and IV supplementation over periods of weeks or months
- **Type III;** Chronic condition in metabolically stable patients who require IV supplementation over months or years. This may be reversible or irreversible

Intestinal adaptation occurs following resection and compensates for structural and functional changes in the intestine, improving absorption of fluid and nutrients in the remaining intestine. The extent of intestinal adaptation varies depending on the anatomy and function of the remaining bowel.[21] Children with SBS-IF are more likely to adapt following surgery than adults.[24] Providing adequate enteral nutrition (EN) is vital in promoting adaptation in children, as well as in promoting intestinal growth.[25]

Stimulation of the intestine through EN and the presence of intestinotrophic growth factors also influence the degree of intestinal adaptation. All patients with SBS will initially require parenteral support after resection.[12] PN is required to provide energy and nutrients, such as amino acids and essential fatty acids, and IV fluids are required to provide fluid and electrolytes.[26] Some patients can be weaned off PS during and after intestinal adaptation, whereas others will require long-term PS to maintain nutrition and hydration.[12]

Table 2. Prognosis and symptom manifestations of SBS according to anatomy and function of the remaining intestine

	Jejunoileal anastomosis	Jejunocolic anastomosis	Jejunostomy
Probability of parenteral support dependence	Low but increased in patients with <35 cm jejunum remaining	Variable† but generally higher in patients with <60–65 cm jejunum remaining	Variable† but higher in patients with <115 cm jejunum remaining
Possible symptom manifestations	Transient gastric acid hypersecretion and impaired digestion	Increased diarrhoea, vitamin B12 deficiency, impaired bile salt resorption, deficiency in fat-soluble vitamins, fat malabsorption and steatorrhea, choleretic diarrhoea	Increased stomal output, significant nutrient and fluid malabsorption, magnesium deficiency, vitamin B12 deficiency, impaired bile salt resorption
Prognosis	Good. Patients often maintain proper hydration and do not frequently develop nutrient deficiency	Fair. Disease is more severe than for jejunoileal anastomosis due to reduced adaptive capacity of the jejunum relative to the ileum	Fair. Patients have more serious malabsorptive issue as they lack both the ileum and the colon and typically require long-term PS

Source: Adapted from Tappenden et al, 2014.[21] †Dependent on length of remaining bowel. Abbreviations: PS, parenteral support.

Post-hoc analyses using data from the phase three trials of teduglutide in adult patients with SBS has been performed in order to investigate whether the magnitude of response to teduglutide, in terms of PS volume reduction and improvement in QoL, is associated with specific disease characteristics among adults with SBS-IF).[6,16,27,28] Results from these post-hoc analyses suggest that SBS-IF characteristics of lower baseline PS volume and non-IBD etiology were associated with the greatest PS reduction benefits with teduglutide in terms of days off per week and enteral autonomy while the largest improvement in QoL was most pronounced among patients with highest baseline PS volume requirement or IBD etiology. These analyses were performed on a very small patient sample size, and the post hoc nature of the analysis further limits generalizations from the outcomes.

When interpreting the QoL findings, several other limiting methodological factors should be considered as well. The power calculations were based on the primary efficacy endpoint of the STEPS study, PS volume reductions, and not on QoL outcomes. Further to this, PS volume reduction is a more objectively defined and measured than QoL, due to the more 'subjective nature' of the QoL. Each individual patient may value and underscore different effects in relation to teduglutide or placebo treatment and therefore response options are subject to a large degree of variety, which adds to the response heterogeneity.[16] SBS-IF patients are highly heterogeneous in nature, as based on their primary diagnosis, remnant intestinal anatomy, function and their need for PS, and the objectively demonstrated effects of teduglutide on PS volume reductions may also be subject to different perception in individual patients.[29] The heterogeneity of several external factors of the lives of patients with SBS-IF (i.e. social situation, educational and relational status) may contribute even further to this response variability.[16,30]

In the preparation for the filing of this application Takeda has engaged with several leading danish experts within SBS-IF and conducted advisory boards in order to better understand whether these analyses could serve to identify subgroups of patients that may experience a higher level of efficacy in a danish clinical setting. From a clinical setting perspective and with reference to the methodological limitations addressed above the consensus and unequivocal feedback from the danish experts within SBS-IF was that these post-hoc analyses could not be used in clinical practice to identify and select individual patients from the entire population for whom teduglutide should be offered.[31] Because of this, these post-hoc analyses will not be further discussed.

5.1.1.4 Prevalence

Based on information provided from Danish Clinical experts treating SBS-IF patients in Denmark, it is estimated that the total patient population that receive HPN in Denmark is around 500-550 adults.[32] Of this population the KOLs estimates 2/3 (approx. 340 adult patients) is due to SBS and of these approx. 50% (approx. 170 adult patients) are SBS chronic intestinal failure (CIF) patients which will require lifelong HPN.[32] These estimates are supported by the source stated below in Table 3.

Of the SBS CIF patients it is estimated by the KOLs that approx. 100 adult patients will be eligible for teduglutid according to the label and the used in- and exclusion criteria in the STEPS studies. However, not all eligible patients will be initiated the treatment immediately and the danish HCPs anticipate a gradual increase in patients over time e.g., 10 patients initiated per year. [32] These estimates assume a recommendation of teduglutide by the Medicine Council for the full adult population. In addition to the adult patients we, based on dialogue with the treating SBS-IF centers for pediatric patients, expect approximately 6 pediatric patients to initiate teduglutide in the year of the recommendation (year 1) and 3 in each subsequent year.
See Table 4.

In addition, the danish KOLs estimates that approx. 50 new HPN patients is identified each year. About 1/3 of these will be SBS-IF chronic patients which will require lifelong HPN. [32] According to the SmPC the patient should be stable following intestinal adaptation.

The prevalence of SBS-IF varies greatly between countries depending on the healthcare system's ability to identify and treat these patients.[33]

Teduglutide is dosed in relation to bodyweight and each vial of teduglutide covers treatment for patients up to 100 kg. As patients suffer from malnutrition and malabsorption only a few patients are assumed to come even close to 100kg.

Table 3 Incidence and prevalence of chronic SBS-IF patients in the past 5 years

Year	2016	2017	2018	2019	2020
Incidence in Denmark[32]	10-20	10-20	10-20	10-20	10-20
Prevalence in Denmark[34]	30 / mio.	30 / mio.	30 / mio.	30 / mio.	30 / mio.
Prevalence in Europe[33]*	2-4 /mio.	2-4 /mio.	2-4 /mio.	2-4 /mio.	2-4 /mio.

* For small patient groups, also describe the worldwide prevalence

Table 4 Number of adult and pediatric patients in Denmark who are estimated to use teduglutide in the coming years

Year	2022	2023	2024	2025	2026
Estimated number of adult patients in Denmark [32]	10-20	20-40	30-50	30-50	30-50
Estimated number of pediatric patients in Denmark	5-7	8-10	11-13	14-16	17-19

5.2 Current treatment options and choice of comparator(s)

5.2.1 Current treatment options

According to several Danish SBS experts, the current standard treatment of SBS-IF in Denmark is home enteral nutrition (HEN) following the *ESPEN guideline on home enteral nutrition*.[35] The guideline is based on current evidence and expert opinion and consists of 61 recommendations that address the indications for HEN, relevant access devices and their use, the products recommended, the monitoring and criteria for termination of HEN, and the structural requirements needed to perform HEN. According to the ESPEN guideline, the treatment of SBS may include nutritional support (home enteral nutrition), medications, surgery and intestinal transplant.[36]

5.2.1.1 Nutritional Support

The main treatment for short bowel syndrome is nutritional support, which may include the following:

- **Oral rehydration** Adults should drink water, sports drinks, sodas without caffeine, and salty broths. Children should drink oral rehydration solutions—special drinks that contain salts and minerals to prevent dehydration—such as Pedialyte, Naturalyte, Infalyte, and CeraLyte, which are sold in most grocery stores and drugstores.
- **Parenteral nutrition** This treatment delivers fluids, electrolytes, and liquid vitamins and minerals into the bloodstream through an intravenous (IV) tube—a tube placed into a vein.
- **Enteral nutrition** This treatment delivers liquid food to the stomach or small intestine through a feeding tube—a small, soft, plastic tube placed through the nose or mouth into the stomach. Gallstones—small, pebblelike substances that develop in the gallbladder—are a complication of enteral nutrition.
- **Vitamin and mineral supplements** A person may need to take vitamin and mineral supplements during or after parenteral or enteral nutrition.
- **Special diet** A health care provider can recommend a specific diet plan for the patient that may include small, frequent feedings avoiding foods that can cause diarrhoea, such as foods high in sugar, protein, and fibre avoiding high-fat foods.

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Home parental nutrition requires a very tight selection and intensive training of patients, which also requires a systematic organization, as patients must be able to cooperate and learn and understand principles of aseptic handling of a central venous catheter.[37]

5.2.1.2 Medications recommended by ESPEN guideline on home enteral nutrition

A health care provider may prescribe medications to treat short bowel syndrome, including:

- Antibiotics to prevent bacterial overgrowth
- Proton pump inhibitors to treat too much gastric acid secretion
- Choleretic agents to improve bile flow and prevent liver disease
- Bile-salt binders to decrease diarrhoea
- Anti-secretin agents to reduce gastric acid in the intestine
- Hypomotility agents to increase the time it takes food to travel through the intestines, leading to increased nutrient absorption
- Growth factors (GH, GLP2-analog (i.e. teduglutide)) to improve intestinal absorption

5.2.1.2.1 Growth factors (GH, GLP2-analog, teduglutide)

According to the updated 2021 ESPEN practical guideline: *Clinical nutrition in chronic intestinal failure,* teduglutide is the recommended first choice for those carefully selected SBS patients who are candidates for growth factor treatment.[38] The statements and flow chart below are taken directly form the ESPEN Guideline:

60) We recommend that patients with CIF due to SBS are carefully informed of the potential benefits and risks associated with growth factor treatments; information should deal with the probability of reducing the need for or the weaning from HPN, the probability of QoL improvement, the expected duration of treatment, the expected effects after cessation of the treatment, the potential adverse effects and risks of the treatment, the cost-effectiveness of the treatment, and the need to undergo careful and regular monitoring. (R52, Grade of evidence: low)

61) We suggest that, for those carefully selected SBS patients who are candidates for growth factor treatment, the GPL2- analogue, teduglutide, is the first choice. (R53, Grade of evidence: moderate) Commentary: see Commentary to Recommendation 63.

62) We recommend the evaluation of the efficacy of growth factor treatment according to standardized protocols measuring fluids, electrolytes and, whenever possible, energy balance. (R54, Grade of evidence: low) Commentary: see Commentary to Recommendation 63.

63) We recommend that intestinal growth factors are only prescribed by experts who are experienced in the diagnosis and management of SBS patients and who have the ability and the facilities to objectively evaluate and balance the benefit and clinical meaningfulness of the interventions versus the inconveniences, adverse effects, potential risks, and cost-effectiveness. (R55, Grade of evidence: low)

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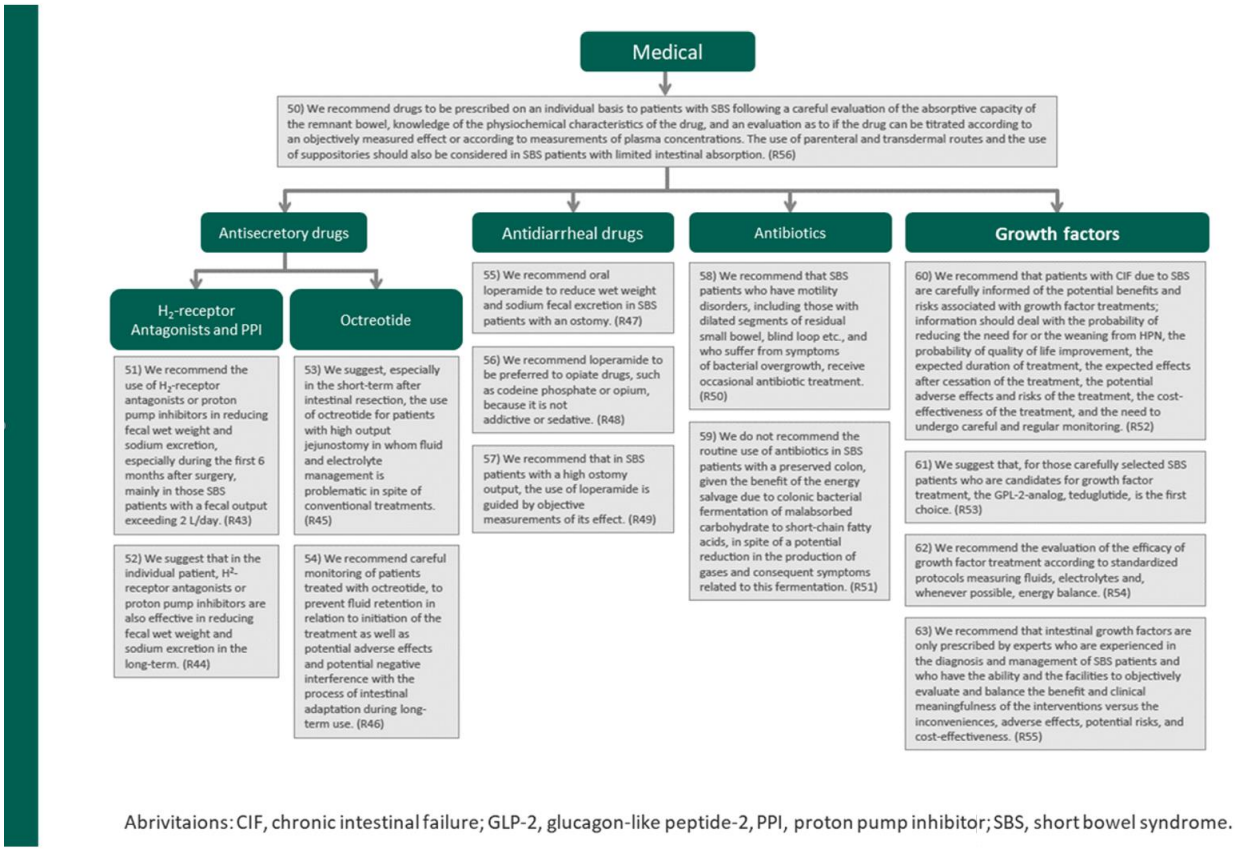
Figure 1 Medical Intestinal rehabilitation guidance from ESPEN guideline.[38]



Abrivitaions: CIF, chronic intestinal failure; GLP-2, glucagon-like peptide-2, PPI, proton pump inhibitor; SBS, short bowel syndrome.

5.2.1.3 Surgery

The goal of surgery is to increase the small intestine's ability to absorb nutrients. Approximately half of the patients with short bowel syndrome need surgery.[39] Surgery used to treat short bowel syndrome includes procedures that:

- Prevent blockage and preserve the length of the small intestine
- Narrow any dilated segment of the small intestine
- Slow the time it takes for food to travel through the small intestine
- Lengthen the small intestine
- Long-term treatment and recovery, which for some may take years, depend in part on
    - what sections of the small intestine were removed
    - how much of the intestine is damaged
    - how well the muscles of the intestine work
    - how well the remaining small intestine adapts over time

5.2.1.4 Intestinal Transplant

An intestinal transplant is surgery to remove a diseased or an injured small intestine and replace it with a healthy small intestine from a donor, either alive or diseased. Transplant surgeons perform the surgery on patients for whom other treatments have failed and who have life threatening complications from long-term parenteral nutrition. An intestinal-transplant team performs the surgery in a hospital. The patient will need anaesthesia. Complications of intestinal transplantation include infections and rejection of the transplanted organ. A successful intestinal transplant can be a life-saving treatment for people with intestinal failure caused by short bowel syndrome.

5.2.2 Choice of comparator(s)

The comparator chosen for adults will be placebo and for pediatric standard of care, as these two comparators were the ones used in the clinical trials used to demonstrate the safety and efficacy of teduglutide in the treatment of patients with SBS-IF.

The introduction of teduglutide for the treatment of adult and pediatric patients with SBS-IF will not replace any pharmaceutical as there is currently no other pharmaceutical approved to treat SBS-IF. Nor any other pharmaceutical that are able to increase the small intestine's ability to absorb nutrients why nutritional support is currently the mainstay in the treatment for short bowel syndrome as previously described.

The introduction of teduglutide will, however, eliminate the need for PS in some patients. Complete enteral autonomy eradicates the risks associated with catheter dependence and chronic PS infusion.[15] Teduglutide will also allow PS reductions for some patients that permit partial weaning and gaining additional days off PS which are also powerful, with the potential to increase quality of life and reduce PS-associated complications. Indeed, among patients with SBS-IF, decreases in PS requirements are associated with significantly higher scores on an SBS-specific quality-of-life instrument.[16]

5.2.3 Description of the comparator(s)

The comparator in the adult studies was placebo and for the pediatric studies it was standard of care. In the core phase III STEPS study in adults the matching placebo, for the subcutaneous teduglutide injection, was provided as a lyophilized powder containing L-histidine, mannitol, and monobasic and dibasic sodium phosphate that was reconstituted using 0.5 mL sterile water for injection.

5.3 The intervention Revestive® (teduglutide)

Dosing: 0.05 mg daily per kg bodyweight

Method of administration: Subcutaneous injection

Treatment duration/criteria for treatment discontinuation: A treatment period of 6 months is recommended after which treatment effect should be evaluated. In children below the age of two years, treatment should be evaluated after 12 weeks. Treatment should be stopped if no overall improvement of the patient's condition is achieved.

Should the pharmaceutical be administered with other medicines? No

Necessary monitoring, during administration, during the treatment period, and after the end of treatment: Optimization and stabilization of intravenous fluid and nutrition support should be performed before initiation of treatment. Efficacy and safety in all patients should be closely monitored on an ongoing basis according to clinical treatment guidelines

Need for diagnostics or other tests (i.e. companion diagnostics): No, but treatment should not be initiated until it is reasonable to assume that a patient is clinical stable following a period of intestinal adaptation

Danish clinical experts within SBS-IF have confirmed that teduglutide would be offered to SBS-IF patients according to the available evidence and EMA approved indication and will be aligned within the recommendation set forth by the Medicines Council.[31] The treatment will follow the same approach as what has been used in the STEPS studies. Depending on the outline of the recommendation from the Medicines Council for teduglutide, the clinical practice for treating type 3 SBS-IF patients will be changed in the way that teduglutide would for the first time offer these patients a reduction in the burden associated with PS. For some patients, treatment with teduglutide would translate into

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partial weaning and gaining additional days off PS and for some complete weaning of PS, with the potential to increase quality of life and reduce PS-associated complications. As described above, among patients with SBS-IF, decreases in PS requirements are associated with significantly higher HRQoL.

6. Literature search and identification of efficacy and safety studies

As per the DMC Methods guide section 3.1 and input received from the DMC Secretariat on 22.11.2021, a systematic literature search for documenting the safety and efficacy of teduglutide versus standard of care was not conducted. We include data from randomized clinical trials that directly compares teduglutide versus standard of care, why a literature search is not likely to provide additional relevant documentation on the safety and efficacy of teduglutide versus standard of care.

6.1 Identification and selection of relevant studies

Not applicable.

6.2 List of relevant studies

Table 5 Relevant studies included in the assessment

Reference	Trial name	NCT number	Dates of study
Randomized placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome. Jeppesen, P. B., Gilroy, R., Pertkiewicz, M., Allard, J. P., Messing, B., & O'Keefe, S. J. Gut 2001, 60(7), 902–914	A Study of the Efficacy and Safety of Teduglutide in Subjects With Parenteral Nutrition-Dependent Short Bowel Syndrome	00081458	25.05.2004-06.07.2007
Teduglutide Reduces Need for Parenteral Support Among Patients With Short Bowel Syndrome With Intestinal Failure. Jeppesen, P. B., Pertkiewicz, M., Messing, B., Iyer, K., Seidner, D. L., O'keefe, S. J. D., Forbes, A., Heinze, H., & Joelsson, B. Gastroenterology 2012:143(6), 1473-1481.e3.	A 24-Week Study of the Efficacy and Safety of Teduglutide in Subjects With Parenteral Nutrition-Dependent Short Bowel Syndrome	00798967	25.11.2008-25.01.2011
Long-Term Teduglutide for the Treatment of Patients With Intestinal Failure Associated With Short Bowel Syndrome. Schwartz, L. K., O'Keefe, S. J. D., Fujioka, K., Gabe, S. M., Lamprecht, G., Pape, U.-F., Li, B., Youssef, N. N., & Jeppesen, P. B. Clinical and Translational Gastroenterology 2016:7(2), e142.	A Long-Term, Open-Label Study With Teduglutide for Subjects With Parenteral Nutrition Dependent Short Bowel Syndrome	00930644	21.09.2009-24.01.2013
Reduction of Parenteral Nutrition and Hydration Support and Safety With Long-Term Teduglutide Treatment in Patients With Short Bowel Syndrome–Associated Intestinal Failure: STEPS-3 Study. Seidner, D. L., Fujioka, K., Boullata, J. I., Iyer, K., Lee, H.-M., & Ziegler, T. R. Nutrition in Clinical Practice 2018: 33(4), 520–527	A One-Year, Open-Label Study With Teduglutide for Subjects With Parenteral Nutrition-dependent Short Bowel Syndrome Who Completed Study CL0600-021	01560403	21.05.2012-23.07.2013
Teduglutide for the treatment of adults with intestinal failure associated with short bowel syndrome: pooled safety data from four clinical trials. Pape U-F, et al. Ther Adv Gastroenterol 2020, Vol. 13: 1–18	Teduglutide for the treatment of adults with intestinal failure associated with short bowel syndrome: pooled safety data from four clinical trials	N/A Pooled safety data set from four prospective clinical trials of teduglutide in	N/A

Reference	Trial name	NCT number	Dates of study
		adult patients with SBS–IF	
Outcomes from a 12-Week, Open-Label, Multicenter Clinical Trial of Teduglutide in Pediatric Short Bowel Syndrome. Carter, B. A., Cohran, V. C., Cole, C. R., Corkins, M. R., Dimmitt, R. A., Duggan, C., Hill, S., Horslen, S., Lim, J. D., Mercer, D. F., Merritt, R. J., Nichol, P. F., Sigurdsson, L., Teitelbaum, D. H., Thompson, J., Vanderpool, C., Vaughan, J. F., Li, B., Youssef, N. N., Kocoshis, S. A. The Journal of Pediatrics 2017: 181, 102-111.e5	A 12-Week Pharmacokinetic, Safety, and Pharmacodynamic Study of Teduglutide in Pediatric Subjects Aged 1 Year Through 17 Years, With Short Bowel Syndrome Who Are Dependent on Parenteral Support	01952080	14.11.2013-09.01.2015
Safety and Efficacy of Teduglutide in Pediatric Patients With Intestinal Failure due to Short Bowel Syndrome: A 24-Week, Phase III Study. Kocoshis, S. A., Merritt, R. J., Hill, S., Protheroe, S., Carter, B. A., Horslen, S., Hu, S., Kaufman, S. S., Mercer, D. F., Pakarinen, M. P., Venick, R. S., Wales, P. W., & Grimm, A. A. Journal of Parenteral and Enteral Nutrition 2019:44(4), 621–631	A 24-Week Double-blind, Safety, Efficacy, and Pharmacodynamic Study Investigating Two Doses of Teduglutide in Pediatric Subjects Through 17 Years of Age With Short Bowel Syndrome Who Are Dependent on Parenteral Support	02682381	23.06.2016-18.08.2017
Safety Findings in Pediatric Patients During Long-Term Treatment With Teduglutide for Short-Bowel Syndrome–Associated Intestinal Failure: Pooled Analysis of 4 Clinical Studies. Hill S, et al. JPEN J Parenter Enteral Nutr. 2021;0:1–10		N/A Pooled safety data set from four prospective clinical trials of teduglutide in pediatric patients with SBS–IF	N/A
Ongoing https://clinicaltrials.gov/ct2/show/NCT02949362	A Retrospective and Prospective, Open-label, Long-term Safety and Efficacy Study of Teduglutide in Pediatric Subjects With Short Bowel Syndrome Who Completed TED-C13-003	02949362	09.12.2016-14.07.2020
Ongoing https://clinicaltrials.gov/ct2/show/NCT02954458	A Prospective, Open-label, Long-term Safety and Efficacy Study of Teduglutide in Pediatric Patients With Short Bowel Syndrome Who Completed TED-C14-006 or SHP633-301	02954458	09.01.2017-05.11.2020
Ongoing https://clinicaltrials.gov/ct2/show/NCT01990040	A Prospective, Multi-center Registry for Patients With Short Bowel Syndrome	01990040	23.06.2014-31.05.2031

For detailed information about included studies please see Appendix B.

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Table 6 Relevant Real-World studies included in the assessment

Study name	Location	Data collection dates (index to cut-off)	Population*	Number of patients receiving teduglutide
Joly 2020[2]	France, multi-centre (15 centres)	Oct 2015 – Sep 2017	Patients with SBS-IF	54
Lam 2018[40]	USA, single centre	2009 – 2015	Adults with SBS-IF	18
Martin 2021[1]	France, single centre	2009 – Dec 2019	Patients with SBS-IF	31
Pevny 2019b[4]	Germany, single centre	Sep 2014 – May 2017	Patients with SBS-IF	19
Puello 2020[41]	USA, single centre	Mar 2013 – May 2019	Adults with SBS-IF	18
Schoeler 2018[3]	Germany, single centre	From Nov 2014	Adults with SBS*	14
Tamara 2020[5]	Spain, single centre	Jan 2018 – Mar 2020	Adults with SBS*	4
Ukleja 2018[42]	USA, single centre	Apr 2013 – Jun 2016	Adults with SBS*	6
Abbreviations: SBS, short bowel syndrome; SBS-IF, short bowel syndrome with type 3 intestinal failure Notes: *In the literature, the terms SBS-IF, SBS and IF are used interchangeably, but in this instance all refer to SBS with type 3 IF (the population of interest in this dossier)				

For detailed information about included Real-World studies please see Appendix P.

7. Efficacy and safety

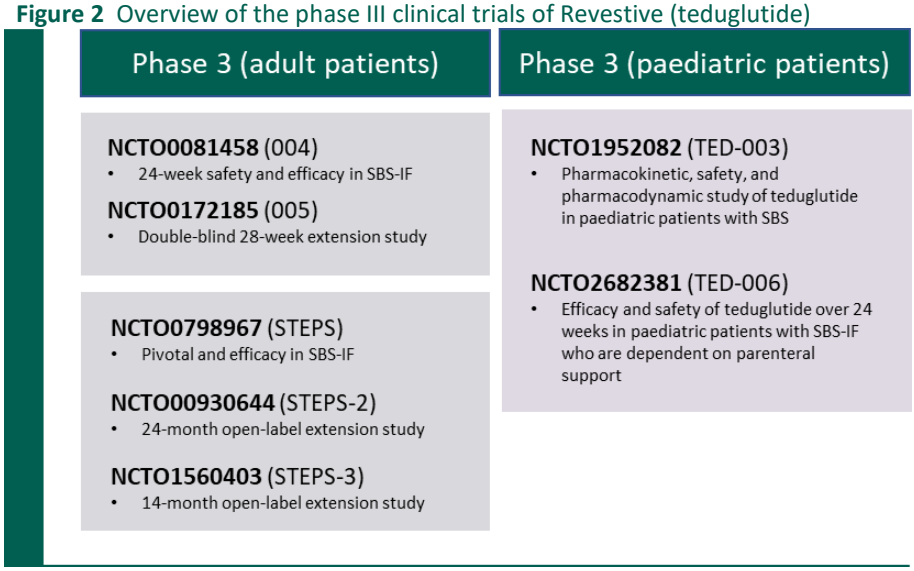
7.1 Efficacy and safety of teduglutide compared to placebo for SBS-IF patients older than 1 year

7.1.1 Relevant studies

For detailed information of study characteristics for the included studies identified by the literature search and described below, please see **Appendix B** *Main characteristics of included studies*.

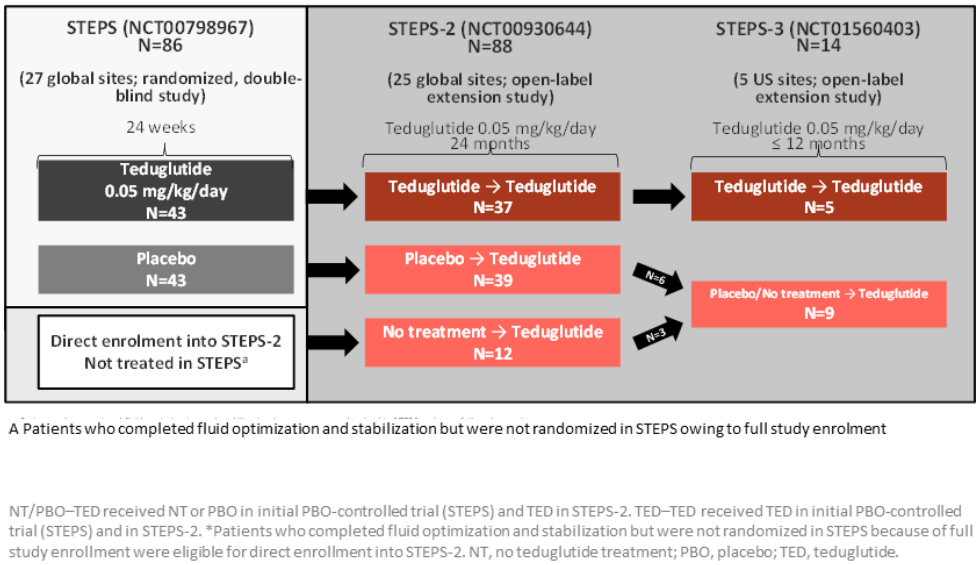
Overall Revestive® (teduglutide) have been investigated five phase III studies of which 5 in adults (18+ years of age) and 2 in children (1-17 years of age). Figure 2 below provides an overview of the 7 phase III clinical trials.

Figure 2 Overview of the phase III clinical trials of Revestive (teduglutide)



The adult pivotal phase III study, STEPS, was followed by 2 open label extension studies. The figure below illustrates the patient flow between the initial STEPS trial (NCT00798967) and its 2 extension studies (NCT00930644 and NCT01560403), and all 7 studies are summarized below in Figure 3.

Figure 3. Flow diagram of patients across the STEPS studies.



Flow diagram of patients across the STEPS studies. NT/PBO–TED received NT or PBO in initial PBO-controlled trial (STEPS) and TED in STEPS-2. TED–TED received TED in initial PBO-controlled trial (STEPS) and in STEPS-2. *Patients who completed fluid optimization and stabilization but were not randomized in STEPS because of full study enrolment were eligible for direct enrolment into STEPS-2. NT, no teduglutide treatment; PBO, placebo; TED, teduglutide.

To demonstrate clinical efficacy and safety in adults data from the two randomized, placebo-controlled clinical trials, **NCT00081458 (004)** and **NCT00798967 (STEPS**) will be used for the comparative analysis of the intervention (teduglutide) and comparator (placebo) as these two studies were the only studies with a placebo arm.

Descriptive data from the two extension studies, **STEPS-2** and **STEPS-3**, will be summarized narratively and only be used to demonstrate long-term efficacy in adults as the studies were open-label with no placebo arm. To demonstrate long term safety data from a pooled safety analysis of 4 clinical trials will be used and described narratively below. The pooled safety analysis of the 4 clinical trials also includes data from the NCT000172185 (005) study, which was a long-term extension study of 004, why this study will not be covered separately. Further to this, the weaning algorithm used in the 004 study is not reflective of current clinical practice as discussed in greater detail below why efficacy data from the 005 extension study will not be used to demonstrate long-term efficacy.

Finally, data from the ongoing prospective SBS-IF registry (NCT01990040) will provide further evidence for the long term effectiveness and safety of teduglutide.

7.1.2 Efficacy and safety – results per study

7.1.2.1 Studies conducted in adult SBS-IF patients

The phase III 004 study. *Jeppesen PB, Gilroy R, Pertkiewicz M, et al. Randomised placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome. Gut 2011; 60: 902–914*

This was a 24-week randomized, double-blind and placebo-controlled study that evaluated the ability of two doses of teduglutide (0.05 mg/kg and 01.0 mg/kg) to reduce parenteral support in adult patients with SBS with intestinal failure.

The primary efficacy end point was a graded response score (GRS), defined as a reduction from baseline in parenteral volume (from 20% to 100%).

Secondary efficacy end points included the number and percentage of subjects who responded (defined as a parenteral volume reduction of $20% from baseline at week 20 and maintained at week 24); the absolute reduction from baseline in parenteral volume and parenteral kilojoules; achievement of at least one day reduction in weekly parenteral administration or total weaning from parenteral support.

Eligible patients were aged ≥18 years with a history of SBS due to intestinal resection and dependent on parenteral support (fluids, electrolytes or nutrients) at least three times per week for a period of at least 12 months prior to the start of the study.

The phase III STEPS study. *Jeppesen PB, Pertkiewicz M, Messing B, et al. Teduglutide reduces need for parenteral support among patients with short bowel syndrome with intestinal failure. Gastroenterology 2012; 143: 1473–1481.e1473.*

This was a 24-week randomized, double-blind and placebo-controlled study that evaluated the ability of 0.05 mg/kg of teduglutide to reduce parenteral support in adult patients with SBS with intestinal failure.

The primary efficacy end point was number of responders (patients with 20% reduction in parenteral support volume from baseline at weeks 20 and 24). The secondary efficacy end points included the percentage and absolute change in PS and the number of patients who stopped PS and their time of discontinuation.

Eligible patients were aged ≥18 years with SBS resulting from intestinal failure caused by a major intestinal resection (e.g., injury, cancer, Crohn's disease, vascular disease, volvulus). At least 12 continuous months of PS dependency (PN and/or IV fluids). PS required ≥3 times weekly to meet caloric, fluid, or electrolyte needs Patients with Crohn's disease had to be in clinical remission for ≥12 wk. before dosing

The STEPS-2 study. *Schwartz LK, et al. , Long-term teduglutide for the treatment of patients with intestinal failure associated with short bowel syndrome. Clin Transl Gastroenterol 2016; 7: e142.*

This was a 2-year, open-label extension of STEPS designed to evaluate long-term safety and efficacy of teduglutide.

The primary patient population for all analyses in STEPS-2 was the intent-to-treat population, defined as all patients who signed informed consent. For efficacy analyses, data for each subgroup were considered separately because patients in the NT/TED subgroup were not randomized in the initial 24-week placebo-controlled study and therefore did not participate in that study's regimented, regularly scheduled study visits, including the protocol-driven efforts at PS reduction. Of the 78 patients who completed the initial placebo-controlled study and were eligible for STEPS-2, 76 enrolled in the extension (n=37 TED/TED; n=39 PBO/TED). An additional 12 patients who were screened and optimized in the placebo-controlled study but not randomized were enrolled directly in STEPS-2. Of the 88 patients enrolled in STEPS-2, 65 (74%) completed the study (n=30/37 TED/TED; n=29/39 PBO/TED; n=6/12 NT/TED).

Be advised that data in Figure 7 (Additional Days Per Week Off PS) represents data for only those patients who completed 30 months of treatment with teduglutide and does thus not represent the intent-to-treat population. This approach may lead to overestimation of the treatment effect.

Including study drug exposure during the placebo-controlled trial STEP, total exposure to teduglutide at the end of STEPS-2 was up to 30 months for TED/TED and up to 24 months for the NT/TED and PBO/TED subgroups, see figure above. During the extension studies, PS volume adjustments of 10–30% were made according to the placebo-

controlled STEP study algorithm. Efficacy end points included the change in PS volume from baseline, the percentage of patients achieving a response (≥20% reduction in PS volume from baseline), duration of response, reduction in days of PS per week, and the number of patients who achieved independence from PS. Descriptive statistics summarized changes in efficacy and safety variables.

Baseline demographics and characteristics of the study population are summarized in Table 81 in **Appendix C**.

Enrolled patients had completed 24 weeks of either teduglutide or placebo in the initial placebo-controlled study or qualified for that study, but were not treated because of full enrollment. Patients received teduglutide 0.05 mg/kg/day for up to 30 months.

The STEPS-3 study. *Seidner, D, et* al. *Reduction of Parenteral Nutrition and Hydration Support and Safety With Long-Term Teduglutide Treatment in Patients With Short Bowel Syndrome–Associated Intestinal Failure: STEPS-3 Study. Nutrition in Clinical Practice 2018: 33(4), 520–527.*

This was a 1-year, open-label extension study in patients with SBS–IF who completed STEPS-2, that further monitored the safety and efficacy of 0.05 mg/kg teduglutide.

Efficacy outcome data using measures from the original STEPS study were collected.

Eligible adult participants in STEPS-3 had completed 24 months of teduglutide treatment in STEPS-2, regardless of whether they had been weaned from PS.

The adult pooled safety analysis of 4 clinical trials. *Pape U-F, et al. Teduglutide for the treatment of adults with intestinal failure associated with short bowel syndrome: pooled safety data from four clinical trials. Ther Adv Gastroenterol 2020, Vol. 13: 1–18.*

In this study safety data from four prospective clinical trials of teduglutide in patients with SBS–IF were assimilated. These were NCT00081458 (004), NCT00798967 (STEPS), NCT00172185 (005) and NCT00930644 (STEPS-2).

AEs were evaluated in patient groups based on treatment received in each study. Safety data are reported for up to 2.5 years, totaling 222 person-years exposure to teduglutide.

AEs were coded using system, organ, class terms, and preferred terms from the Medical Dictionary for Regulatory Activities version 12.0.

The SBS-IF Registry. *Allard PJ, et al. A Prospective, Multicenter Registry for Patients with Short Bowel Syndrome and Intestinal Failure (SBS-IF Registry): Interim Effectiveness Analysis of Teduglutide Treatment. Presented at the ASPEN Nutrition Science & Practice Conference 2021, March 20–23, 2021, Denver, CO, USA. [abstract]*

This is an ongoing prospective, observational, multinational SBS-IF registry. The study was initiated in 2014 and enrollment is planned for 7 years with at least 10 years of follow-up for each patient. The SBS-IF registry includes teduglutide-exposed and teduglutide-unexposed patients with SBS-IF of any age.

The aim of the interim analysis aimed was to evaluate the effectiveness of teduglutide in adults in a routine clinical setting.

Effectiveness outcomes were assessed between study entry (baseline) and follow-up and included: absolute and relative changes in PS volume (L/week), absolute changes in the frequency of PS (days/week) and the proportion of patients weaned off PS. The comparison between treatments is conducted using summary statistics.

The presented interim analysis (data cutoff June 30, 2020) compared effectiveness outcomes between adult patients treated with teduglutide ('ever-treated' patients) and adult patients treated with standard of care and never exposed to teduglutide ('never-treated' patients).

[redacted]

Please see the detailed study characteristics in **Appendix C**.

7.1.2.1.1 Limitations to Adult studies

As previously mentioned, meta-analysis of NCT00081458 (004) and NCT0079867 (STEPS) cannot be conducted as the two studies used two different PS weaning algorithms. The change in weaning algorithm was a direct result of the learnings from the initial trial (004) where, contrary to the expectations of a dose response, a 0.10-mg/kg/d dosage did not meet the primary end point of PS reduction, but significant findings from the ad hoc analysis of a 0.05-mg/kg/d dosage in the 004 study suggested that these differences could be explained by the limitation of PS volume reductions to no more than 10% of baseline levels, beginning only at the fourth week of dosing, along with a trend toward larger baseline PS volume requirements in the 0.10-mg/kg/d group. Therefore, the primary objective of the subsequent study 005, the largest double-blind, randomized, placebo-controlled trial performed in patients with SBS-IF, was to evaluate whether teduglutide at the 0.05 mg/kg/d dosage and with a protocol allowing for earlier (i.e., at second week of dosing) and more aggressive PS reductions of 10% to 30% of baseline levels of PN/IV fluid could reduce PS volume in these patients.

While study 004 provides further evidence for the superior efficacy of teduglutide 0.05 mg/kg/day compared to placebo, the study has weak external validity as the PS weaning algorithm in 004 is not reflective of clinical practice. This is because the PS weaning algorithm used in 004 is unduly restrictive (reductions of up to 10% of baseline PS volume at each visit) compared to PS weaning used in the subsequent clinical phase 3 trial and in the real world.

The unduly restrictive algorithm used in 004 can be further illustrated by comparing response rates between 004 and STEPS (similarly designed trials, although STEPS had a less restrictive PS weaning algorithm allowing reductions of up to 30% of baseline PS volume). The less restrictive PS weaning algorithm is reflected in the higher response rates for both the teduglutide 0.05 mg/kg/day arm and placebo arm in STEPS compared to 004, see Table 7.

Table 7 Comparison of responder rates in trial 004 and STEPS.

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

Abbreviations: PS, parenteral support
Source: STEPS primary publications (Jeppesen, 2011)[43]; 004 primary publication (Jeppesen, 2012)[44]

Thus, for the evaluation of teduglutide in adults we believe that the STEPS study is the most relevant study.

Another limitation one needs to consider when assessing efficacy data of teduglutide vs. placebo from the STEPS study is the high placebo response seen in the study, which does not reflect results with standard care in clinical practice according to the principal investigator of the study, Dr. Palle Jeppesen. The high placebo response rate is an artefact of the PS weaning algorithm and led to patients receiving placebo risking dehydration and losing weight, and the

principal investigator of the trial stated this should be viewed as a protocol violation.[45] This is discussed in detail in greater detail in the section below.[45]

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7.1.2.1.1.1 Placebo response in STEPS

A feature of the STEPS results is the apparent efficacy of placebo: a response rate of 30%, an average PS reduction of -2.3 L/week and 23.1% (n=9/39) of patients reaching an additional day per week off PS (all measured at week 24 and relative to baseline). Professor Palle Jeppesen, principal investigator of the STEPS study with more than 25 years of gastroenterology experience and over 20 years of clinical research experience with GLP-2 analogues, such as teduglutide, has clearly stressed that these results are not being reflective of standard care in clinical practice. In an expert statement, Prof. Jeppesen describes this placebo rate as 'artificially high' and that it represents 'a protocol violation'.[45]

Teduglutide has shown to improve intestinal absorption and allowing patients to reduce PS and increase oral fluid/nutrition intake. It should be noted first that the PS reductions in the placebo arm of STEPS are not likely due to increased intestinal absorption. All patients entering STEPS underwent a process of PS optimisation in order to achieve suitable urine output and stabilisation to ensure PS volume received matched PS volume prescribed. Furthermore, patients in the placebo arm of STEPS had been receiving PS for on average 5.9 years (SD 5.7) after which time spontaneous adaptation of the intestine is described by Professor Jeppesen as 'highly unlikely'.[45]

Professor Jeppesen points to usual biological fluctuations in patients' urine output combined with the STEPS weaning algorithm to explain the high response rate in the placebo arm. In clinical practice, a patient would only be able to reduce their PS if the absorptive capacity of their intestine improved, such that they could effectively receive more nutrients and fluid by mouth and meet their nutritional demands. Improved intestinal absorption can be observed through decreased faecal wet weight (as more fluid is absorbed by the intestine), and in phase 2 studies of teduglutide, decreased faecal wet weight was seen to correlate with increased urine volume. As urine volume was more feasible to measure, subsequent clinical trials used urine volume as a marker of intestinal adaptation and as a guide to reducing PS volume. Therefore, in STEPS, PS volumes could be reduced (by up to 30% of baseline) if urine volume was ≥10% above baseline. However, Professor Jeppesen notes that a spontaneous increase in urine production of >10% has been previously observed in 25% of patients with SBS, even with fixed oral fluid intake. Coupled with the STEPS PS weaning algorithm, normal fluctuations in urine volume (rather than increased intestinal absorption) may have triggered PS volume reductions in patients receiving placebo.

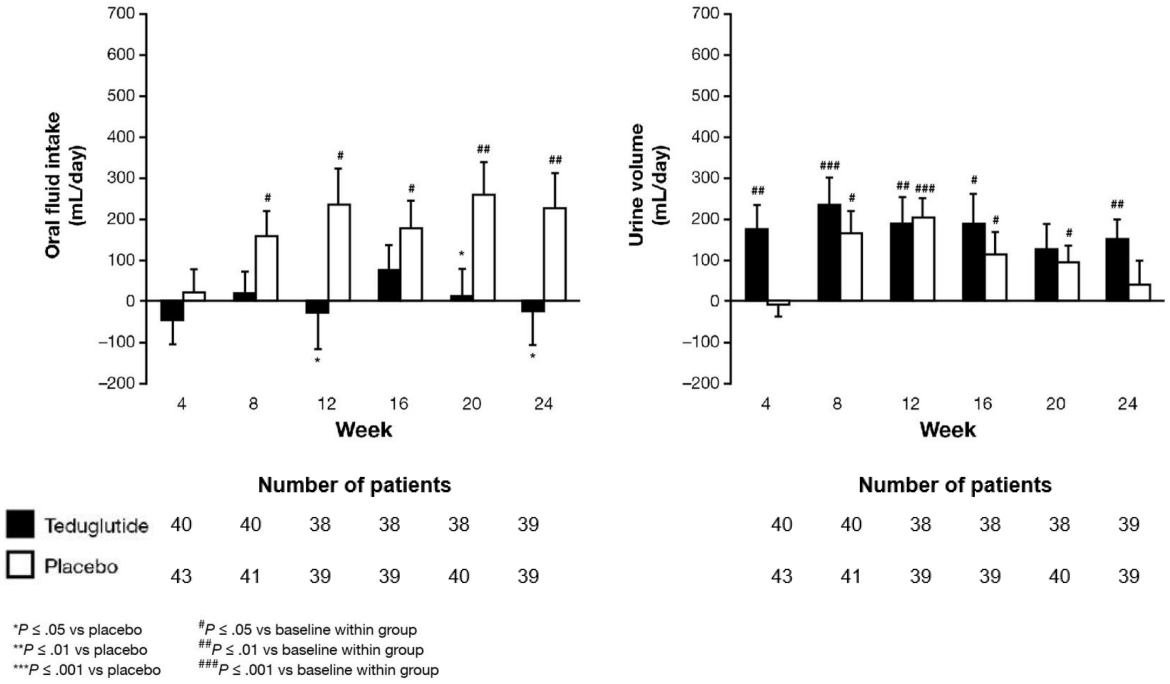
Whilst urine volume fluctuations may explain the placebo response rate, we should also consider to what degree weaning in the teduglutide arm of STEPS was also driven by these fluctuations rather than reduced PS need, and therefore may also have not been appropriate.

Professor Jeppesen addresses this question by considering further clinical data from STEPS, which suggests that patients receiving placebo may have struggled to remain hydrated over the course of the 24 week study, whilst patients receiving teduglutide did not. As PS volume (which contains IV fluids for hydration) decreased in both arms over the study, patients in the placebo arm had to significantly increase their oral fluid intake (1.6 ± 3.6 L/wk. at week 24; p=0.009 vs baseline; Figure 4A, below) in order to compensate for this loss of IV fluid (the increased oral fluid intake was not lost as increased urine production, see Figure 4B below). Patients receiving teduglutide did not increase their oral fluid intake as their IV fluid intake decreased; we can infer this was because their intestine was able to absorb more fluid from their existing oral intake. For a graphical illustration of this situation, see Figure 5.

Urine production in both arms increased from baseline but otherwise stayed fairly constant over the study, supporting the above interpretation (Figure 5B). Professor Jeppesen emphasises that changes in fluid intake as occurred among the placebo patients were not intended by the study design. He is emphatic in stressing that patients increasing oral

fluid intake while not increasing urine production should be viewed as a protocol violation, and that these patients should have had their PS increased in response.

Figure 4 Change in A) oral fluid intake and B) urine volume from baseline in teduglutide and placebo arms; STEPS trial. Source: STEPS primary publication; STTEPS Clinical Study Report.



Professor Jeppesen also points to data on patients' weight to emphasise that the placebo response in STEPS was not healthy or sustainable. At week 24 compared to baseline, patients in the teduglutide arm had a mean body weight increase of 1.0 kg; in the placebo arm, there was a mean body weight decrease of 0.6 kg.[47] This suggests that patients in the placebo arm were not receiving enough PS to meet their energy and/or hydration needs, whereas patients receiving teduglutide were receiving appropriate PS. He additionally points out that the magnitude of PS volume decrease seen in the teduglutide arm could have actually been larger, given that urine volumes in the teduglutide arm were significantly higher than baseline at week 24 (suggesting these patients were receiving more fluid than needed; Figure 5B).

In summary, Professor Jeppesen concludes that PS weaning in the placebo arm of STEPS was driven by natural fluctuations in urine volume combined with the weaning algorithm and led to patients increasing their oral fluid intake to try to avoid dehydration, and loss of weight. In the teduglutide arm, PS weaning was driven by enhanced intestinal absorption; patients did not have to increase their oral fluid intake to make up for decreased PS and were able to gain weight.

[redacted]

7.1.2.1.1.2 Measuring Quality of Life in patients with SBS-IF

Quality of Life has in the STEPS study been measured using the SBS-QoL™ questionnaire. The clinical relevance and validity of the measure is, however, subject to debate. The SBS-QoL was developed in 2013 but has rarely been used since that time. This is despite short bowel syndrome being widely researched. In a confidential report prepared by the first published MCID (18.4) was determined by an approach combining the measured error and experts' opinions, and was not anchored on a clinical change that is meaningful to patients, which is the preferred methodology recommended by the FDA.[16,48] [redacted]

[redacted]

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In a cross-sectional study from 2018 by Nordsten et al it was found that PS volume (L/day) was significantly correlated with SBS-QoL score with an estimate of 7 QoL points per L/day (95% CI:1 to 13; P = 0.044).[50] As of today however, no clinical consensus has been reached on what the MCID is, and the benchmark is developing as more research is conducted on the QoL of patients with SBS.[50]

7.1.2.1.1.3 Limitations of the extension studies

Limitations of the extension studies include the open-label design and lack of a control arm; additionally, the study population was a small, selected cohort that met inclusion requirements for longer-term follow-up. The study population, however, is necessarily small, given the rarity of the condition.

These extension studies, undertaken at the end of the clinical development program for drug approval, had a study design and a data analysis plan that was descriptive and was not intended to be sufficiently powered for statistical significance analysis. Even with this limitation, this type of study design can provide important information on outcomes, and as reported here for the STEPS-2 and 3 data, observed results that were in line with those of previous studies. These factors may limit the applicability of the current findings to patients in the real-world clinical setting with a broader range of disease and clinical characteristics. However, findings from several real world prospective and retrospective cohort studies are in line with findings from the clinical development program of teduglutide and the two extensions studies providing further support for the clinical utility of teduglutide in the treatment of SBS-IF. Because the extension studies were not placebo-controlled, it cannot be ruled out that observed reductions in PS were partially caused by spontaneous adaptation. However, in this context, it is noteworthy that the observed PS volume reductions were greatest in the subgroups with the longest duration of exposure to teduglutide.

One further limitation is related to protocol differences in the algorithm for PS weaning between the initial placebo-controlled study (STEPS) and the extension studies STEPS-2 and STEPS 3 that may account for some of the variation in response among treatment subgroups. The initial placebo-controlled STEPS study, which was designed to assess the efficacy of teduglutide relative to placebo, implemented a stricter protocol for PS weaning than did the extensions studies, which was designed to provide long-term, open-label safety and efficacy data, with less frequent study visits (on average, every 3 months). Although they did not receive teduglutide treatment in the initial placebo-controlled study, patients in the PBO/TED subgroup benefited from the more aggressive weaning algorithm. As a result of this intensive management, patients in the placebo group in the initial placebo-controlled study achieved a 2.3 L/week

(21%) reduction in PS volume requirements at the end of that study. These patients, who had lower baseline PS requirements at the start of STEPS-2, achieved an additional 3.1 L/week (28%) reduction in PS volume requirements with 24 months of teduglutide during the extension study. Between Months 3 and 24 of STEPS-2, patients were evaluated for PS reductions less frequently than during the initial placebo-controlled study; this may partially explain why the response to teduglutide treatment in the NT/TED group at Month 24 was somewhat weaker than the response in the teduglutide arm in the initial placebo-controlled study at Month 6 (−4.0 vs. −4.4 L/week, respectively). However, the small size of the subgroups, particularly the NT/TED subgroup (n=12), limits the ability to draw firm conclusions from subgroup comparisons.

7.1.2.2 Studies conducted in pediatric SBS-IF patients

To demonstrate clinical efficacy and safety in paediatrics data from the two clinical trials, **NCT0001952080 (TED-003)** and **NCT02682381 (TED-006)** will be used for the comparative analysis of the intervention (teduglutide) and comparator (SOC, standard-of-care). Meta-analysis of the two studies is deemed inappropriate/not feasible due to the following reasons; huge discrepancies in study length (12 vs. 24 weeks), data analysis for the primary endpoint in the 24 weeks study (TED-006, the number of patients who achieved a ≥20% reduction in parenteral support (PS) from baseline at week 24, has neither been published nor conducted for week 12 and finally, according to the EMA approved SmPC for Revestive (teduglutide) a treatment period of 6 months is recommended before treatment effect should be evaluated.

To demonstrate long term safety in paediatrics data from a pooled safety analysis of 4 clinical trials will be used and described narratively below.

The pediatric phase III TED-003 study. Carter, B. A., et al. Outcomes from a 12-Week, Open-Label, Multicenter Clinical Trial of Teduglutide in Pediatric Short Bowel Syndrome. The Journal of Pediatrics 2017: 181, 102-111.e5
This study was a 12-week, open-label, multicenter, phase 3 study that evaluated the safety and pharmacodynamics/efficacy of teduglutide in children with intestinal failure associated with short bowel syndrome (SBS-IF). Patients enrolled sequentially into 3 teduglutide cohorts (0.0125 mg/kg/d [n = 8], 0.025 mg/ kg/d [n = 14], 0.05 mg/kg/d [n = 15]) or received standard of care (SOC, n = 5).

Because of the small pool of eligible patients, the study analysis was descriptive in nature and was not designed or sufficiently powered to determine the statistical significance of safety or PD/efficacy endpoints. Treatment-emergent adverse events (TEAEs) and treatment emergent serious adverse events (TESAEs) were recorded. The following PD/efficacy endpoints included changes in PN requirements, including the number of patients that achieved complete PN independence; change in EN tolerance and changes in hours per day of PN infusion and enteral feeding volumes.

Eligible patients were aged 1-17 years who had a ≥12-month history of SBS and dependence on PN (defined as PN and/or intravenous fluids) for at least 30% of caloric and/or fluid/electrolyte needs. PN needs were required to be stable at baseline, without any clinically meaningful or substantial reduction in PN or advancement in enteral nutrition (EN; oral and/or tube feeding) for ≥3 months.

In the current study, 4 patients were weaned successfully from PN with teduglutide after up to 12 years of PN dependence. PN had to be resumed in 2 of these patients at week 16 (4 weeks after teduglutide discontinuation), suggestive of a treatment-related improvement while on treatment.

The pediatric phase III TED-006 study. Kocoshis, S. A., et al **.** Safety and Efficacy of Teduglutide in Pediatric Patients With Intestinal Failure due to Short Bowel Syndrome: A 24-Week, Phase III Study. Journal of Parenteral and Enteral Nutrition 2019:44(4), 621–631.
This study was a 24-week, phase III trial with 2 randomized, double-blind teduglutide dose groups (0.025 mg/kg and 0.05 mg/kg) and a nonblinded standard of care (SOC) arm. The purpose of the study was to evaluate the safety and efficacy of teduglutide in pediatric patients with short bowel syndrome–associated intestinal failure (SBS-IF).

The primary efficacy/pharmacodynamic end point was the number of patients who achieved a ≥20% reduction in parenteral support (PS) from baseline at week 24. Secondary end points included the PS and EN volume and calories change from baseline at week 24, enteral autonomy at EOT (i.e., no prescribed PS at EOT and no recorded PS administration for the week before EOT), and the change from baseline in days per week and hours per day of PS.

Given the rarity of SBS, the planned sample size was based on the estimated feasibility of enrollment in the pediatric population with SBS rather than on power calculations, and no statistical hypothesis testing of efficacy was therefore prespecified in the protocol. However, because of unexpectedly high enrollment, post hoc statistical analysis of the primary end point and the mean reduction in PS volume was performed.

Inclusion and exclusion criteria were similar to those of the previous 12-week study described above.

The pediatric pooled safety analysis of 4 clinical trials. Hill S, et al. Safety Findings in Pediatric Patients During Long-Term Treatment With Teduglutide for Short-Bowel Syndrome–Associated Intestinal Failure: Pooled Analysis of 4 Clinical Studies. JPEN J Parenter Enteral Nutr. 2021;0:1–10

In this analysis, safety data from teduglutide-treated patients in 4 clinical trials were pooled: Final data from the completed 12-week and 24-week phase 3 core studies (NCT01952080 (TED-003) and NCT02682381 (TED-006) and interim data from two ongoing open-label extensions (NCT02949362 and NCT02954458) of the 12- and 24-week trials, respectively.

Outcomes assessed were study drug exposure, adverse events (AEs), vital signs, growth trajectories, laboratory findings, and occurrence of anti-teduglutide antibodies. AEs were pooled and summarized using descriptive statistics. AEs that occurred during no-teduglutide treatment periods between treatment cycles in the extension studies were included in the analysis.

Patients were eligible for inclusion in the extension studies if they completed the 12-week or 24-week core study in either the teduglutide or SOC arm.

In the ongoing extension studies, teduglutide is provided to children with SBS–IF in treatment cycles consisting of 24 weeks of 0.05 mg/kg teduglutide once daily followed by a 4-week follow-up period. After a teduglutide treatment period, teduglutide is only reinitiated if a patient's PS plateaus or deteriorates. At the end of the 4-week follow-up, patients who have not reinitiated teduglutide can enter a "no-teduglutide treatment" period of observation with safety and clinical data collection approximately every 12 weeks.

7.1.2.2.1 Limitations to pediatric studies

Limitations of the 12-week phase 3 clinical studies in pediatrics relate to the open-label design with no randomization, and the short-term treatment period. Due to the inherent nature of the rarity of the disease, the pool of eligible patients is small, and, as such, the sample size was based on the available patient population rather than on a statistical power calculation. Moreover, recruitment into the SOC cohort in this open-label study was hindered by lack of interest or perceived benefit among patients and guardians, and this cohort included no patients older than 3 years of age. Thus, the study was not powered sufficiently to determine the statistical significance of safety or PD/efficacy endpoints, and only descriptive statistics were used. These limitations can be attributed to the fact that pediatric SBS is an orphan condition, making the stratification of the small number of patients enrolled by age, diagnosis, bowel length, or baseline intestinal function impossible.

Limitations of the 24-week study include open-label treatment allocation and the ability to choose teduglutide vs SOC treatment, allowing selection and reporting bias. It is possible that patients with less frequent or severe complications

of SBS at baseline may have chosen SOC rather than teduglutide. Selection bias may also account for the higher baseline weight and height z-scores in the SOC arm. The nonblinded SOC arm also makes the safety data for teduglutide vulnerable to reporting bias for AEs.

7.1.3 Comparative analyses of efficacy and safety

7.1.3.1 Efficacy and safety data from RCTs and pivotal registration studies

The key efficacy and safety data for each study are summarized below. Detailed information for each endpoint and the statistical calculation used is described in appendix D. Additional safety information is provided in appendix E. For all endpoint data the 0,05 mg/kg dose of teduglutide has been used.

7.1.3.1.1 Efficacy and safety data for adult patients

The phase III 004 study

Jeppesen PB, Gilroy R, Pertkiewicz M*, et al*. Randomized placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome. *Gut* 2011; 60: 902–914

Primary endpoint: For the primary efficacy endpoint, **a graded response score (criterion that accounted for both intensity and duration of a response at the end of the 24-week period)**, teduglutide demonstrated a statistically and clinically significant better effect compared to placebo (45.7% vs 6.3%; absolute risk difference: 39.46% (95% CI 0.37% to 309.25%)

Key secondary endpoints:

For the secondary efficacy endpoint, **proportion of subjects achieving a 20% reduction of PN at both Week 20 and Week 24**, teduglutide demonstrated a statistically and clinically significant better effect compared to placebo (45.7% vs 6.3%; absolute risk difference: 39.46%; 95% CI 0.37% to 309.27%)

For the secondary efficacy endpoint, **number and percentage of subjects who achieved at least a 1-day reduction in weekly PN (week 24)**, teduglutide demonstrated no significant better effect compared to placebo (31.4% vs 25%; absolute risk difference: 6.43 (95% CI -13.20% to 58.71%)

Safety The number of subjects reporting an AE (94%) and the number of AEs were distributed similarly across the teduglutide groups and placebo. The distribution of the number of subjects reporting SAEs was 37% for the teduglutide group and 31% for the placebo group. The most common AEs in the teduglutide treatment groups were abdominal pain (24%), headache (24%), nausea (22%), nasopharyngitis (16%) and vomiting (15%). The most frequently reported SAEs were catheter-related complications, catheter sepsis, catheter site infection, small intestinal obstruction and fever.

The phase III STEPS study

Jeppesen PB, Pertkiewicz M, Messing B, et al. Teduglutide reduces need for parenteral support among patients with short bowel syndrome with intestinal failure. Gastroenterology 2012; 143: 1473–1481.e1473.

Primary endpoint: For the primary endpoint, **percentage of subjects who responded (a ≥20% reduction of PN) at Week 20 and week 24 (responder)**, teduglutide demonstrated a statistically and clinically significant better effect compared to placebo (62.8% vs. 30.2%; absolute risk difference: 32.56% (95% CI 7.51 to 74.23)

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Key secondary endpoints:
For the secondary endpoint, the absolute change in PN/I.V. volume (L/wk) between baseline and last dosing visit (w24), teduglutide demonstrated a statistically and clinically significant better effect compared to placebo (-4.37 vs. -2.29 L; absolute difference: -2.08 L (95% CI -3.23 to -0.93)

For the secondary endpoint, number of patients who stopped PS, teduglutide did not demonstrate a statistically significant better effect compared to placebo (0.00% vs. 2.33%; absolute difference: -0.05%, 95%-CI: -0.16% to 0.05%

For the secondary endpoint, **percentage of subjects with a duration of response for ≥3 consecutive visits (duration of response)**, teduglutide demonstrated a statistically and clinically significant better effect compared to placebo (55.8% vs. 27.9%; absolute risk difference: 27.91% (95% CI 4.32 to 68.75)

For the secondary endpoint, **reduction in days on PN/I.V. (the percentage of subjects with at least a 1-day reduction in weekly actual PN/I.V. use at Week 24)**, teduglutide demonstrated a statistically and clinically significant better effect compared to placebo (53.8% vs. 23.1%; absolute risk difference: 30.77% (95% CI 5.25 to 79.29).

Safety: The number of patients with AEs, serious AEs, treatment-emergent AEs (TEAEs), or discontinuations due to treatment-emergent serious AEs was comparable between treatment groups. The most frequently reported TEAEs in the teduglutide group were of gastrointestinal origin, such as abdominal pain, nausea, gastrointestinal stoma complication, or abdominal distension.

In the efficacy analyses, N is 43 (ITT, all randomized), which is also the case for the calculation of all rates. For safety, N=42 is used, as one subject did not receive at least one dose of study drug. N=43 for the continuous data, but there are 4 missing observations at week 24, why the subsequent analyses are based on n=39.

Please see meta-analysis of 005 and STEPS in Appendix T.

7.1.3.1.2 Efficacy and safety data for pediatric patients

The pediatric phase III TED—003 study
Carter, B. A., et al. Outcomes from a 12-Week, Open-Label, Multicenter Clinical Trial of Teduglutide in Pediatric Short Bowel Syndrome. The Journal of Pediatrics 2017: 181, 102-111.e5

Primary endpoint: For the primary endpoint**, ≥ 10% reduction in PN/IV support (week 12)**, teduglutide demonstrated a statistically and clinically significant better effect compared to SOC 60.0% vs. 0%; absolute risk difference: 60.0% (95% CI 35.21 to 84.79)

Key secondary endpoint: For the secondary endpoint**, a ≥ 20% reduction in PN/IV support (week 12)**, teduglutide demonstrated a non-statistically but numerically and clinically significant better effect compared to SOC (53.3% vs. 0%; absolute risk difference: 53.33% (95% 28.09% to 78.58%)

In the current study, 4 patients were weaned successfully from PN with teduglutide after up to 12 years of PN dependence. PN had to be resumed in 2 of these patients at week 16 (4 weeks after teduglutide discontinuation), suggestive of a treatment-related improvement while on treatment.

Safety: Teduglutide had a generally good safety profile and was well tolerated by pediatric patients at the doses tested. GI events were reported at a relatively low frequency overall, but most were more common in teduglutide dose cohorts than in the SOC cohort. Despite GI events, most patients treated with teduglutide completed the study.

The overall safety profile was consistent with the adult SBS population described above. The most commonly reported TEAEs in the teduglutide-treated population were GI-related AEs, upper respiratory tract infection, catheter-related complications, and pyrexia, all of which were observed in the short-term studies of teduglutide in adult patients

The pediatric phase III TED-006 study

Kocoshis, S. A., et al. Safety and Efficacy of Teduglutide in Pediatric Patients With Intestinal Failure due to Short Bowel Syndrome: A 24-Week, Phase III Study. Journal of Parenteral and Enteral Nutrition 2019:44(4), 621–631.

Primary endpoint: For the primary endpoint, **a reduction in weight-normalized PS volume of at least 20% at Week 24 (or EOT) from baseline**, teduglutide demonstrated statistically and clinically significant better effect compared to SOC (69.2% vs. 11.1%; absolute risk difference: 58.12% (95% CI 31.0 to 85.3)

Key secondary endpoint: For the secondary endpoint, **a 100% reduction in PN/IV volume (complete weaning of PN/IV support) at Week 24 (or EOT)** compared to baseline, teduglutide demonstrated a non-statistically but numerically and clinically relevant better effect compared to SOC (11.54% vs. 0%; absolute risk difference: 11.54% (95% CI -0.74 to 23.82)

Safety: Safety data support findings of the prior 12-week dosing study of teduglutide in pediatric Patients summarized above. Most TEAEs considered by a study investigator to be teduglutide related were single patient events. AEs of abdominal pain, a known reaction to teduglutide, occurred more frequently in the teduglutide dose groups than the SOC arm. The spectrum of TEAEs was similar between the teduglutide dose groups, and none led to treatment discontinuation or death. More patients in the teduglutide dose groups than in the SOC arm reported TESAEs, but only 2 teduglutide-treated patients experienced a TESAE considered treatment related by an investigator.

7.1.3.2 Efficacy and safety data from long-term extension studies

The long term efficacy and safety of Revestive in adults has been evaluated in STEPS-2[51], which was a 2-year, open-label extension of the STEP study, and STEPS-3[52], a further 1-year open-label extension of STEPS-2, see Figure 3 in section 7.1.1. Efficacy outcomes will be summarized for each STEP extension study below and long-term safety outcome will be covered separately by a 4 study pooled safety analysis.

7.1.3.2.1 STEPS-2

In STEPS-2 clinically relevant improvements were observed for all efficacy endpoints and across all subgroups, see Table 8 below, with the greatest reductions seen in the subgroup with the longest duration of exposure to teduglutide, TED/TED.

Table 8 Parenteral support volume reductions in STEPS-2

	All patients[a] (N=88)			Completers (n=65)		
	TED/TED (n=37)	PBO/TED (n=39)	NT/TED (n=12)	TED/TED (n=30)	PBO/TED (n=29)	NT/TED (n=6)
Baseline PS requirement, l/week[b]	12.3	11.4	14.2	12.4	10.4	12.8
Clinical response,[c] n (%)[d]	33 (89)	18 (46)	6 (50)	28 (93)	16 (55)	4 (67)
Mean PS reduction from baseline, l/week (s.d.)	6.8 (4.9)	2.9 (3.9)	3.3 (3.7)	7.6 (4.9)	3.1 (3.9)	4.0 (2.9)
Percentage reduction[e]	59	25	19	66	28	39

ITT, intent-to-treat; NT/TED, received no treatment in the initial placebo-controlled study and teduglutide in STEPS-2; PBO/TED, received placebo in the initial placebo-controlled study and teduglutide in STEPS-2; PS, parenteral support (parenteral nutrition and/or intravenous fluids); TED/TED, received teduglutide in the initial placebo-controlled study and in STEPS-2.

[a] Last dosing visit in the ITT population.

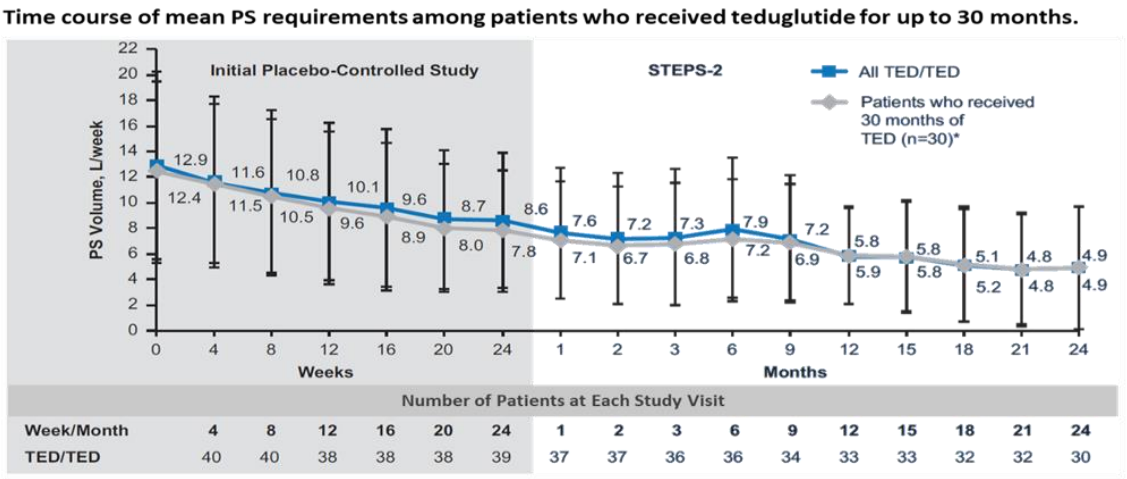
[b] Last dosing visit population is n =36, n=36, n =10, respectively. Baseline determined by start of teduglutide treatment: at randomization in the initial placebo-controlled study for TED/TED patients (30 months of teduglutide treatment) and at start of STEPS-2 for PBO/TED and NT/TED patients (24 months of teduglutide treatment).

[c] 20–100% PS volume reduction from baseline.

[d] Last dosing visit ITT population is n =37, n=39, n=12, respectively.

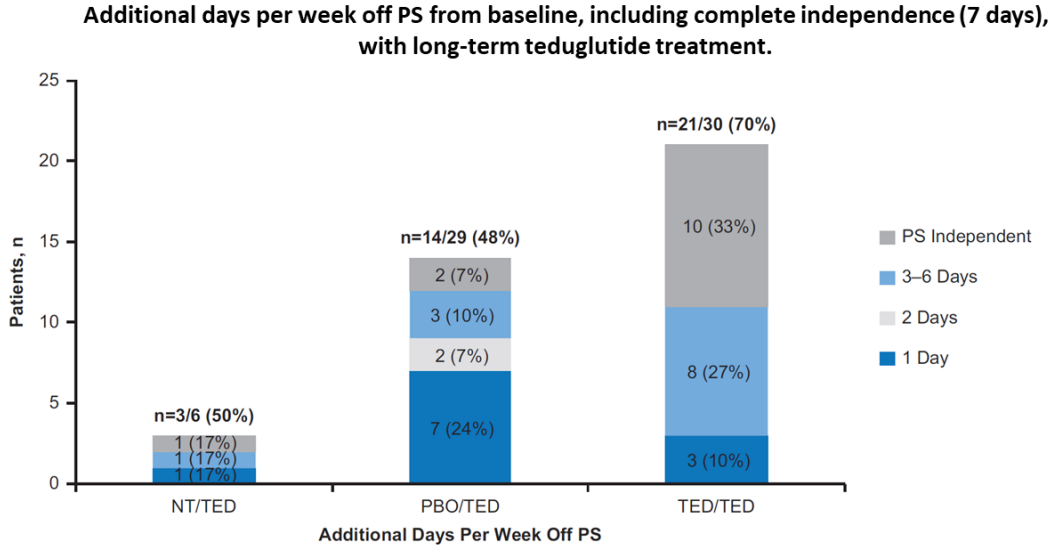
[E] Last dosing visit ITT population is n =36, n=36, n=10, respectively.

Figure 6 PS reductions in patients with SBS who received long-term teduglutide treatment.



Time course of mean PS requirements among patients who received teduglutide for up to 30 months. Squares represent the ITT TED/TED data set (table below figure has the number of patients corresponding to each time point), and diamonds represent the data set from the 30 TED/TED patients who completed the study. Error bars represent s.d.

Figure 7 PS reductions in patients with SBS who received long-term teduglutide treatment.



*Represents data for only those patients who completed 30 months of treatment with teduglutide. ITT, intent-to-treat; NT/TED, received no treatment in the initial placebo-controlled study and teduglutide in STEPS-2; PBO/TED, received placebo in the initial placebo-controlled study and teduglutide in STEPS-2; PS, parenteral support (parenteral nutrition and/or intravenous fluids); SBS, short bowel syndrome; TED/TED, received teduglutide in the initial placebocontrolled study and in STEPS-2.

PS reductions in patients with SBS who received long-term teduglutide treatment. (a) Time course of mean PS requirements among patients who received teduglutide for up to 30 months. Squares represent the ITT TED/TED data set (table below figure has the number of patients corresponding to each time point), and diamonds represent the data set from the 30 TED/TED patients who completed the study. Error bars represent s.d. (b) Additional days per week off PS from baseline, including complete independence (7 days), with long-term teduglutide treatment. *Represents data for only those patients who completed 30 months of treatment with teduglutide. ITT, intent-to-treat; NT/TED, received no treatment in the initial placebo-controlled study and teduglutide in STEPS-2; PBO/TED,

received placebo in the initial placebo-controlled study and teduglutide in STEPS-2; PS, parenteral support (parenteral nutrition and/or intravenous fluids); SBS, short bowel syndrome; TED/TED, received teduglutide in the initial placebo-controlled study and in STEPS-2.

The greatest improvements with teduglutide were observed in the TED/TED subgroup, which received the longest duration of therapy (up to 30 months). The difference between the groups in terms of the progressive increase in clinical benefit observed with long-term teduglutide treatment is probably due to the mechanism of action of teduglutide, some patients are late responders and further to this, the protocol differences between the 2 studies (STEPS and STEPS-2) and selection into the follow-up study may account for some of the variation in response among treatment subgroups. The initial placebo-controlled study, which was designed to assess the efficacy of teduglutide relative to placebo, implemented a stricter protocol for PS weaning than did the extension study, which was designed to provide long-term, open-label safety and efficacy data, with less frequent study visits (on average, every 3 months). Although they did not receive teduglutide treatment in the initial placebo-controlled study, patients in the PBO/TED subgroup benefited from the more aggressive weaning algorithm. As a result of this intensive management, patients in the placebo group in the initial placebo-controlled study achieved a 2.3-l/week (21%) reduction in PS volume requirements at the end of that study. These patients, who had lower baseline PS requirements at the start of STEPS-2, achieved an additional 3.1-l/week (28%) reduction in PS volume requirements with 24 months of teduglutide during the extension study. Between Months 3 and 24 of STEPS-2, patients were evaluated for PS reductions less frequently than during the initial placebo-controlled study; this may partially explain why the response to teduglutide treatment in the NT/TED group at Month 24 was somewhat weaker than the response in the teduglutide arm in the initial placebo-controlled study at Month 6 (−4.0 vs. −4.4 l/week, respectively). However, the small size of the subgroups, particularly the NT/TED subgroup (n=12), limits the ability to draw firm conclusions from subgroup comparisons.

7.1.3.2.2 STEPS-3

In STEPS-3 clinically relevant improvements were observed for all efficacy endpoints and across all subgroups, see Table 9 and Figure 8 below. Similar to what was observed in STEPS-2, the greatest reductions were seen in the subgroup with the longest duration of exposure to teduglutide, TED/TED.

Table 9 Parenteral support volume reductions in STEPS 3.

	NT/PBO-TED (n=9)	TED-TED (n=5)
Baseline PS requirement, L/week (s.d.)	10.5 (7.5)	13.4 (11.6)
Mean PS reduction from baseline, L/week (s.d.)	3.9 (2.8)	9.8 (14.4)
Percentage reduction (s.d.)	47.8% (42.9%)	49.7% (72.4%)
Reduction in days receiving PS	2.1 (2.2)	3.0 (4.6)

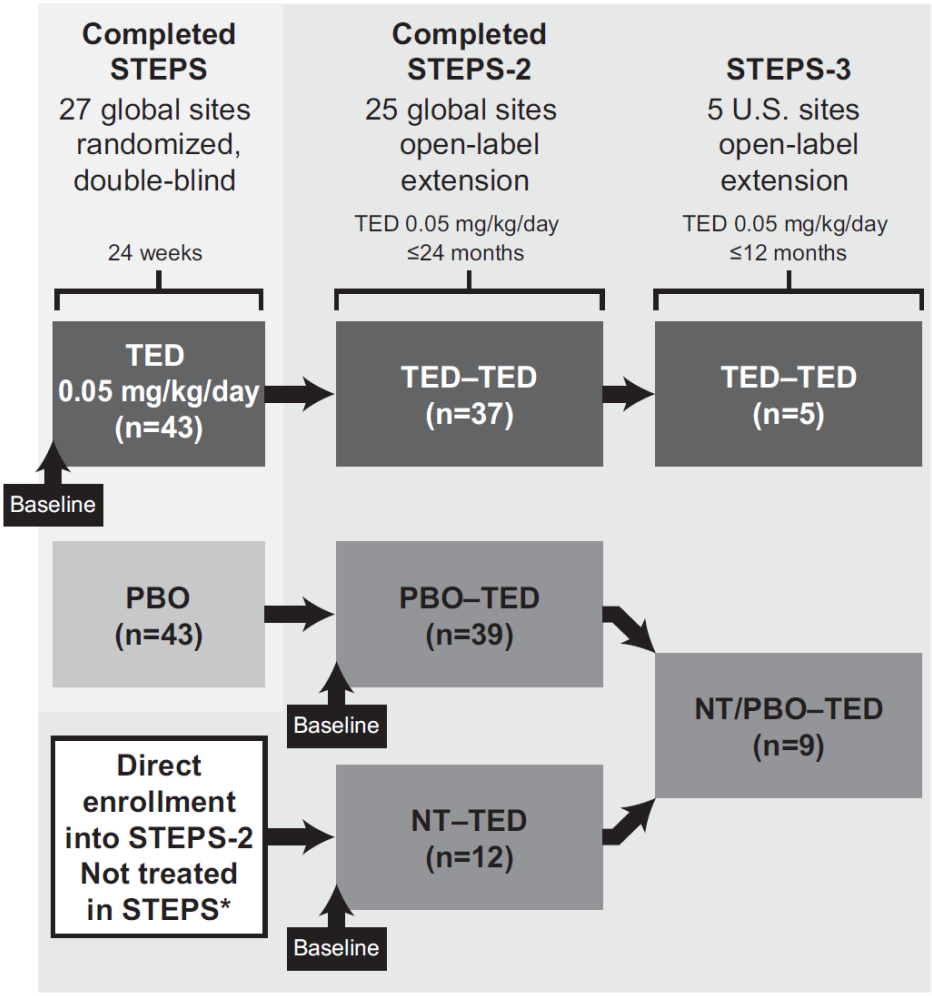
S.D., standard deviation. NT/PBO-TED, received no treatment or placebo in the initial placebo-controlled trial (STEPS) and teduglutide in STEPS-2; TED/TED, received teduglutide in the initial placebo-controlled trial and teduglutide in STEPS-2; PS, parenteral support (parenteral nutrition and/or intravenous fluids).

For the TED-TED group baseline values (BL) is from the enrollment in STEPS and for the PBO-TED and NT/TED groups baseline values is from the enrollment in STEPS 2 (see Figure 8 below). Study visits in STEPS-3 were conducted every 3 months.

The confluence of the rolling start dates and the study end date meant that all patients did not receive 12 months of TED treatment. The mean (SD) duration of exposure to TED during STEPS-3 was 38.9 (9.8) weeks for the overall

population, 41.5 (8.4) weeks for NT/PBO–TED, and 34.3 (11.3) weeks for TED–TED. Combined with the TED treatment in the STEPS-2 study, the total TED exposure time was 36 months for NT/PBO–TED and 42 months for TED–TED.

Figure 8 Flow diagram of patients across the STEPS studies



NT/PBO–TED received NT or PBO in initial PBO-controlled trial (STEPS) and TED in STEPS-2. TED–TED received TED in initial PBO-controlled trial (STEPS) and in STEPS-2. *Patients who completed fluid optimization and stabilization but were not randomized in STEPS because of full study enrollment were eligible for direct enrollment into STEPS-2. NT, no teduglutide treatment; PBO, placebo; TED, teduglutide.

7.1.3.2.3 Overall conclusion on efficacy outcomes from the two RCTs and outcomes from long-term use of teduglutide from the two extension studies STEPS-2 and STEPS-3

Efficacy data from the two RCTs and the two open-label STEPS extension studies provide general support for the clinical utility of TED in the treatment of adults with SBS–IF and shows that efficacy of TED is maintained or enhanced during treatment courses ≥36 months which was associated with continued efficacy as reflected by continued reductions in PS volume, a gain in number of days off PS per week, and achieving complete independence from PS.

Patients maintained and improved nutrition status in the presence of PS volume reductions during long-term treatment and it is notable that stable or improved nutrition status found in the STEPS-3 1-year extension study is similar to that reported in the previous 2-year STEPS-2 study. It is also noteworthy that some patients who achieved enteral autonomy in STEPS-2 maintained such independence with continuous long-term teduglutide in STEPS-3. However, the finding that other patients reached enteral autonomy for the first time after approximately 2 years of treatment with TED in STEPS-3 suggests that some patients may need longer exposure to TED to achieve PS independence. In STEPS and STEPS-2, only few patients were seen to escalate in PS requirements, measured as weekly PS-days, between visits. Table 85 in **Appendix C** below presents the number of patients that escalate in PS requirements between visits.

Drawing comparison to other pharmaceutical drugs the durability of the effects of teduglutide and the progressive increase in clinical benefit with long-term treatment is highly noteworthy and something that is very seldom seen. Loss of response or attenuated effect is very common with other biologic agents in the treatment of GI diseases.[53] Almost all patients (21/22) in the TED/TED subgroup who achieved a clinical response (≥20% reduction from baseline in weekly PS volume at Weeks 20 and 24) with teduglutide in the initial placebo-controlled study maintained their response after an additional 24 months of treatment. In addition, a progressive increase in clinical benefit was observed with long-term teduglutide treatment. Mean PS volume requirements declined steadily over 36 months of treatment among patients who received teduglutide in both the initial 24-week placebo-controlled study and the STEPS-2 and STEPS-3 extension studies. Furthermore, the percentage of patients achieving additional days off PS increased with longer treatment time; among teduglutide treated patients who completed 30 months of treatment in the initial placebo-controlled study and STEPS-2, 60% (18/30) achieved a ≥2-day reduction in PS infusions per week compared with 21% (8/39) of patients who received teduglutide for 24 weeks in the initial placebo-controlled study.

One of the greatest values associated with teduglutide is the potential to eliminate the need for PS in some patients. Complete enteral autonomy eradicates the risks associated with catheter dependence and chronic PS infusion.[15] However, PS reductions that permit partial weaning and gaining additional days off PS are also powerful, with the potential to increase quality of life and reduce PS-associated complications. Indeed, among patients with SBS-IF, decreases in PS requirements are associated with significantly higher scores on an SBS-specific quality-of-life instrument.[16]

7.1.3.3 Safety data in adult patients

The safety analysis for adults is based on pooled safety data from four prospective clinical trials of teduglutide in patients with SBS-IF conducted from May 2004 through January 2013, see Figure 9.[54]

- Jeppesen PB, Gilroy R, Pertkiewicz M*, et al*. Randomized placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome. *Gut* 2011; 60: 902–914. **(CL0600-004)**

- Jeppesen PB, Pertkiewicz M, Messing B*, et al*. Teduglutide reduces need for parenteral support among patients with short bowel syndrome with intestinal failure. *Gastroenterology* 2012; 143: 1473–1481.e1473. **(STEPS)**

- O'Keefe SJ, Jeppesen PB, Gilroy R, *et al*. Safety and efficacy of teduglutide after 52 weeks of treatment in patients with short bowel intestinal failure. *Clin Gastroenterol Hepatol* 2013; 11: 815–823. **(CL0600-005)**

- Schwartz LK, O'Keefe SJ, Fujioka K*, et al*. Long-term teduglutide for the treatment of patients

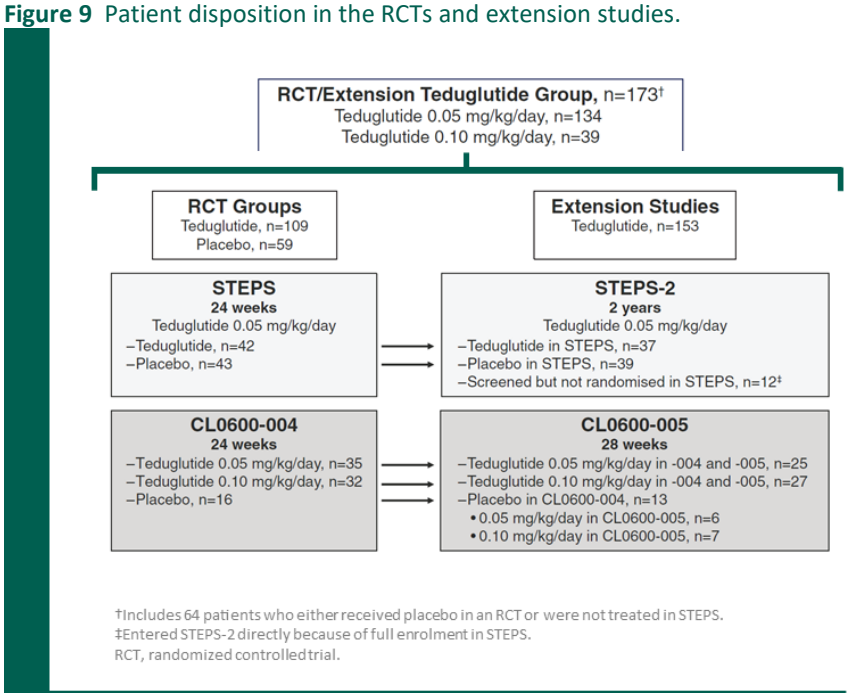
with intestinal failure associated with short bowel syndrome. *Clin Transl Gastroenterol* 2016; 7: e142. **(STEPS-2)**

Pooled safety data are reported for up to 2.5 years of exposure to teduglutide. Mean duration in weeks (SD) of exposure to teduglutide was 22.6 (6.62) for the RCT teduglutide group, 66.9 (42.11) for the RCT/extension teduglutide group and 23.1 (4.46) for the RCT placebo group.

AEs were coded using system, organ, class terms, and preferred terms from the Medical Dictionary for Regulatory Activities version 12.0. In some cases, preferred terms representing medically similar terms were combined into groupings of AEs, as indicated in the text and tables and figures. AEs were reported as mild, moderate or severe. Mild AEs were usually transient, requiring no special treatment and generally did not interfere with daily activities. Moderate AEs impaired usual activities and required simple therapeutic action. Severe AEs resulted in an interruption of usual activities and required vigorous therapeutic intervention.

Rates of central line-associated blood stream infections (CLABSI) were estimated by calculating the number of catheter-related sepsis and catheter-related bacteremia events (preferred terms) per 1000 catheter-days during the study period. For determination of CLABSI rates, it was assumed that patients had central lines throughout the study period and that other catheter-related Treatment Emergent Adverse Event (TEAE) categories were not blood stream infections.

Figure 9 Patient disposition in the RCTs and extension studies.



Data were summarized using descriptive statistics and are reported as mean (SD) unless indicated otherwise. TEAEs were reported by frequency without correction for duration of exposure to study drug. Patients in the RCT teduglutide and RCT placebo groups were treated with teduglutide or placebo for equivalent periods of time, facilitating direct comparisons of safety outcomes; the RCT/extension teduglutide group was included in the analysis to permit assessment of the cumulative spectrum and frequency of TEAEs over a longer exposure period.
Overview of TEAEs and TESAEs are available in Table 99, Table 100, Table 101 and Table 102 in **Appendix E**.

7.1.3.3.1 Overall conclusion of adult safety data

Integrated safety data for 222 person-years of exposure to teduglutide in four clinical trials demonstrated that teduglutide has a safety profile in adult patients with SBS–IF consistent with prior studies. The overall occurrence of TEAEs was comparable between the RCT teduglutide group and the RCT placebo group (90.8% and 83.1% of patients reporting TEAEs, respectively). Several of the most common TEAEs with teduglutide were gastrointestinal events that were consistent with the underlying disease state and its management.
All AEs of polyps were mild in severity.

The percentage of patients reporting TESAEs was comparable between the RCT teduglutide group and the RCT placebo group (35.8% versus 28.8%, respectively). The percentage of patients reporting TESAEs in the RCT/extension teduglutide group was higher (58.4%; Table 2); however, the person-years of exposure in this group was approximately 5 times greater owing to the longer treatment time in the extension studies (221.86 person-years versus 46.42 person-years in the RCT teduglutide group and 26.10 person-years in the RCT placebo group).
Rates of CLABSI (preferred terms of catheter-related sepsis and catheter-related bacteremia) TEAEs with teduglutide were 0.68 to 1.18 events per 1000 catheter-days, which is within the ranges reported in the literature for standard of care.[55]

Data from the clinical controlled trials suggests, that teduglutide is well tolerated when compared to placebo and standard of care.

In the STEP study only 2/42 (5%) patients in the teduglutide group vs. 3/43 (7%) in the placebo group experienced TEAEs leading to discontinuation within the 24 weeks of treatment.

In the 004 study subjects with any AE or SAE leading to study discontinuation, was 1 (6%), 2 (6%) and 6 (17%) for placebo (N=16), teduglutide 0.01 mg/kg (N=32) and teduglutide 0.05 mg/kg (N=35), respectively. The small sample size of the subgroups in the 004 study, limits the ability to draw firm conclusions from subgroup comparisons in terms of AEs leading to study discontinuation.

[redacted]

Long-term PS is associated with increased risk of liver damage, and advanced liver disease has been reported in 0%–50% of patients receiving chronic PS; the greatest risk is in patients with ultrashort bowel (<50 cm). During the preceding STEPS-2 study, serum concentrations of liver enzymes either declined or remained stable during 2.0–2.5 years of TED treatment in the study group as a whole. The improvement in liver biochemical values seen in STEPS-2 continued in the STEPS-3 study, with mean decreases from baseline in ALP, ALT, AST, GGT, and bilirubin levels observed at the end of treatment. Together, the results of the extension studies support previous findings indicating that in patients receiving teduglutide, chronic PS can be reduced with corresponding improvements in liver function.

Because of the intestinotrophic mechanism of action of teduglutide and reports of an increased incidence of dysplastic changes and neoplasms in rodent models exposed to exogenous GLP-2,[56] events of intestinal polyp growth and neoplasia during teduglutide treatment are of special interest. In the pooled safety analysis of adults treated with teduglutide for up to 3.5 years, polyps were reported in 9 of 50 patients with colon in continuity who underwent postexposure colonoscopy. Seven of these polyps had histology available; none were malignant or showed high-grade dysplasia.[57]

Strengths of this integrated analysis of phase III trials include the large, pooled sample of patients treated with teduglutide for up to 2.5 years in a clinical trial program with quality data for a rare disease state. A major study limitation was the relatively high patient study discontinuation rate due to TEAEs. Patient withdrawal subsequent to TEAEs may have confounded outcomes, particularly with respect to the analysis of TEAEs by treatment duration. Conversely, however, this study was also limited by a potential for reporting bias, particularly for mild events, because patients receiving teduglutide may be more closely monitored during the open-label extension trials.

7.1.3.4 Long-term efficacy in pediatric patients

Long term efficacy data is available from an interim analysis in which most pediatric patients had completed ≥6 months (data cut-off: Feb 4 2018), for patients who completed the phase three 24-week study NCT02682381) and enrolled in its corresponding prospective, long-term open-label extension study (NCT02954458). Data has been presented as conference abstract only.[58]

Data trends from the open-label extension study indicate that teduglutide treatment further reduced PS dependence and increased EN intake in children with SBS whose intestinal rehabilitation had plateaued, see Table 11 below. From the beginning of the core study, 7/44 teduglutide treated patients (15.9%) achieved enteral autonomy after 48 weeks of cumulative teduglutide treatment (C1W24).

Table 11 Percent Reduction in PS During Cycle 1 in patients who received Revestive (teduglutide) in the initial study and the extension study.

	PS Volume*	n
Baseline, mL/kg/day	61.3 ± 27.56	39
Change from baseline, %		
C1D1	-33.7±33.27	33
C1W1	-34.0±33.44	38
C1W2	-35.0±34.51	37
C1W4	-34.7±33.91	35
C1W6	-35.7±33.00	36
C1W9	-37.0±33.09	36
C1W12	-39.1±32.22	34
C1W16	-35.4±34.33	34
C1W20	-42.2±36.81	30
C1W24	-40.0±36.91	25

C1D1=cycle 1 day 1; C1W1-24=cycle 1 WEEK 1-24; PS=parenteral support.
*Data are mean ± SD.

7.1.3.5 Safety in pediatric patients

In the 12-week study by Carter et al., the proportion of subjects experiencing an adverse or serious adverse event in the teduglutid group vs. The standard of care group was somewhat similar, 100% vs. 100% and 53.3% vs. 60%, respectively. There was no difference with regards to AE or SAEs leading to study discontinuation. For a complete overview of AEs please see Table 97.

In the 24-week double blind study by Kocoshis et al., the proportion of subjects who experienced an adverse in the teduglutid group were on par with the standard of care group, 98% vs. 100% respectively. For the proportion of subjects who experienced a serious adverse event the number of events were much higher in the teduglutide group compared to the placebo group, 76.9% vs. 44.4% respectively. However, the proportion of subjects with any AE or SAE leading to study discontinuation were similar between the teduglutide and placebo group, both 0%. For a complete overview of AEs please see Table 98.

The safety analysis for pediatrics is based on the pooled safety data from four prospective clinical trials of teduglutide in children with SBS-IF:[59] 2 completed Phase 3 clinical trials core studies described in detail in appendix B and appendix D (12-week study: NCT01952080; 24-week study: NCT02682381) and 2 ongoing studies NCT02949362 and NCT02954458 which are the open-label extension studies of the 12- and 24-week trials, respectively. Together, this provides a combined safety data set based on a median of 52 weeks of teduglutide treatment and 83 weeks of prospective follow-up.

AEs were pooled and summarized using descriptive statistics. AEs that occurred during no-teduglutide treatment periods between treatment cycles in the extension studies were included in the analysis.
Overview of AEs and SAEs is available in Table 103, Table 104 and Table 105 in appendix E.

This analysis included 89 patients who were treated with teduglutide at some point in the pediatric SBS–IF clinical study program Figure 10.

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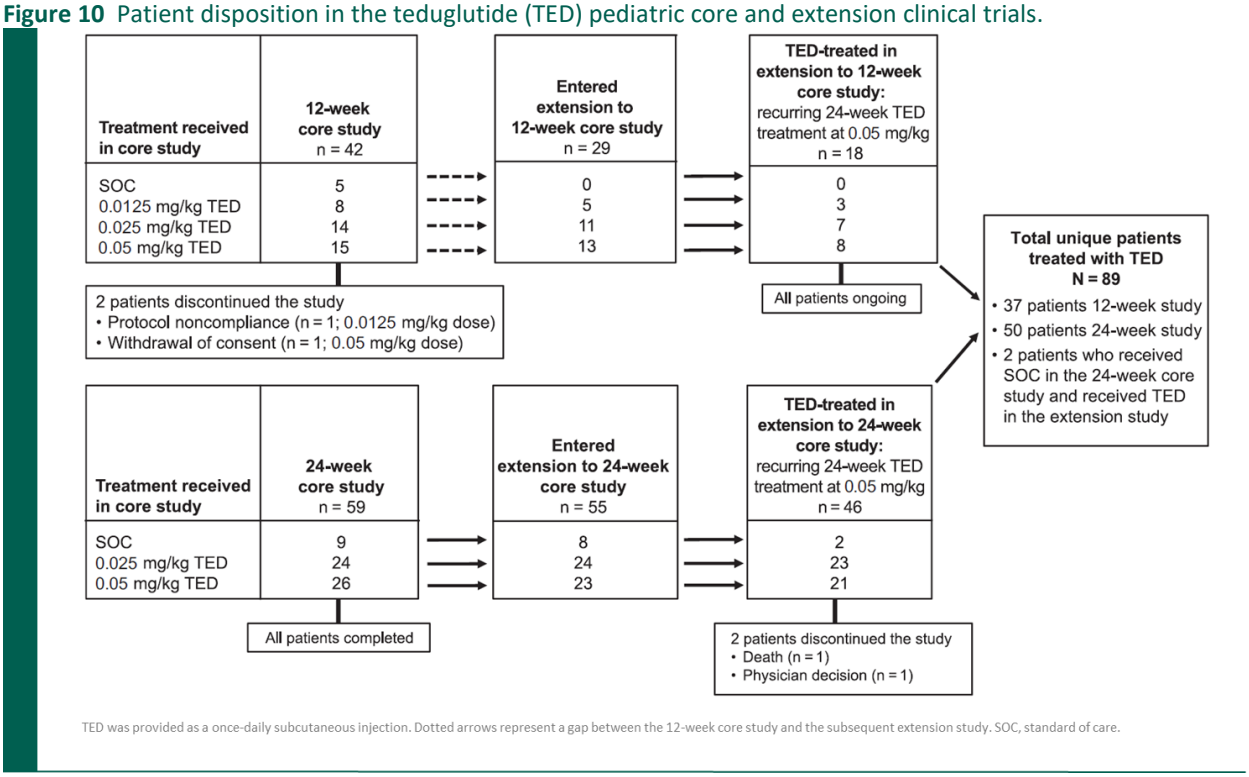
Figure 10 Patient disposition in the teduglutide (TED) pediatric core and extension clinical trials.

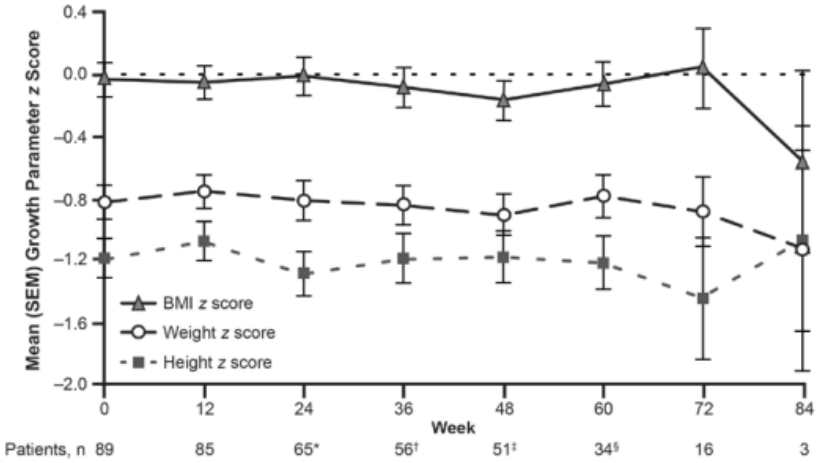


7.1.3.6 Overall conclusion on pediatric long-term safety and efficacy

In this pooled safety data set of combined 133 weeks of teduglutide treatment no new safety risks were identified. The spectrum of gastrointestinal AEs in teduglutide-treated patients was generally comparable to that occurring in patients in the SOC arms of the phase 3 pediatric studies. The spectrum of AEs was also similar to that reported in the integrated analysis of safety data from the adult clinical studies of teduglutide described above.

As expected for this patient population, catheter-related infection was the second most frequent SAE in this analysis. Therapies that enhance intestinal adaptation and reduce PS dependence would be expected to reduce the risk of complications in these patients, particularly if they lead to earlier enteral autonomy and permit removal of the central venous catheter.[60] The sample size and duration of observation in this data set is insufficient to determine whether long-term treatment with teduglutide reduces the rate of catheter-related infections in children with SBS–IF. Weight, height, and body mass index z-scores did not change substantially during long-term treatment with teduglutide (see **Appendix E**, Figure 11).

Figure 11 Growth parameters over time in pedatrics during Long-Term Treatment With Teduglutide for Short-Bowel Syndrome–Associated Intestinal Failure: Pooled Analysis of 4 Clinical Studies[59]



*n=66 for weight *z* score; †n=57 for weight *z* score; ‡n=55 for weight *z* score; §n=36 for weight *z* score.
BMI, body mass index.

Elevations in aminotransferases were observed in some pediatric patients. These rates are similar to those reported in a recent cohort of 148 children with SBS–IF who were not treated with teduglutide, of whom 19% had abnormal liver function tests.[61]

Because of the intestinotrophic mechanism of action of teduglutide and reports of an increased incidence of dysplastic changes and neoplasms in rodent models exposed to exogenous GLP-2, events of intestinal polyp growth and neoplasia during teduglutide treatment are of special interest. In the pooled clinical studies of pediatric patients, only 1 polyp, a cecal polyp, was detected, which was not biopsied or confirmed on repeat colonoscopy.

This analysis of the 4 clinical studies was limited by the long-term, open-label treatment period that lacks control group comparisons. In addition to the overall small sample size, a subset of the analysis population (n= 18) had a treatment gap of up to 3.3 years that occurred between the initial 12-week core study and enrollment in the extension to that study.
Data trends from the open-label extension study indicate that teduglutide treatment further reduced PS dependence and increased EN intake in children with SBS whose intestinal rehabilitation had plateaued.

7.1.4 Real World Evidence for teduglutide

Published non-interventional real-world evidence studies were identified by a systematic literature search (**Appendix P**). Only efficacy and safety data from studies that have been published as full manuscripts (rather than presented as abstracts/posters at conferences only, as more and higher quality data are available in the manuscripts) will be used to demonstrate the real-world effectiveness and safety of teduglutide.

The real-world evidence literature review identified 28 non-interventional studies of teduglutide (see **Appendix P** for a list of all included and excluded studies); of which eight of them are published as full papers. All eight studies investigated teduglutide 0.05 mg/kg/day in adults with SBS-IF.

Data from these eight studies are highly relevant to the decision problem because they provide data on the real-world effectiveness of teduglutide, and therefore are representative of the outcomes that could be expected if teduglutide

became available for danish patients. The data also illustrate the effectiveness of teduglutide outside of the artificial constraints of a clinical trial environment, and notably in an environment where restrictive PS weaning algorithms are not used. The real-world data thus addresses some critical limitations in the RCTs as described in greater detail previously.

Data from these eight studies will be presented alongside data from patients treated with teduglutide in STEPS and STEPS-2. This allows a descriptive comparison of teduglutide's effectiveness in environments where PS weaning algorithms are used (STEPS/STEPS-2) and not used (the real-world). [redacted]

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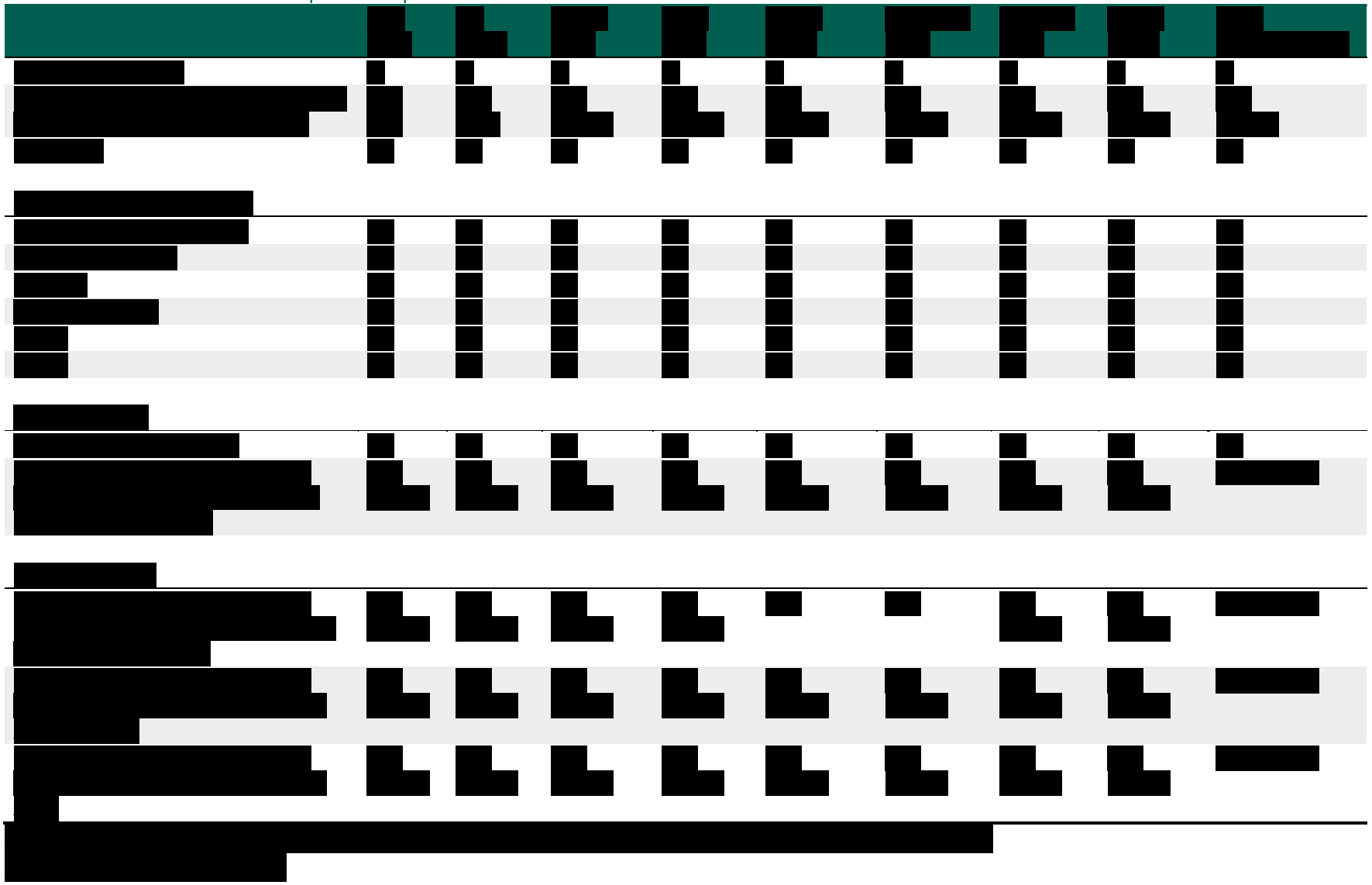
Table 12 Baseline characteristics of patients in published real-world studies and STEPS



7.1.4.1 Limitations of the full-paper RWE studies

The 8 full-paper publications reporting on non-randomized trials and observational studies were quality-assessed using the Downs and Black checklist[62] (see Table 13 below), consistent with current NICE guidance.[63]

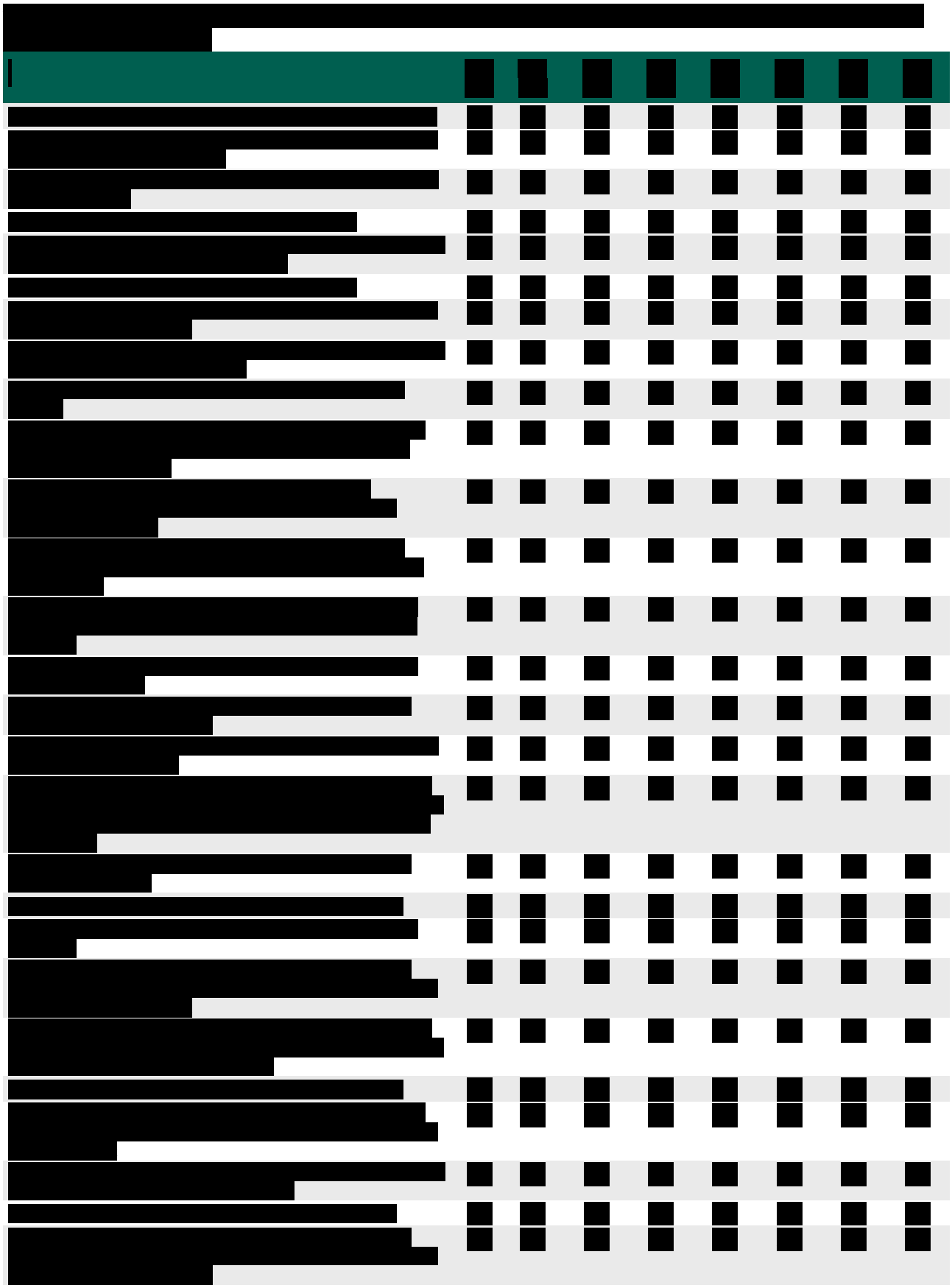
Overall, the included studies were relatively clearly reported but methodologically limited; as with most RWE, the majority of studies were retrospective in nature, and none involved blinding of study participants or investigators.

For the purpose of this descriptive comparison to STEPS and STEPS-2, the following two outcomes below from the eight real-world studies will be presented because these were the most consistently reported across the eight studies and in the clinical trial programme of teduglutide:

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

[redacted]

[redacted]



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7.1.5 Registry data for teduglutide - data cutoff June 30, 2020

Efficacy data from the SBS-IF interim registry analysis (NCT01990040) encompassing 328 ever-treated teduglutide patients and 675 never-treated patients indicate that teduglutide has the potential to provide long-term reductions in PS requirements in patients with SBS-IF in a real-world setting after up to 4 years of treatment, see Figure 18, Figure 19, Figure 20, Figure 21 and Table 14 below. Patient demographics and baseline characteristics were generally comparable between the ever-treated teduglutide patients and never-treated patients, see **Appendix C**.

[redacted]

Other potential limitations of the study are:

- Participation in the study is voluntary for patients. Difficulty in recruiting patients may occur with consequently smaller sample sizes, reduced statistical power, and limited generalizability of results. This limitation, however, is addressed by making the study open to all patients with SBS who have been on PS for at least 6 months and not limiting patient recruitment to centers that participated in teduglutide clinical trials.
- Following patients over 10 years may be difficult with subsequent loss to follow-up of patients. This loss to follow-up can reduce the statistical power of the study and result in a selection bias in long-term follow-up data. The latter can limit the generalizability of study findings. In the statistical analysis all PY of follow-up a patient contributes, until they are lost to follow-up.
- In general, missing data was not imputed. Data were analyzed as they were recorded.

Like all observational studies, unmeasured patient and clinical variables related to both teduglutide use and study outcomes may confound the study results. Examples of this are factors leading to confounding by indication. This study depends on patient information in the investigators' medical records; the medical records are assumed to be a valid source of data of the information and all primary and secondary safety outcomes including the following efficacy outcomes; *Actual volume change in parenteral support, Percentage volume change in parenteral support, Actual*

change in the number of days per week on parenteral support, Percentage change in the number of days per week on parenteral support, Percent of patients weaning from parental support, will undergo validation. To the extent that the medical record validity assumption is true will dictate the degree of potential information bias in the study; the direction and degree of this information bias is not known.

[redacted]

All-cause mortality appeared to be lower in the ever-treated group than in the never-treated group (27/467 vs 60/675; IR, 25.5 vs 42.7 per 1000 PY; hazard ratio, 0.89 [95% CI: 0.78, 1.00]).

As of the data cutoff (data cutoff June 30, 2020) there were no occurrences of new colorectal cancer during the study period. During follow-up, the incidence rates of new or worsening diagnosis of other malignancies of any type were similar in the ever-treated and never-treated groups (17.9 vs 19.2 per 1000 patient-years).

Colorectal polyps were observed with teduglutide treatment in the clinical trials in adults with SBS and post hoc analysis of the pivotal placebo-controlled phase 3 study (STEPS) and its open-label extensions (STEPS-2 and STEPS-3) reported that 18% of patients (9/50) had colorectal polyps after 24–36 months of teduglutide treatment compared with 12% of patients (9/73) at baseline (i.e. pre-treatment). As a point of reference for comparison, a population-based US registry analysis of over 6100 screening colonoscopies in individuals 50 years of age or older reported rates for adenomas and serrated polyps of 25% and 8%, respectively.[66]

The SBS-IF registry analysis also showed that more ever-treated patients had benign neoplasia of the gastrointestinal tract (other than colorectal polyps) than never-treated patients, although few patients in either group had benign neoplasia of the hepatobiliary system or the pancreas. A new or worsening diagnosis of benign neoplasia of the gastrointestinal tract (other than colorectal polyps) was reported for 12 ever-treated and 3 never-treated patients (IR, 19.8 vs 2.8 per 1000 PY.

No unexpected safety signals were observed during follow-up. Overall, 79.0% of ever-treated teduglutide and 64.9% of never-treated teduglutide patients had ≥1 adverse event (AE) and 55.7% and 45.9%, respectively, had ≥1 serious AE (SAE). Among ever-treated patients, 27.6% and 9.0% had a teduglutide-related AE and SAE, respectively, and 19.9% had an AE leading to treatment interruption or discontinuation. All-cause mortality rate appeared to be lower in the ever-treated group than in the never-treated group (27/467 vs 60/675; IR, 25.5 vs 42.7 per 1000 PY; hazard ratio [95% CI] 0.89 [0.78, 1.00]; p = 0.050).[67]

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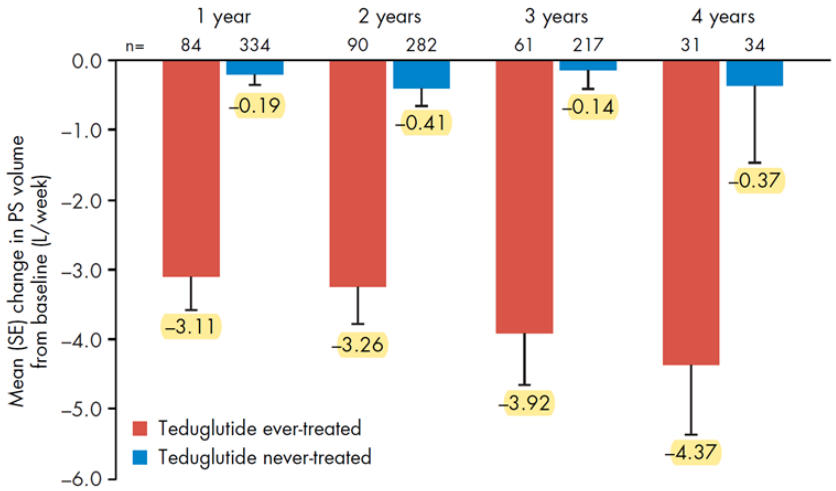
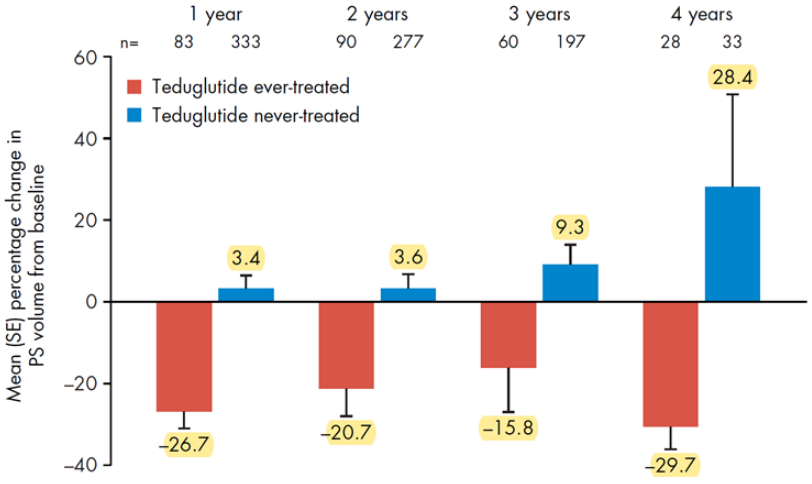
Figure 18 Mean Change in Absolute PS Volume from Baseline.



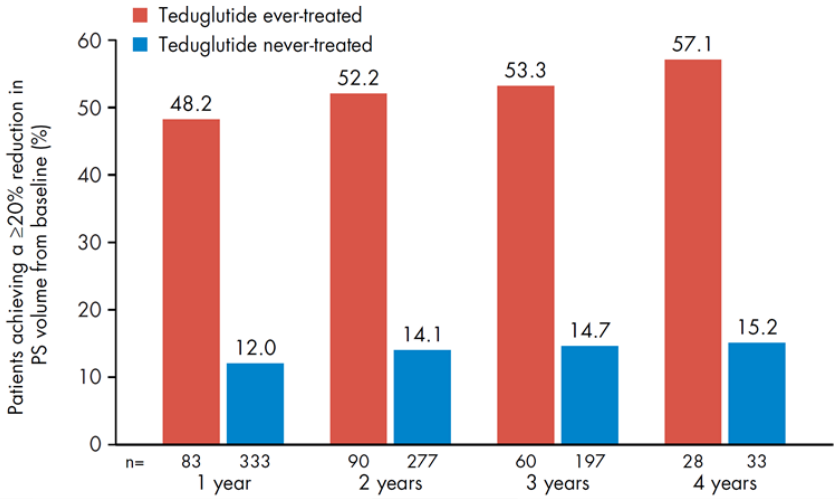
Data are presented for patients with a PS volume assessment at the given time point. Note that patients with a missing assessment at a given time point (e.g. year 1) are included at other time points (e.g. year 2) at which they have a valid assessment. Baseline is PS use at registry enrollment for never-treated patients, immediately prior to treatment initiation for patients starting teduglutide after enrollment, or within 3 months prior to starting teduglutide for patients receiving teduglutide at enrollment. PS, parenteral support; SE, standard error.

Figure 19 Mean Percentage Change in PS Volume from Baseline.



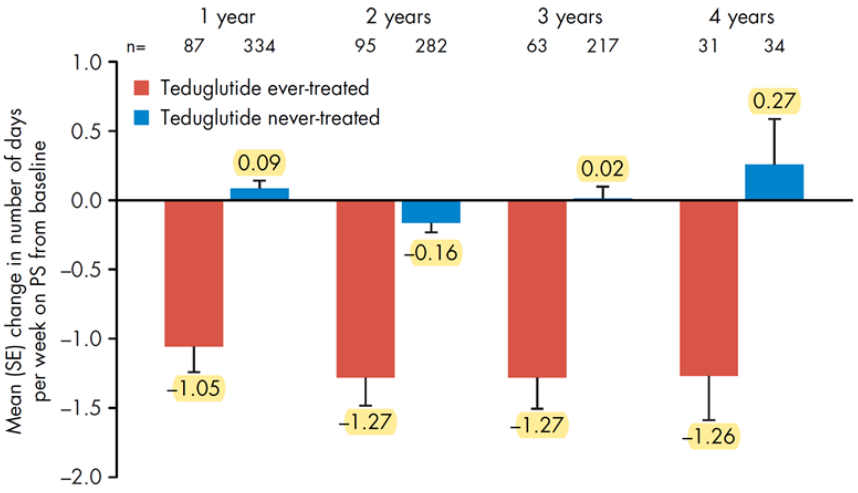
Data are presented for patients with a PS volume assessment at the given time point. Note that patients with a missing assessment at a given time point (e.g. year 1) are included at other time points (e.g. year 2) at which they have a valid assessment. Baseline is PS use at registry enrollment for never-treated patients, immediately prior to treatment initiation for patients starting teduglutide after enrollment, or within 3 months prior to starting teduglutide for patients receiving teduglutide at enrollment. PS, parenteral support; SE, standard error.

Figure 20 Proportion of Patients Achieving a Reduction of at Least 20% in PS Volume from Baseline.



Data are presented for patients with a PS volume assessment at the given time point. Note that patients with a missing assessment at a given time point (e.g. year 1) are included at other time points (e.g. year 2) at which they have a valid assessment. Baseline is PS use at registry enrollment for never-treated patients, immediately prior to treatment initiation for patients starting teduglutide after enrollment, or within 3 months prior to starting teduglutide for patients receiving teduglutide at enrollment. PS, parenteral support.

Figure 21 Mean Change in Frequency of PS from Baseline.



Data are presented for patients with a PS volume assessment at the given time point. Note that patients with a missing assessment at a given time point (e.g. year 1) are included at other time points (e.g. year 2) at which they have a valid assessment. Baseline is PS use at registry enrollment for never-treated patients, immediately prior to treatment initiation for patients starting teduglutide after enrollment, or within 3 months prior to starting teduglutide for patients receiving teduglutide at enrollment. PS, parenteral support; SE, standard error.

[redacted]

[redacted]

Table 14 Proportion of Patients Achieving Reductions in PS Volume from Baseline.

	Teduglutide ever-treated (N=328)	Teduglutide never-treated (N=675)
1 year, n	83	333
<0% reduction[a]	8.4 (7)	17.4 (58)
0 to <20% reduction	43.4 (36)	70.6 (235)
≥20% reduction	**48.2 (40)**	**12.0 (40)**
≥20% to <40% reduction	10.8 (9)	6.0 (20)
≥40% to <60% reduction	21.7 (18)	2.1 (7)
≥60% to <80% reduction	6.0 (5)	1.5 (5)
≥80% to <100% reduction	2.4 (2)	0 (0)
100% reduction (wean off)	7.2 (6)	0 (0)
2 years, n	90	277
<0% reduction[a]	13.3 (12)	20.9 (58)
0 to <20% reduction	34.4 (31)	65.0 (180)
≥20% reduction	**52.2 (47)**	**14.1 (39)**
≥20% to <40% reduction	12.2 (11)	5.8 (16)
≥40% to <60% reduction	22.2 (20)	4.0 (11)
≥60% to <80% reduction	10.0 (9)	2.2 (6)
≥80% to <100% reduction	1.1 (1)	0 (0)
100% reduction (wean off)	6.7 (6)	0 (0)
3 years, n	60	197
<0% reduction[a]	15.0 (9)	25.9 (51)
0 to <20% reduction	31.7 (19)	59.4 (117)
≥20% reduction	53.3 (32)	14.7 (29)
≥20% to <40% reduction	11.7 (7)	6.1 (12)
≥40% to <60% reduction	21.7 (13)	4.1 (8)
≥60% to <80% reduction	13.3 (8)	3.0 (6)
≥80% to <100% reduction	3.3 (2)	0.5 (1)
100% reduction (wean off)	3.3 (2)	1.0 (2)
4 years, n	28	33
<0% reduction[a]	7.1 (2)	27.3 (9)
0 to <20% reduction	35.7 (10)	57.6 (19)
≥20% reduction	57.1 (16)	15.2 (5)
≥20% to <40% reduction	10.7 (3)	9.1 (3)
≥40% to <60% reduction	32.1 (9)	0 (0)
≥60% to <80% reduction	3.6 (1)	3.0 (1)
≥80% to <100% reduction	10.7 (3)	0 (0)
100% reduction (wean off)	0 (0)	3.0 (1)

[ai.e]. PS volume increase. Source: NCT01990040; EUPAS7973[67]

Data are presented for patients with a PS volume assessment at the given time point. Note that patients with a missing assessment at a given time point (e.g., year 1) are included at other time points (e.g., year 2) at which they have a valid assessment. Baseline is PS use at registry enrollment for never-treated patients, immediately prior to treatment initiation for patients starting teduglutide after enrollment, or within 3 months prior to starting teduglutide for patients receiving teduglutide at enrollment. PS, parenteral support.

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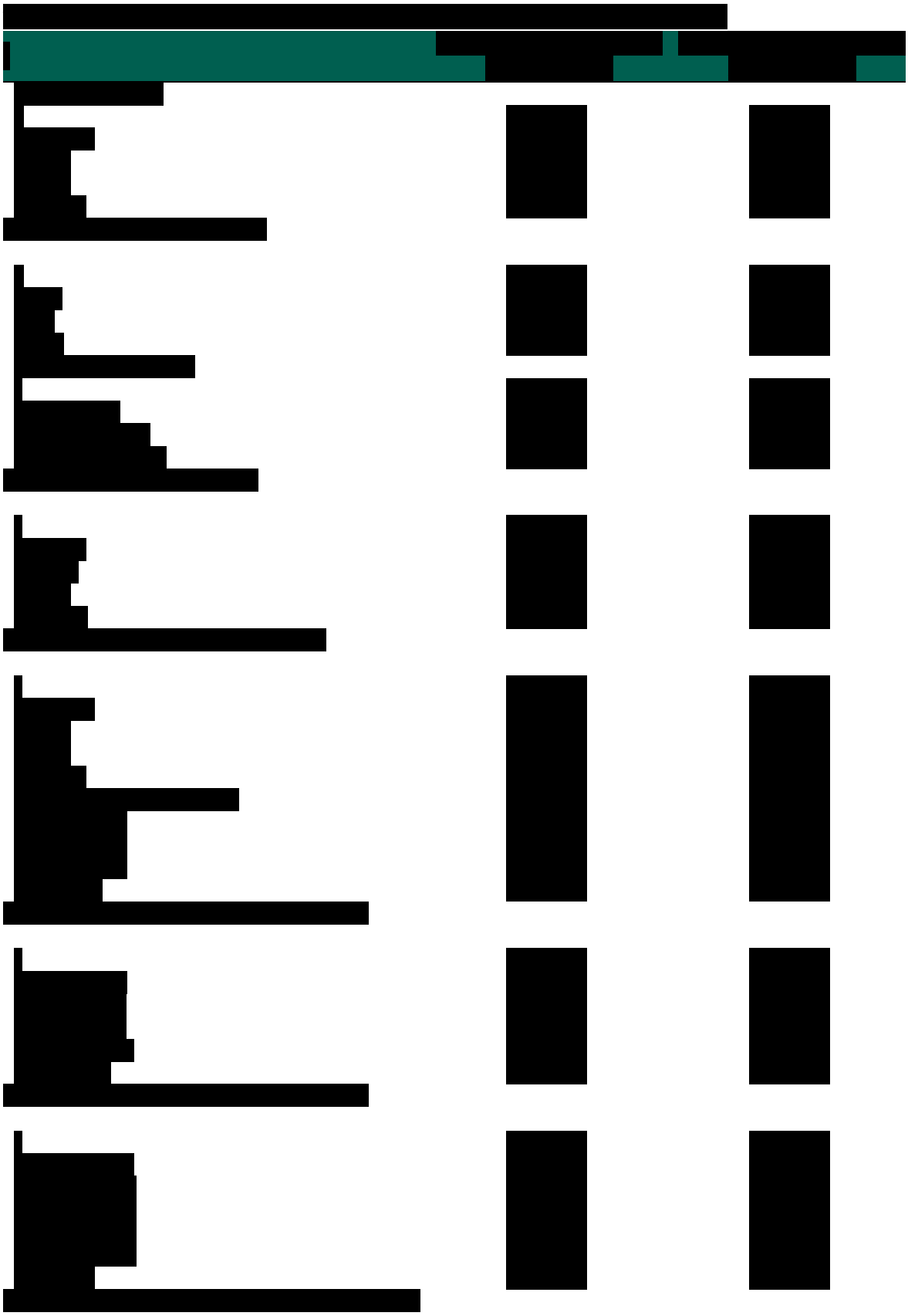

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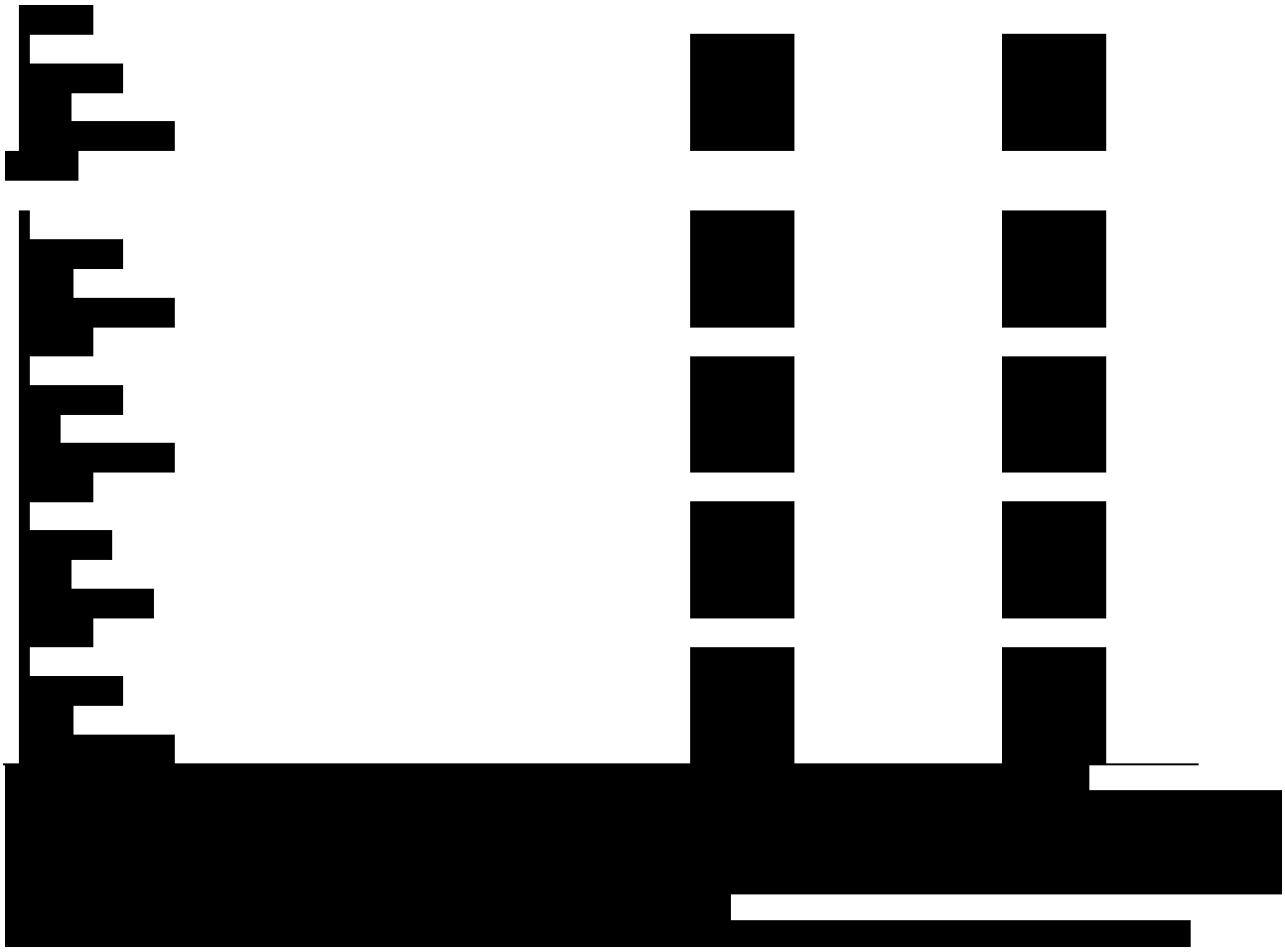

Other Key Results

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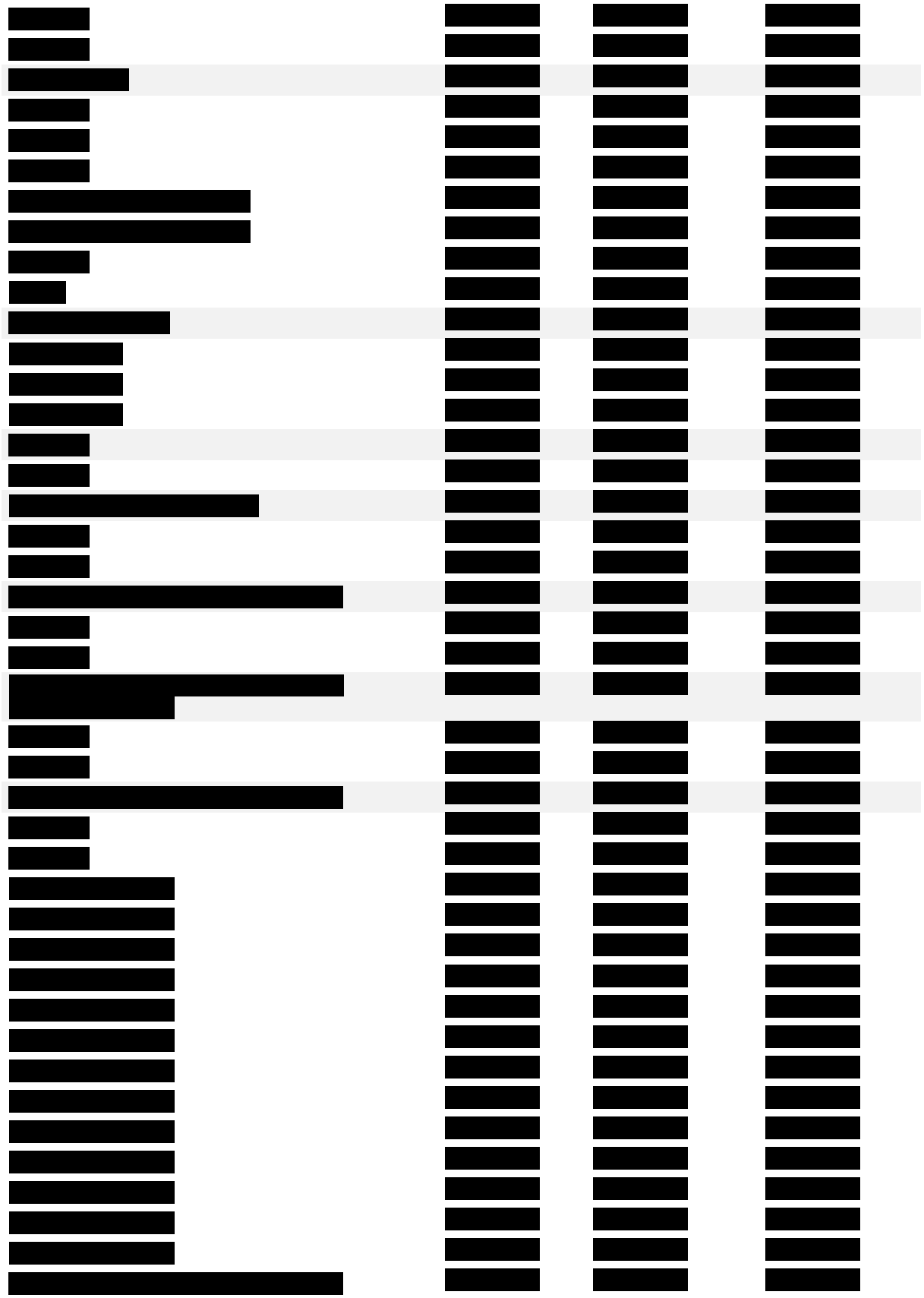

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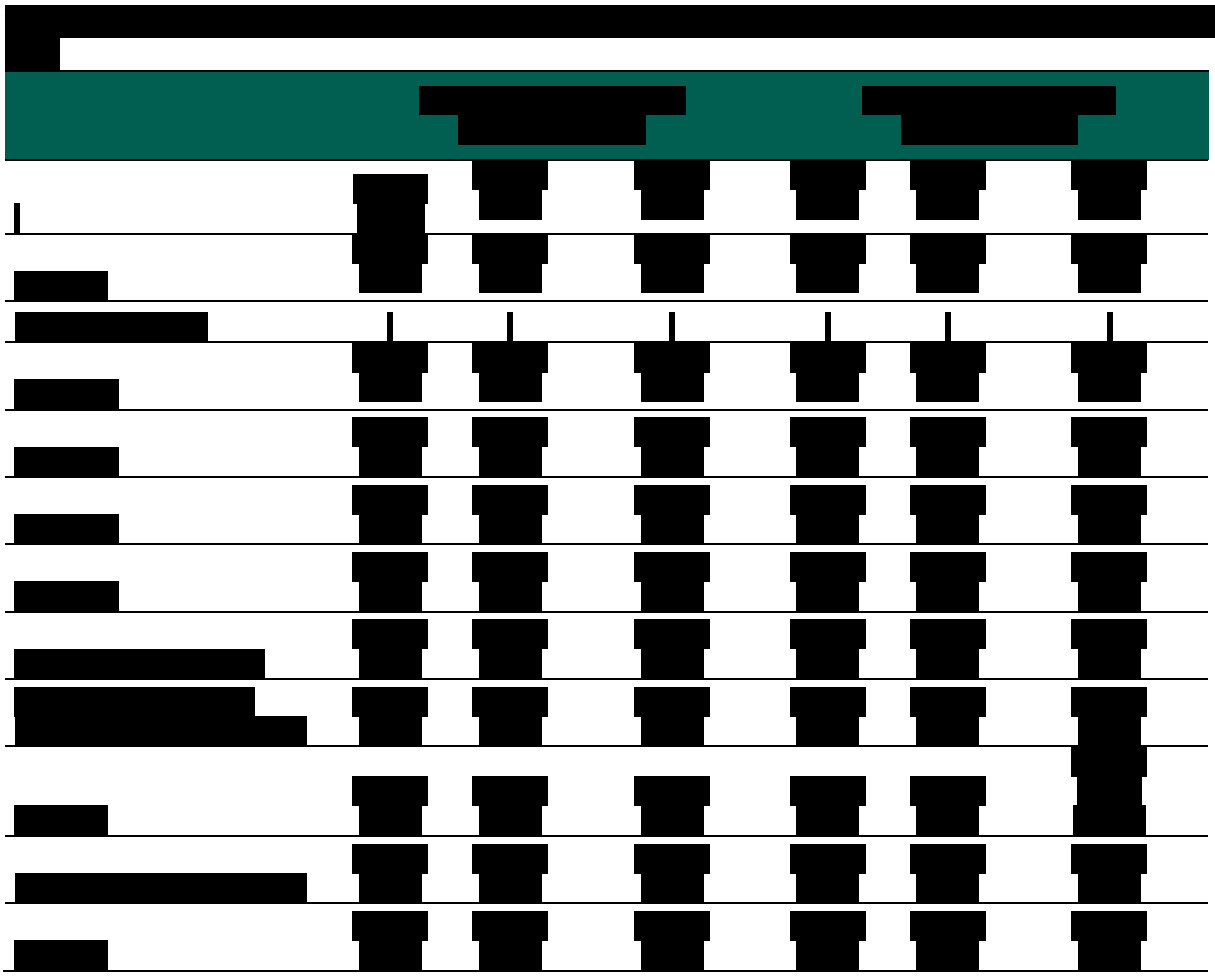

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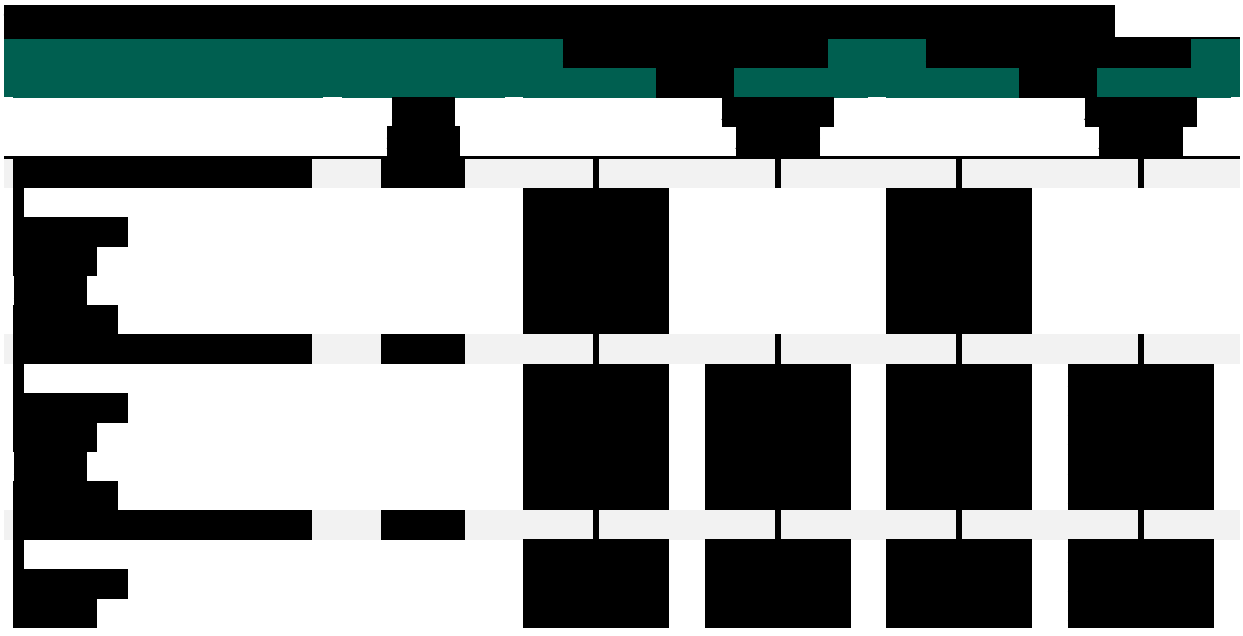

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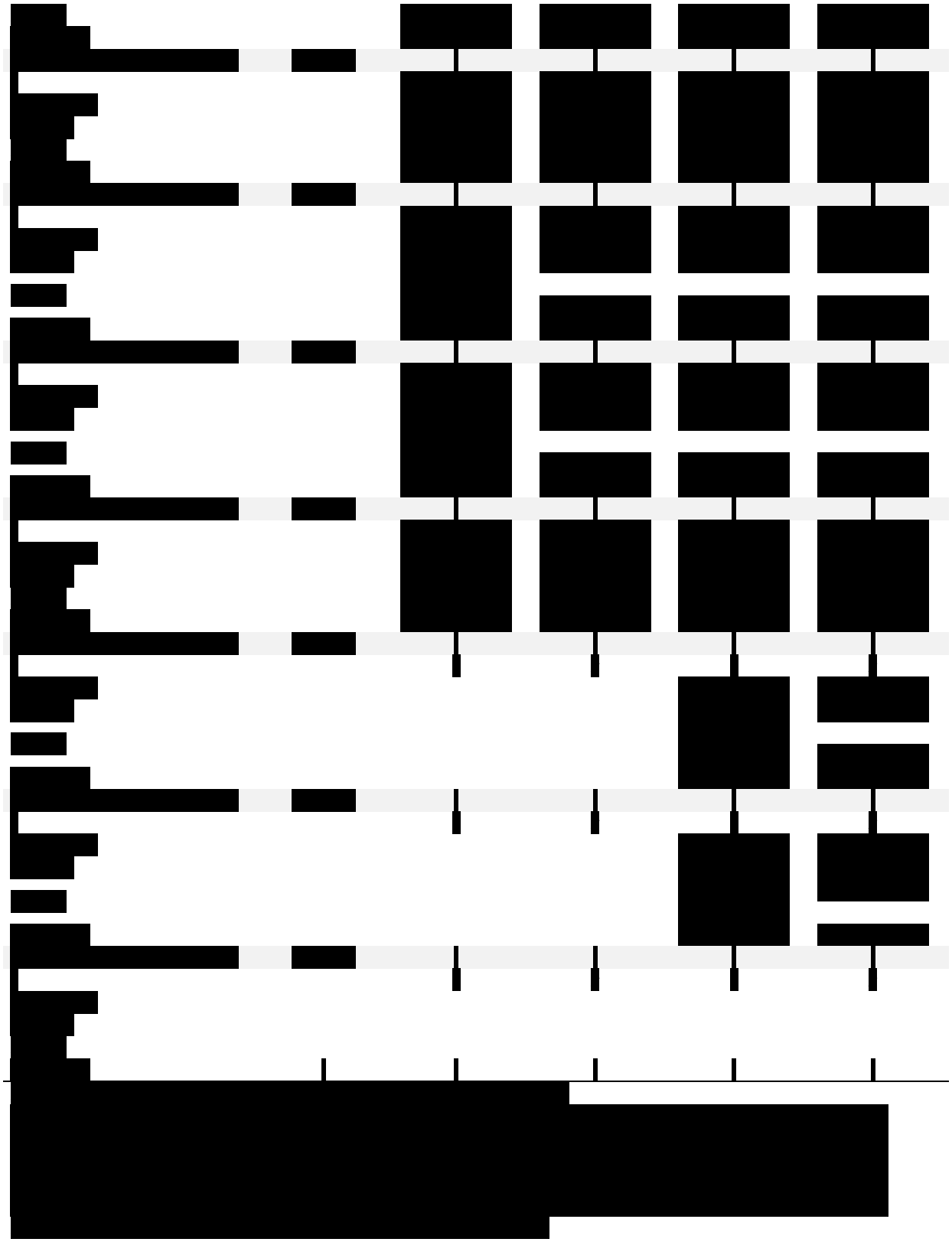

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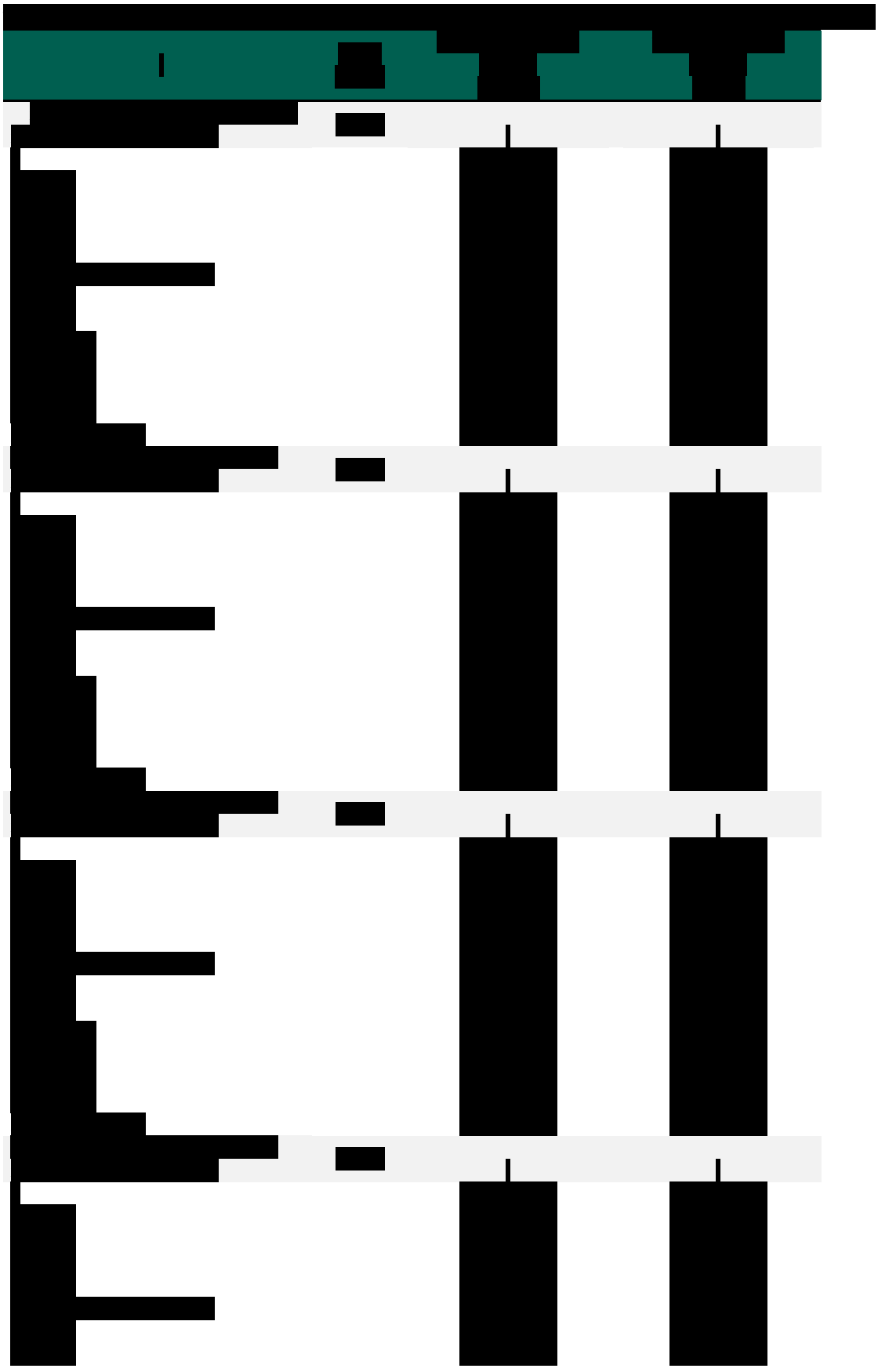

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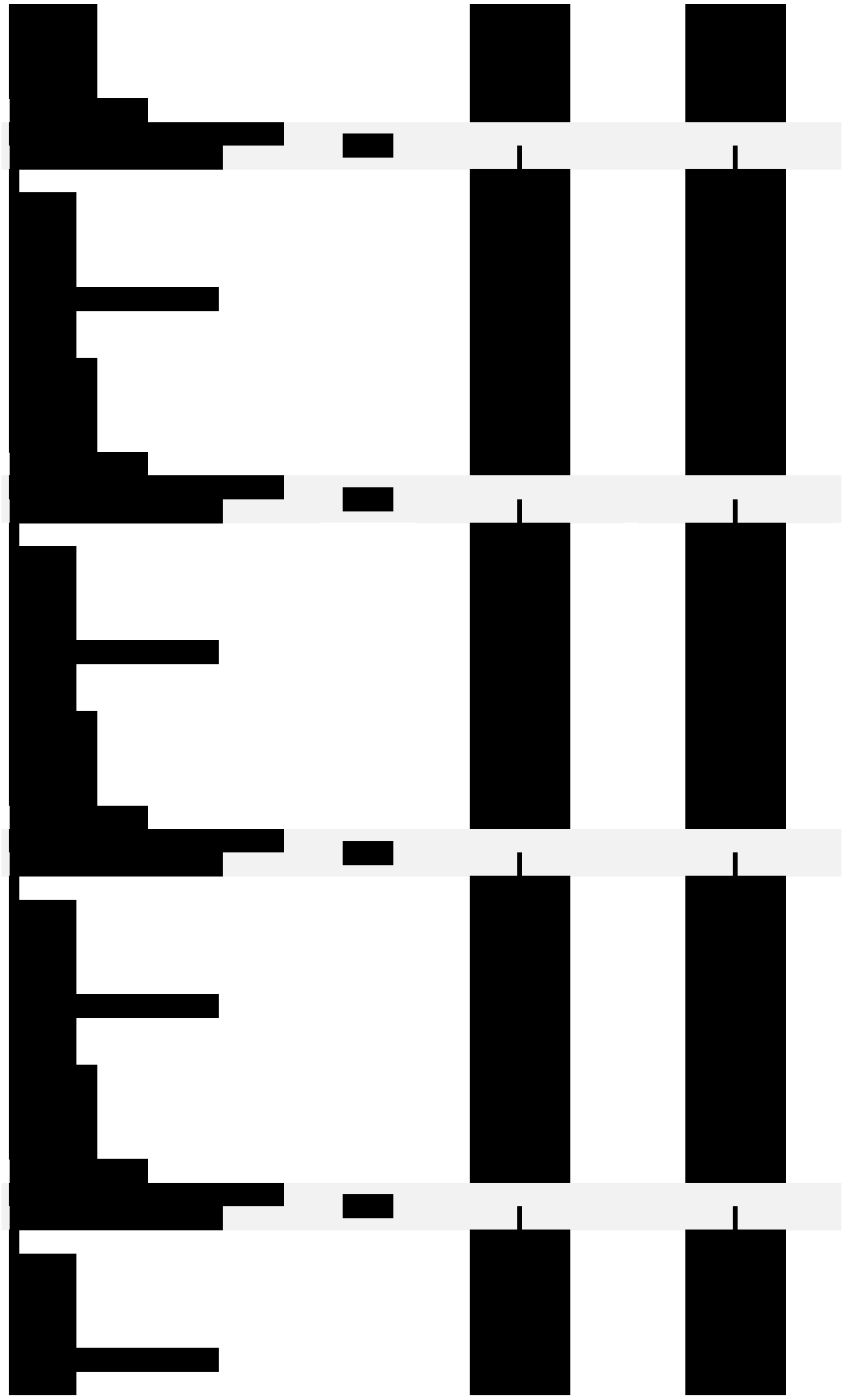

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7.1.7 Rationale for not conducting a meta-analysis in adults

Two randomized, placebo-controlled 24 weeks phase 3 studies have investigated the efficacy and safety of teduglutide in adults with SBS-IF, NCT00081458 (004) and NCT00798967 (STEPS). After careful reviewing study design, it was decided not to conduct a meta-analysis on the two studies due to clinically relevant differences in the protocol pertaining the PN weaning algorithm as the second study by Jeppesen at al. used a different protocol allowing for earlier (i.e., at second week of dosing) and more aggressive PS reductions (i.e. 10% to 30% of baseline levels of PN/IV fluid). This is addressed in detail in section **7.1.1**. Data for the two studies are summarized in **Appendix D**.

7.1.8 Rationale for not conducting a meta-analysis in pediatrics

Two relevant clinical trials have investigated the efficacy and safety of teduglutide in pediatrics with SBS-IF (NCT0001952080 (TED-003) and NCT02682381 (TED-006). Meta-analysis of the two studies is deemed inappropriate/not feasible due to the following reasons; huge discrepancies in study length (12 vs. 24 weeks), data analysis for the primary endpoint in the 24 weeks study (TED-006, the number of patients who achieved a ≥20% reduction in parenteral support (PS) from baseline at week 24, has neither been published nor conducted for week 12 and finally, according to the EMA approved SmPC for Revestive® (teduglutide) a treatment period of 6 months is recommended before treatment effect should be evaluated. Finally, the 12-week study did not use randomization. Data for the two studies are summarized in **Appendix D**.

8. Health economic analysis

8.1 Model

The cost-effectiveness model was developed using a Markov cohort methodology, using mutually exclusive Markovian health states to capture the benefits associated with reduced PS-dependency, including costs and health-related quality of life (HRQoL). The model consists of nine unique, core health states, including death, that patients can transition between over time, alongside two concurrent, separately modeled complications. A health state represents patients at a similar course of their disease who incur the same costs and have the same quality of life. These health states are detailed below in Table 21 and are presented in Figure 22. At each 28-day model cycle, patients can either remain in their current PS state, transition to any other PS state, or die.

Table 21 Health states used in the cost-effectiveness model

Health state	Description
PS0	No PS is required (enteral autonomy)
PS1	PS is required 1 day per week
PS2	PS is required 2 day per week
PS3	PS is required 3 day per week
PS4	PS is required 4 day per week
PS5	PS is required 5 day per week
PS6	PS is required 6 day per week
PS7	PS is required 7 day per week
Death	Dead
IFALD	Intestinal Failure Associated Liver Disease
CKD	Chronic Kidney Disease

Key: PS, parenteral support

Complications

Two concurrent complications, Intestinal failure-associated liver disease (IFALD) and stage V Chronic Kidney Disease (CKD), are modelled separately alongside the eight PS-related health states and the death state. The probabilities of developing these complications depend on the level of PS dependency, divided into: No PS (PS0), Low PS (PS1-PS3), Mid PS (PS4-PS5) and High PS (PS6-PS7).

Liver complications

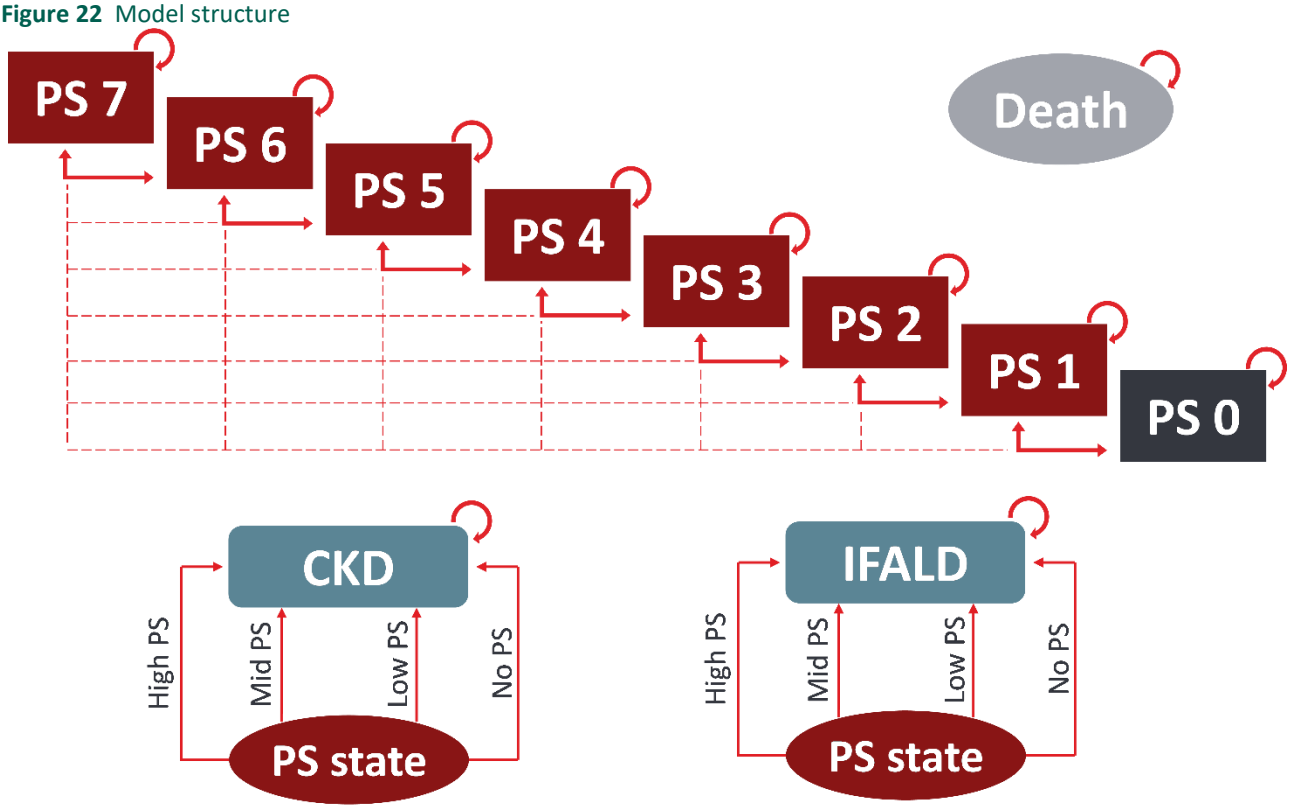
IFALD is simulated separately from PS states using a sub-model which estimates rates of IFALD in parallel to the estimation of PS state populations. Patients can transition between the PS health states irrespective of IFALD status. IFALD is included in the base scenario but can be disabled in the 'Controls' sheet of the Excel model.
As no clinical data were available from Denmark, all information on IFALD development rates among teduglutide eligible patients was derived using Delphi processes including UK clinical experts (**Appendix K**). IFALD is not assumed to affect overall survival.

Chronic Kidney Disease (CKD)

CKD can be activated in the model because it is a known consequence of PS. However, CKD is not included in the base case, based on input from clinical experts in Denmark[9] and the UK (Delphi Panel, described in **Appendix K**) on the rarity of CKD due to improvements in PS. The sub-model can be activated in the 'Controls' sheet of the Excel model. Similar to IFALD, CKD is modelled separately, and a patient can develop CKD from any PS health state, and patients with CKD continue to transition between PS health states. As no clinical data were available from Denmark, CKD

development rates are derived from a Delphi process using UK clinical experts (**Appendix K**). CKD is not assumed to affect overall survival.

Figure 22 Model structure



Key: CKD, Chronic Kidney Disease; IFALD, Intestinal failure-related liver disease; PS, parenteral support. **Notes**: The 'Death' health state is an absorbing state and can be entered from any state. No PS, PS0; Low PS, PS1-PS3; Mid PS, PS4-PS5; High PS, PS6-PS7.

Adult and pediatric indications

The analyses performed using the economic model aim to assess the cost-effectiveness of teduglutide in the licensed population, as outlined in **5.1.1**; patients aged 1 year and above with SBS-IF who are stable following a period of intestinal adaptation after surgery.

Two separate base case analyses are presented to demonstrate the cost-effectiveness of teduglutide in the adult (aged ≥18 years) and pediatric (aged 1–17 years) populations, respectively. This approach is appropriate as SBS-IF is a disease with different aetiologies in children and adults, and the potential for intestinal adaptation is greater in children **(7.1.1)**. There is overlap in terms of the model inputs in the adult and pediatric base case analyses. Mainly, the primary data sources used to inform the effectiveness of teduglutide are the same in both, as both analyses use the STEPS clinical trial program, which recruited adults with SBS-IF on PS ≥3 days per week (**7.1.1**). The two base cases analyses are different with respect to the following:

- Starting age: 50 years old in adults, 6 years old in children
- Time horizon: 40 years in adults, 94 years in children
- Pediatric-specific survival: See **8.2.2.6**
- Pediatric-specific costs: See **8.5.6**

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

- Data from the pediatric clinical trials suggest that children can achieve greater reductions in PS when receiving teduglutide than adults (see **7.1.1**), likely because children have an increased potential for intestinal adaptation.
- Our model assumes that PS-related complications are less frequent when patients reduce PS (following teduglutide treatment), and therefore, that teduglutide generates cost savings from the reduced cost of treating complications. Of the complications modeled, catheter-related infections and liver disease are expected to be more common in children with SBS-IF than adults.[68,69] However, as there are little data quantifying the rates of these complications in children, our pediatric base case analysis conservatively assumes the same rates of complications in children as in adults, favoring standard of care.
- For children with a body weight of less than 20 kg, the smaller 1.25 mg vial of teduglutide will cover a daily dose at a lower cost compared to the 5 mg vial. However, the model assumes that all children weigh ≥20 kg, which leads to an underestimation of the true cost-effectiveness of teduglutide in a pediatric population where some patients weigh less than 20 kg.

Cycle length and time horizon

Time is reflected in the model in fixed monthly cycles, defined as 28 days in length. This cycle length was selected for consistency with the STEPS assessment schedule, where patient's PS requirements were recorded every 28 days, making it possible to estimate monthly time-varying transition probabilities between PS states based directly on STEPS trial evidence.[44] Assessments were made every three months in the STEPS-2 extension trial, which only allowed us to calculate transition probabilities between PS health states every three months after the first 24 weeks.[51]

Because the cycle length exceeds one week, a half-cycle correction was incorporated to adjust for issues with the timing of transitions relative to the accrual of costs and quality-adjusted life years (QALYs) in the model. Half cycle correction can be deactivated in the controls sheet of the model.

Patients receiving teduglutide have a reduced need for PS, which is associated with reductions in resource use and complications throughout the entire life of a patient. To capture potential lifetime treatment and effects of teduglutide, the time horizon of the model is a lifetime horizon. The average baseline age across the 0.05 mg/kg arms and placebo arms of the STEPS studies is 50 years. Therefore, in the base case analysis for adults, a 40-year horizon was selected to represent a lifetime horizon. The corresponding baseline mean age in the pediatric trial was 6 years, and a 94-year horizon is assumed to represent a lifetime horizon for children. The sum of the starting age and the time horizon for adults is 90 years, and 100 years for pediatrics. This choice was made to reflect an increased life expectancy for younger generations. Alternative time horizons can be selected in the 'Controls' sheet of the Excel model.

Treatment duration

Long term teduglutide treatment should only be considered for responders, for whom the treatment is potentially a lifetime treatment. To accommodate for this in the model, a series of stopping-rules can be imposed directly in the 'Controls' sheet of the Excel model. Model options for stopping rules are described in **8.2.2.2**.

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Discount Rates

Costs and health outcomes are discounted using the current annual socio-economic discount rates available at www.fm.dk. The applied discount rates are presented in Table 22.

Table 22 Applied annual discount rates

Period	Annual discount rate
0-35 years	3.5%
36-70 years	2.5%
>70 years	1.5%

Source: https://fm.dk/media/18371/dokumentationsnotat-for-den-samfundsoekonomiske-diskonteringsrente_7-januar-2021.pdf

8.2 Relationship between the data for relative efficacy, parameters used in the model and relevance for Danish clinical practice

8.2.1 Presentation of input data used in the model and how they were obtained

The STEPS study is used to inform the first 24 weeks of both the teduglutide and standard care model arms. After 24 weeks, the teduglutide arm of the model is informed by STEPS-2 and the standard care arm of the model is extrapolated from the STEPS placebo arm. An alternative set of data pooling 004 trial data with STEPS data is included as an option in the model. STEPS-3 was a 1-year open-label study for patients in the United States having completed STEPS-2. STEPS-3 data is not utilized in the model. All studies mentioned are described in detail in section **7.1.1**.

Liver complications

IFALD is modelled in parallel to PS states through adding the associated costs and QALY losses. There is a clinical belief and plausibility that teduglutide treatment may reduce incidence of liver failure by reducing PS requirement. We initially sought out to have these beliefs confirmed by Danish clinical experts in a Danish Delphi panel exercise, but the feedback from the Danish clinical experts was that they were unable to provide sufficiently accurate input for a Danish clinical setting. However, the beliefs were confirmed in two rounds of questionnaires completed by UK clinical experts in a Delphi process (**Appendix K**) related to a previous NICE submission for teduglutide. Cavicchi 2000[70] report 2, 4, 6, and 8-year PS-related liver disease prevalence (as defined by bilirubin >60, decompensation or fibrosis/cirrhosis on biopsy), but Harrison 2014[71] state that these are extreme estimates. The majority of the experts asked in the Delphi panel also thought these estimates were too high.

Therefore, the rates of liver failure are based on estimates given by the experts in the Delphi meeting IFALD development rates are dependent on the PS health state a patient is in. The model also includes the estimates from the Delphi questionnaire which preceded the Delphi meeting, in which the attending experts agreed the estimates from the questionnaire were too high. The proportion of patients with IFALD is calculated in each cycle based on the number of patients that are in each PS health and alive.

The model also has the option to model progression of liver disease. For this scenario Cavicchi 2000[70] is used. In this paper, the number of adult patients with extensive fibrosis and with cirrhosis are given for certain time points. By manually calibrating and estimating the curves, the development rates from IFALD to extensive fibrosis and from extensive fibrosis to cirrhosis were estimated (see Table 24).

In the model base-case, IFALD is included with the development rate estimated by the Delphi meeting. Mortality associated with IFALD is assumed to be the same as PS dependent mortality, as the Delphi panel estimated rates were considered by the clinical experts advising NICE in a previous teduglutide submission to be too high.

Table 23 IFALD prevalence estimates from UK Delphi meeting and calculated development rates per 28 days

	Non-PS	PS1-2	PS3-5	PS6-7
Prevalence at 2 year	0.00%	0.33%	0.67%	1.00%
Prevalence at 6 years	0.00%	0.67%	1.33%	2.00%
Prevalence at 10 years	0.00%	1.00%	2.00%	3.00%
Development rate years 0-2	0.000%	0.013%	0.026%	0.039%
Development rate years 2-6	0.000%	0.006%	0.013%	0.019%
Development rate years 10+	0.000%	0.006%	0.013%	0.020%

Key: IFALD, intestinal failure associated liver disease. **Source: Appendix K**

Table 24 Development rates per 28 days of extensive fibrosis and cirrhosis

Extensive Fibrosis	Development rate	Cirrhosis	Development rate
Years 0-2.167	2.38%	Years 0-3.083	1.30%
Years 2.167+	0.98%	Years 3.083+	1.20%

Source: Cavicchi 2000[70]

Chronic Kidney Disease

Another complication that is clinically believed to be associated with SBS and PS is stage V CKD. CKD is modelled in a similar way to IFALD, in parallel to the main disease model. Costs accrued and QALYs lost owing to CKD are added into the patient expected totals to model their effect on the cost-effectiveness of teduglutide. Mortality and rates of development are based on estimates from the UK Delphi meeting (see **Appendix K**). These estimates are used in the model to calculate the proportion of patients with CKD stage V, like is done for IFALD (see Table 25). CKD is not included in the base-case of the model, as clinical experts advised that CKD less of an issue in modern practice, due to improvements in PS over time (**Appendix K**).[9] However, the inclusion of CKD is tested in a scenario analysis.

Table 25 CKD prevalence estimates from Delphi meeting and calculated development rates per 28 days

	Non-PS	PS1-2	PS3-5	PS6-7
Prevalence at 1 year	0.00%	0.33%	0.67%	1.00%
Prevalence at 2 years	0.00%	0.67%	1.33%	2.00%
Prevalence at 10 years	0.00%	1.67%	3.33%	5.00%
Development rate years 0-1	0.000%	0.026%	0.051%	0.077%
Development rate years 1-2	0.000%	0.026%	0.052%	0.078%
Development rate years 2+	0.000%	0.010%	0.020%	0.030%

Key: CKD, chronic kidney disease. **Source: Appendix K**

Table 26 Summarizes the input data used in the cost-effectiveness model.

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Table 26 Input data used in the model

Name of estimates	Result source	Input value used in the model	How is the input value obtained/estimated
Transition probabilities ***Days per week dependent on parenteral support***	STEPS, STEPS-2 (**8.2.2.4**)	See **Appendix L**	See **8.2.2.4**
Parenteral support-related health states (utility)	Literature-based (**8.4.1**)	See Table 39	See **8.4.1**, **8.4.2**
Parenteral support-related health states (resource use)	Based on input from UK Evidence Review Group (ERG), Danish clinical expert opinion and assumptions (**8.5.1**)	See Table 45	See **8.5.1**
Parenteral support-related health states (unit prices)	Mainly based on DRG tariffs[7] and the DMC cost catalogue,[8] and medicinpriser.dk	See Table 46	See **8.5.1**
Treatment cost and posology	Medicinpriser.dk and SmPC[72] (**8.5.1**)	See section **8.5.1** and Table 40	See **8.5.1**
Treatment administration/monitoring costs (teduglutide)	DRG tariffs[7] and the DMC cost catalogue[8] (**8.5.2**, **8.5.3**)	See Table 41, Table 42	See **8.5.2**, **8.5.3**
Patient population	STEPS, STEPS-2 (**8.2.2.1**)	See Table 27	See **8.2.2.1**
Complications (occurrence)	UK Delphi panel (**Appendix K**)	See Table 23, Table 24, Table 25	See **8.2.1**
Complications (costs)	DRG tariffs	See Table 44	See **8.5.5**
Complications (utility)	Literature-based (**8.4.1**)	See Table 39	See **8.4.1**, **8.4.2**
Survival	Modeled based on literature (**8.2.2.6**)	Adult: See Figure 25 Pediatrics: See Figure 28	See **8.2.2.6**
Carer utilities (not in base base)	*UK Delphi panel (**Appendix K**)*	*See Table 131*	*See **Appendix M***
Adverse events (occurrence)	STEPS, STEPS-2 (**8.2.2.5**)	See Table 33	See **8.2.2.5**
Adverse events (costs)	DRG tariffs (**8.5.4**)	See Table 43	See **8.5.4**
Adverse events (utility)	Literature-based (**8.4.2**)	See Table 39	See **8.4.2**

8.2.2 Relationship between the clinical documentation, data used in the model and Danish clinical practice

8.2.2.1 Patient population

The Danish patient population: See **5.1**, **5.1.1**
Patient population in the clinical documentation submitted: See **7.1.1**
Patient population in the health economic analysis submitted: STEPS baseline population, see **7.1.1**

As described in **5.1**, we do not have a perfect understanding of the current Danish patient population to compare against the STEPS baseline population, which is also the baseline population of the health economic model. However, we do expect differences between the STEPS population and the Danish patient population (**5.1.1**) in several aspects that are important to the external validity of the health economic modeling, as further detailed in **Appendix C**. One of these differences is the baseline PS dependency; in STEPS, all included subjects had 3 PS days per week or more, which may affect the external validity and transferability of the results of our model to patients with a baseline PS dependency of only 1-2 days per week. Alternative assumptions for baseline populations can be inputted into the 'Controls' sheet of the Excel model.

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Table 27 Patient population

Important baseline characteristics	Clinical documentation	Used in the model	Danish clinical practice
Mean age	Adult model: 50 years (STEPS) Pediatric model: 6 years (006)	Adult model: 50 years (STEPS) Pediatric model: 6 years (006)	N/A (see **5.1**, **5.1.1)**
% female	53.3% (STEPS)	53.3% (STEPS)	N/A (see **5.1**, **5.1.1)**
PS days	Baseline PS level in STEPS (based on pooled data from teduglutide and placebo arms) • PS0: 0% • PS1: 0% • PS2: 0% • PS3: 11% • PS4: 13% • PS5: 6% • PS6: 18% • PS7: 51%	Baseline PS level in STEPS (based on pooled data from teduglutide and placebo arms) • PS0: 0% • PS1: 0% • PS2: 0% • PS3: 11% • PS4: 13% • PS5: 6% • PS6: 18% • PS7: 51%	N/A (see **5.1**, **5.1.1)**

Key: PS, Parenteral support. **Source**: STEPS; 006 (see **7.1.1**)

8.2.2.2 Intervention

Teduglutide is expected to be used according to its SmPC[72] and clinical studies, which is what we have based our cost-effectiveness model on.

Treatment discontinuation

Different rules for treatment discontinuation can be activated in the 'Controls' sheet of the Excel model. If not activated, patients will all continue to be treated with teduglutide for life. We have based our model on the assumption that only responders continue treatment with teduglutide, as we expect non-responders in a Danish clinical setting to discontinue treatment with teduglutide. These treatment discontinuation rules use *post hoc* analysis of trial evidence to establish the proportion of patients in each PS state at the end of trial follow-up that have or have not achieved a certain response criterion. Patients that satisfy the selected condition for response continue to be treated with teduglutide for life, whilst patients failing to meet the criteria discontinue treatment. Stopping rules include any permutation of the below two elements:

1) **Non-response** [failing to achieve a set of criteria at a certain assessment time point, analyzed using patient level data from STEPS (with or without 004)]
    a. PS volume reduction compared to baseline PS volume reduction
    b. PS 1+ days per week reduction compared to baseline PS days per week
    c. PS 2+ days per week reduction compared to baseline PS days per week

Non-response-based stopping rules are applied at 24 weeks in the model base case, but the user can change this assumption through changing the value directly in the 'Controls' sheet of the Excel model.

2) **Response** (i.e., achieving PS independence)
    a. PS independent at X years

The independence-based stopping rule is exploratory in nature and was incorporated into the model during discussions with the NICE evidence review group (ERG), and decision support unit (DSU), related to a previous teduglutide submission. We advise against its use without extensive clinical validation and have consequently not

used it in the base-case of the model. The PS independence-based stopping rule is for patients that achieve PS independence and is applied at the point in time specified by the user.

Non-response-based stopping rules use data from clinical trial evidence and are much more clinically valid. These can be applied to patients that fail to achieve a given PS volume reduction (either 20% compared to baseline, in line with clinical endpoint of STEPS or at least a 1-day or 2-day reduction in days per week dependent on PS). Patients that have discontinued because of lack of response are assumed to remain in the same PS health state post discontinuation of treatment where they are subject to standard of care transition probabilities throughout the remaining model cycles. The model also includes the option for these patients to revert to baseline PS requirements before being subject to standard of care transition probabilities throughout the remaining model cycles (see **8.3.2**). The stopping rule for non-response is active in the base case and is based on 20% volume reduction or at least a 1-day reduction in PS days per week, based on data from STEPS, and is applied after 24 weeks, aligning with the duration of STEPS.

Table 28 Intervention (teduglutid)

Intervention	Clinical documentation	Used in the model	Expected Danish clinical practice
Posology	0.05 mg/kg body weight once daily (STEPS, STEPS-2)	0.05 mg/kg body weight once daily (STEPS, STEPS-2)	0.05 mg/kg body weight once daily (SmPC[72])
Length of treatment (time on treatment) (mean/median)	The overall extent of exposure to teduglutide 0.05mg/kg/d (mean ± SD) during the 24-week STEPS study was 22.72 ± 5.98 weeks. In STEPS-2, in addition to prior exposure from STEPS, the overall exposure was 84.97 ± 34.75 weeks (up to 30 months total).	See stopping rules in section **8.2.2.2**	N/A – we recommend that the Clinical Committee for Inflammatory Bowel Diseases and the Medicines Council discuss potential guiding criteria for treatment continuation/ discontinuation
Criteria for discontinuation	Development of any exclusion criteria that interfered with analysis of the study results (i.e., compromised PN/I.V.)	Patients that do not achieve at least one of the following after 24 weeks are discontinued: • Clinical response (at least 20% PS volume reduction) • 1-day reduction in weekly PS days See stopping rules in section **8.2.2.2**	From the SmPC: *Treatment effect should be evaluated after 6 months. Limited data from clinical studies have shown that some patients may take longer to respond to treatment (i.e., those who still have presence of colon-in-continuity or distal/terminal ileum); if no overall improvement is achieved after 12 months, the need for continued treatment should be reconsidered.*
The pharmaceutical's position in Danish clinical practice	Add-on treatment to PS for SBS-IF patients that have been stable following a period of intestinal adaptation after surgery.	Add-on treatment to PS for SBS-IF patients that have been stable following a period of intestinal adaptation after surgery.	Add-on treatment to PS for SBS-IF patients that have been stable following a period of intestinal adaptation after surgery.

Key: PN, parenteral nutrition; PS, parenteral support; I.V., intravenous; SBS-IF, short bowel syndrome with intestinal failure; SmPC, summary of product characteristics

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Treatment discontinuation in clinical practice is expected to follow the guidance from the SmPC[72], stating that: *Treatment effect should be evaluated after 6 months. Limited data from clinical studies have shown that some patients may take longer to respond to treatment (i.e., those who still have presence of colon-in-continuity or distal/terminal ileum); if no overall improvement is achieved after 12 months, the need for continued treatment should be reconsidered.*

Having tried to establish relevant criteria for continuing or discontinuing teduglutide treatment with clinical experts, including Prof. Palle Jeppesen, it has not been possible to define a criterion that applies for all patients indicated for treatment with teduglutide, or even selected subgroups of patients. We recommend that the Secretariate and the Clinical Committee for Inflammatory Bowel Diseases discuss and co-create guiding principles for treatment discontinuation after the first 6 months of treatment with teduglutide. At the same time, we do not suggest imposing any strict threshold values, as these will not be able to accommodate for any potential individual considerations.

8.2.2.3 Comparators

The current Danish clinical practice: See **5.2.1** (standard care)
Comparator(s) in the clinical documentation submitted: See **5.2** (placebo/standard care)
Comparator(s) in the health economic analysis submitted: See **5.2** (standard care)

Table 29 Comparator (standard care)

Comparator	Clinical documentation	Used in the model	Expected Danish clinical practice
Posology	Standard care (see **5.2**)	Standard care (see **5.2**)	Standard care (see **5.2**)
Length of treatment	Standard care (see**5.2**)	Standard care (see **5.2**)	Standard care (see **5.2**)
The comparator's position in the Danish clinical practice	Standard care (see **5.2**)	Standard care (see **5.2**)	Standard care (see**5.2**)

Treatment with teduglutide is an add-on treatment to home parenteral nutrition. The comparator in the health economic analysis submitted is consequently standard care, as described in **5.2**. However, it is worth re-emphasizing here that even though parenteral support should not be a comparator to teduglutide treatment, teduglutide treatment can reduce or sometimes even remove the need for parenteral support (**5.3**).

8.2.2.4 Relative efficacy outcomes

Transition probabilities

Patients were typically observed to transition up or down by a maximum of one PS state between assessments. However, there were a few exceptions to this, so the model does not place any restriction on patient movements between states per cycle. Six sets of teduglutide transition probabilities and placebo transition probabilities were estimated using either the pooled STEPS and 004 data, or the STEPS data alone (24 weeks of data), based upon patient movements between monthly assessments. Patient movements in the placebo arms of these trials were used to characterize standard care transition probabilities in the model. The base case uses only STEPS data, as that is the pivotal trial used for registration purposes. For teduglutide arm, transitions between PS states were observed. Disaggregated patient PS health states at 24 weeks are reported in Table 30.

Patient movements beyond 24 weeks are only available for teduglutide patients, using the single-arm STEPS-2 extension study-data. In total, 75% of patients receiving teduglutide in the STEPS trial continued into the STEPS-2 trial. Only the movements of patients who remained on teduglutide were evaluated; patients who switched from placebo were excluded. From cycle 6 to cycle 9, patient movements were informed by trial assessments taken each month, thereby providing monthly transition probabilities. After this point, trial assessments occurred less frequently –

corresponding to every three cycles – until the final assessment at month 30. Therefore, STEPS-2 provides ten teduglutide transition matrices, in addition to the six that precede it based upon STEPS data.

The transition probabilities are based directly on the PS volumes observed in STEPS and STEPS-2. All transitions are therefore clinically possible. Due to the sparsity of the data, some transition probabilities will be based on a few observations only, which could lead to clinically implausible transitions if these observations are not representative. All observed data on transitions used in the model are listed in the 'Lists' sheet of the Excel mode.

The decrease in PN observed in the placebo arm of the STEPS trial was not due to a classic placebo effect itself; the aggressive PN reduction affected only the placebo arm: here patients were becoming dehydrated (as shown by weight loss and urine output falling), while the same did not happen in the teduglutide arm. The investigator should have reinstated the PN in the placebo arm rather than allowing them to drink more. This was considered a protocol violation.

The decrease in PN in the placebo arm would only be temporary and not sustainable after the end of the trial, as explained by the principal investigator's statement **Appendix S**. It is important to note that the same issue was not observed in the teduglutide arm, as there was no sign of dehydration in these patients.

It is therefore unlikely that a similar 'placebo response' would be observed in standard of care in actual clinical practice, why the artificially high placebo response is not clinically plausible. We have included the placebo response in the model anyway, which leads to a conservative cost-effectiveness estimate favoring standard of care.

Table 30 Disaggregated patient PS health states at 24 weeks

PS state	Teduglutide	Placebo	Total	% at 24 weeks
No PS	0	1	1	1%
PS1	1	1	2	3%
PS2	3	1	4	5%
PS3	6	4	10	13%
PS4	9	2	11	14%
PS5	3	1	4	5%
PS6	6	9	15	19%
PS7	11	20	31	40%
Total	**39**	**39**	**78**	**100%**

Key: PS, parenteral support. **Source**: STEPS data (completers)

Beyond 9 cycles in the model, in those cycles that lie in between three-monthly assessments, the 'identity matrix' is applied, whereby patients remain in their current health state unless they die. Further information regarding extrapolation beyond observed data can be found in **8.3.2**. The patient level data and the resulting transition probabilities are provided in the 'Lists' worksheet of the Excel model, and the base case transition probabilities are provided in **Appendix L**.

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Table 31 Summary of text regarding *value*

Clinical efficacy outcome	Clinical documentation	Used in the model (value)
Proportion of patients achieving clinical response (≥20% reduction in parenteral support volume)	STEPS (base case: teduglutide + standard care arm), STEPS-2 (base case: teduglutide arm), STEPS-3 (does not inform model), 004 (scenario: teduglutide + standard care arm)	Informs stopping rules (see **8.2.2.2**)
Proportion of patients achieving enteral autonomy	STEPS (base case: teduglutide + standard care arm), STEPS-2 (base case: teduglutide arm), STEPS-3 (does not inform model), 004 (scenario: teduglutide + standard care arm)	Informs stopping rules (see **8.2.2.2**)
Days per week on parenteral support	STEPS (base case: teduglutide + standard care arm), STEPS-2 (base case: teduglutide arm), STEPS-3 (does not inform model), 004 (scenario: teduglutide + standard care arm)	Informs time varying transition probabilities. Methodology is described in **8.2.2.4** and the base case transition probabilities are presented in **Appendix L**.

Parenteral support is associated with reduced quality of life and increased healthcare cost. Reducing the burden of parenteral support is therefore a relevant treatment goal in Danish clinical practice. As no two patients are alike, it is impossible to define a single clinical endpoint or outcome that is equally relevant, or achievable, for all SBS-IF patients. While a 20% reduction in PS volume may be a major improvement for a patient receiving a high PS volume, it may not be a clinically meaningful outcome for a patient receiving a low PS volume. Consequently, the definition of clinical response of at least a 20% reduction in parenteral support volume was chosen for the clinical trials as it, on average, corresponds to a 1-day reduction in weekly PS days for patients requiring PS for 5-7 days per week (**7.1**). During a dialogue meeting,[9] the Chairman and other members of the Clinical Committee for Inflammatory Bowel Diseases agreed with our assumption that, while the value of treatment can be different for different patients, freeing a patient with SBS-IF from PS for 1 (additional) day or more per week is a clinically meaningful outcome that is relevant to the patient.

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Table 32 Summary of text regarding *relevance*

Clinical efficacy outcome	Clinical documentation (measurement method)	Relevance of outcome for Danish clinical practice	Relevance of measurement method for Danish clinical practice
Proportion of patients achieving clinical response (≥20% reduction in parenteral support volume)	STEPS (base case: teduglutide + standard care arm), STEPS-2 (base case: teduglutide arm), STEPS-3 (does not inform model), 004 (scenario: teduglutide + standard care arm) (see **7.1.1**)	Relevance discussed in **7.1** and **Appendix D**	Relevant: PS volume is monitored in Danish clinical practice.
Proportion of patients achieving enteral autonomy	STEPS (base case: teduglutide + standard care arm), STEPS-2 (base case: teduglutide arm), STEPS-3 (does not inform model), 004 (scenario: teduglutide + standard care arm) (see **7.1.1)**	Relevance discussed in **7.1** and **Appendix D**	Relevant: Enteral autonomy corresponds to 100% PS volume reduction.
Days per week on parenteral support	STEPS (base case: teduglutide + standard care arm), STEPS-2 (base case: teduglutide arm), 004 (scenario: teduglutide + standard care arm) (see **7.1.1** and **8.2.2.4**)	Relevance discussed in **7.1** and **Appendix D**	Relevant: Days per week on PS is monitored is Danish clinical practice.

Key: PS, parenteral support

8.2.2.5 Adverse reaction outcomes

Adverse reaction outcomes in the clinical documentation submitted: See **7.1.2**
Adverse reaction outcomes in the health economic analysis submitted: Based on STEPS and STEPS-2, see **7.1.2**

All adverse events (AEs) that occurred in at least 5% of patients in either arm of the STEPS trial were originally considered for the economic model. Based upon clinical assessment, 32 of the total 35 AEs were included as important relevant AEs in the model. The three AEs that were excluded were device dislocation, epistaxis and nasopharyngitis. These were omitted due to their low cost and minimal patient burden, indicating that they would have negligible impact on the cost-effectiveness model. The model also has the option to include serious AEs only (see control sheet of the Excel model).

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

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obtained from the placebo arm of STEPS. With only 6 months of data, these rates are not time-variable. Patients who discontinued teduglutide became subject to the AE rates associated with standard care. Reducing the rate of AEs after 6 months for patients who continue teduglutide only is justified because treatment with teduglutide and reduced PS dependency are both associated with reduced AE rates. Patients in the teduglutide arm who discontinue teduglutide and all patients in the standard care arm are consequently not subject to the same reductions in AE rates in the model. Given the limitations due to the sparsity of the data, this is the best alternative to having separate AE rates per PS state. The individual rate per cycle for each included AE is presented in Table 33.

Table 33 Adverse Events included in the model and their 28-day rates

Adverse reaction outcome	Teduglutide months 0-6 *Source: STEPS (TED)*	Teduglutide after month 6 *Source: STEPS-2 (all arms)*	Standard Care *Source: STEPS (SC)*
Abdominal distension	0.054	0.010	0.008
Abdominal pain	0.054	0.015	0.054
Arthralgia	0.012	0.003	0.012
Bacteraemia	0.000	0.001	0.012
Catheter related infection	0.023	0.005	0.004
Central line infection	0.012	0.008	0.016
Constipation	0.004	0.001	0.012
Decreased appetite	0.012	0.000	0.004
Dehydration	0,008	0.007	0.012
Diarrhoea	0.016	0.012	0.027
Dizziness	0.004	0.002	0.012
Dyspnoea	0.012	0.001	0.000
Fatigue	0.019	0.001	0.012
Flatulence	0.019	0.008	0.012
Gastrointestinal stoma complication	0.043	0.011	0.012
Headache	0.008	0.006	0.043
Injection site haematoma	0.008	0.001	0.012
Injection site pain	0.016	0.000	0.000
Muscle spasms	0.008	0.007	0.016
Nausea	0.074	0.009	0.047
Peripheral oedema	0.031	0.011	0.012
Bacterial overgrowth	0.016	0.000	0.000
Pain	0.000	0.001	0.012
Procedural site reactions	0.012	0.006	0.004
Pyrexia	0.019	0.008	0.019
Renal colic	0.039	0.011	0.000
Small intestinal stenosis	0.012	0.000	0.000
Upper respiratory tract infection	0.008	0.000	0.016
Urinary tract infection	0.023	0.015	0.019
Vomiting	0.019	0.005	0.039
Decreased weight	0.004	0.017	0.027

Key: TED, teduglutide; SC, standard care. **Source**: STEPS and STEPS-2 clinical study reports; individual patient-level data from STEPS and STEPS-2

8.2.2.6 Survival

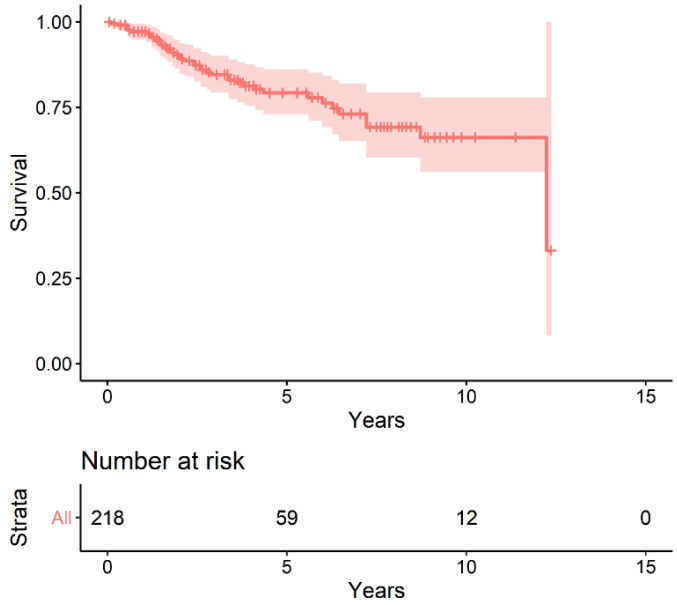
The model does not include relative efficacy data on survival. However, to assess the cost-effectiveness of a long-term treatment such as teduglutide, it is important to accurately estimate the proportion of patients alive at any time over the lifetime horizon of the model. Data from the STEPS program, with a maximum of 42 months of follow-up, provide insufficient data to evaluate lifetime survival: only 3 deaths occurred during STEPS and STEPS-2. This does not allow us

to model long term survival in patients with SBS-IF, and certainly does not allow any consideration of a potential treatment effect on mortality.

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

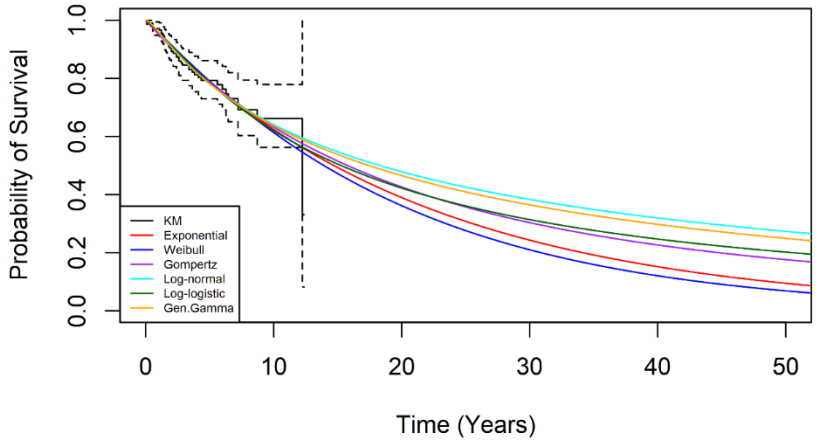
The most relevant study providing the latest data on survival associated with SBS-IF, identified via review of studies obtained through the clinical systematic literature review, is Salazar 2021.[73] This study provided survival data for 218 patients with SBS-IF who were receiving PS and followed-up for up to 15 years (2003 to 2018) as part of a Canadian PS registry. Importantly, this study presented the Kaplan-Meyer (KM) plot for survival alongside the number of patients at risk in 5-year increments, allowing digitization and estimation of pseudo individual patient data (IPD).
The KM plot was digitized and pseudo-IPD were estimated using the algorithm developed in Guyot (2012).[74] The resulting KM plot using the pseudo-IPD is presented in Figure 23.

Figure 23 Survival of SBS-IF patients from Salazar 2021



The pseudo-IPD generated from this process was used to fit survival curves using the *flexsurv* package of *R*. Standard parametric models (exponential, Weibull, Gompertz, log-normal, log-logistic and generalized gamma) were fitted. Statistical fit was evaluated based on assessment of the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC), while the plausibility of the extrapolations was evaluated by visual inspection. The resulting fitted survival curves are shown in Figure 24 and the corresponding goodness-of-fit statistics are given in Table 34.

Figure 24 Survival curves fitted to Salazar 2021 data



Key: KM, Kaplan-Mayer. **Source**: Salazar 2021[73]

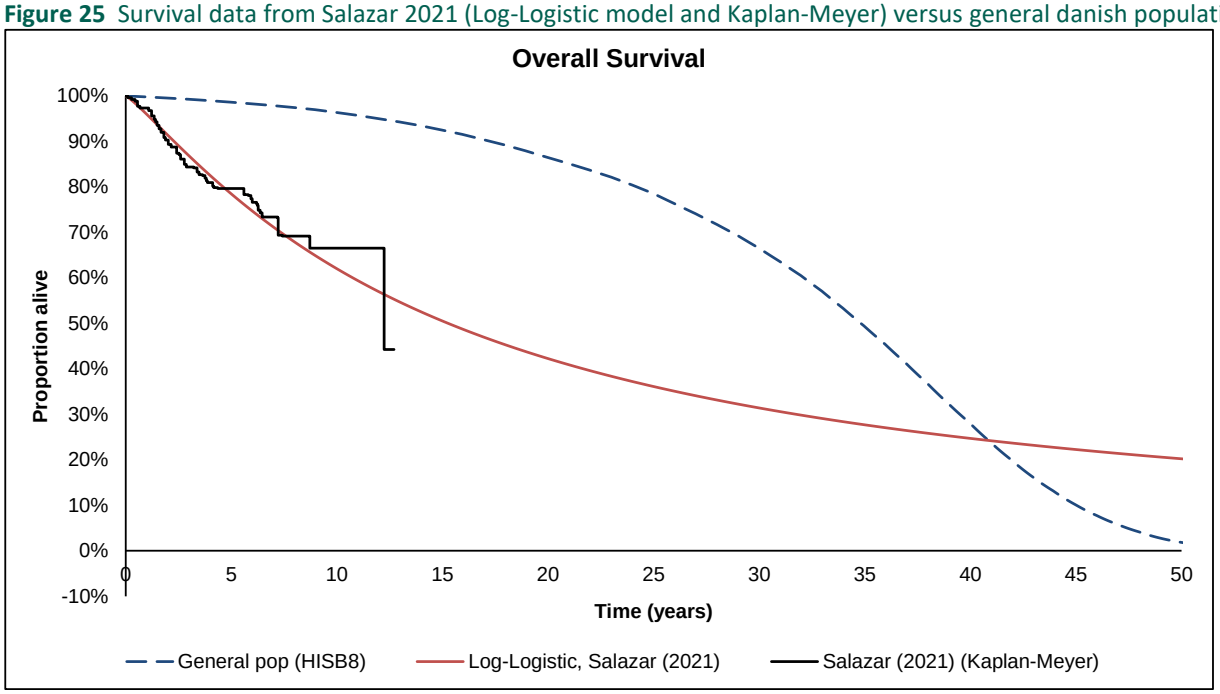
Table 34 Goodness-of-fit statistics for Salazar 2021 survival models

Parametric model	AIC	BIC
Exponential	334.48	337.86
Weibull	336.30	343.07
Gompertz	336.42	343.19
Log-normal	334.62	341.39
Log-logistic	335.47	342.23
Generalised gamma	336.58	346.73

Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterio. **Source**: Salazar 2021[73]

The best fitting curve according to AIC and BIC was the exponential. However, the Log-Normal was a close second, especially when comparing the AIC statistics, which were almost identical. The statistical fit according to AIC and BIC are similar and satisfactory across models. While the exponential model provides the best statistical fit, the assumption of a constant hazard is generally too simplistic to capture the diminishing rate of mortality. When visually assessing the plausibility of the extrapolations against the shape of the KM plot and beyond, the exponential and Log-Normal extrapolations are both extremes. Due to the satisfactory statistical fit across models, we have opted for the Log-Logistic model in the base case analysis, because the curve appears to be in the middle of the range upon visual inspection. Survival probabilities were adjusted by using the hazards of death from Danish Life Tables for the general Danish population from Statistics Denmark (HISB8[75]). If the hazard rate of the fitted survival model went below the rate of the Danish population data, then the Danish population mortality rate was applied.

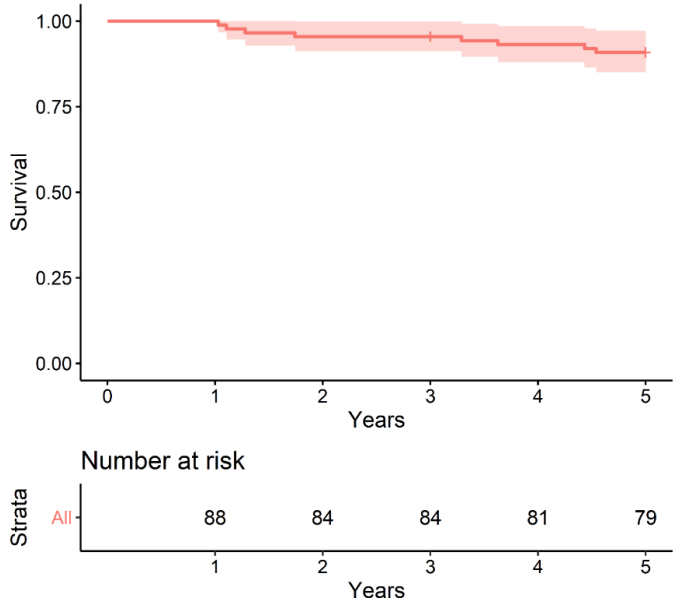
Figure 25 Survival data from Salazar 2021 (Log-Logistic model and Kaplan-Meyer) versus general danish population



Sources: General population (HISB8) https://www.statistikbanken.dk/statbank5a/default.asp?w=2560; Salazar 2021[73]

The same approach was taken for the pediatric model using a pediatric-specific source of survival data. The largest and most recent source of survival data relating to the pediatric population was identified as Pironi (2011),[76] which provides up to 5 years of follow-up data for 88 children. The plot provided was digitized to estimate pseudo-IPD and the resulting KM plot is given in Figure 26.

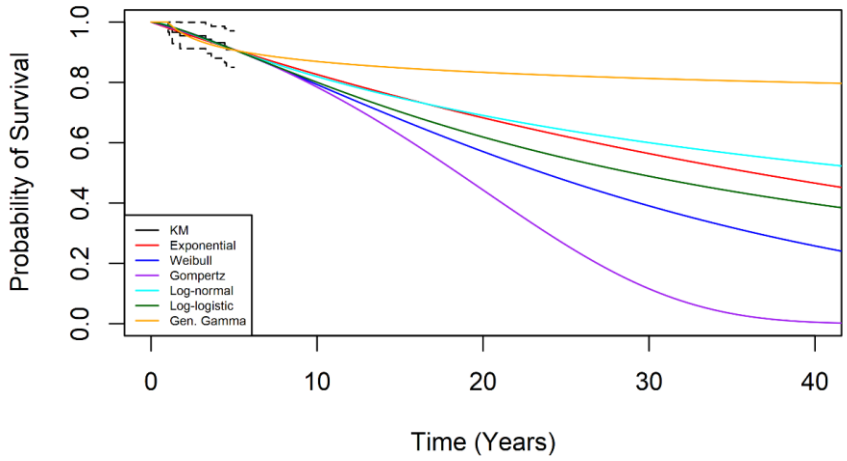
Figure 26 Survival of SBS-IF patients from Pironi 2011



Key: SBS-IF, short bowel syndrome with type 3 intestinal failure. **Source**: Pironi 2011[76]

Pseudo-IPD generated using the Guyot 2012[74] algorithm was used to fit survival curves using the *flexsurv* package of *R*. Standard parametric models (exponential, Weibull, Gompertz, log-normal, log-logistic and generalized gamma) were fitted, with the best fitting models chosen based on assessment of the AIC and BIC goodness-of-fit statistics, as well as the plausibility of the extrapolations. The resulting fitted survival curves are shown in Figure 27 and the corresponding goodness-of-fit statistics are given in Table 35.

Figure 27 Curves fitted to Pironi 2011 data



Sources: Pironi 2011[76]

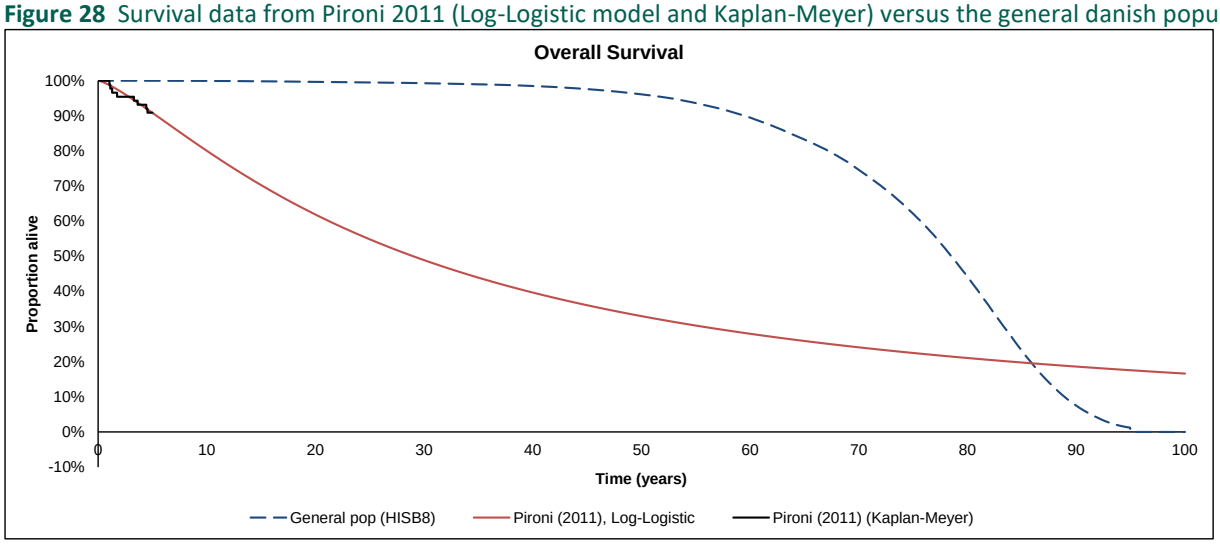
Table 35 Goodness-of-fit statistics for Pironi 2011 survival models

Parametric model	AIC	BIC
Exponential	81.34	83.81
Weibull	82.89	87.84
Gompertz	83.21	88.17
Log-normal	82.38	87.33
Log-logistic	82.85	87.81
Generalised gamma	79.94	87.73

Key: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterio. **Source**: Pironi 2011[76]

The AIC statistics appear to show that the most complex 3-parameter generalized gamma curve has the best fit to the data, but this is closely followed by the single-parameter exponential curve. Based on the BIC statistics, however, the exponential demonstrates the best fit with no close second place. As for the adult survival models, the constant hazard assumption of the exponential model is deemed too simplistic to model mortality. With no obvious preferred model based on the goodness-of-fit statistics, we opted for the Log-Logistic model, which appeared to be in the middle of the range of the models upon visual inspection of the plausibility of the extrapolations.

Figure 28 Survival data from Pironi 2011 (Log-Logistic model and Kaplan-Meyer) versus the general danish population



Sources: General population (HISB8) https://www.statistikbanken.dk/statbank5a/default.asp?w=2560; Pironi 2011[76]

8.3 Extrapolation of relative efficacy

8.3.1 Time to event data – summarized:

No time to event data on efficacy was extrapolated. Extrapolation of survival data is included in section **8.2.2.6**.

8.3.2 Extrapolation of efficacy beyond observed data

With only 24 weeks of teduglutide data from STEPS, and only a further 2 years of teduglutide data beyond that point from STEPS-2, with a reflective time horizon of 40 years (adults) and 94 years (pediatrics), assumptions are required to extrapolate future patient movements between PS health states.

In the base case analysis, the model repeats the final set of observed transition probabilities (from cycle 27 to cycle 30), applied at three-month intervals beyond cycle 30 of the model until 5 years from baseline for teduglutide patients. Following that, patients remain in the same PS state. Patients only transition beyond this point if they die. This is justified because of the continued improvements beyond 2.5 years observed in STEPS-3, which was a one-year extension study following STEPS-2. For the 5 patients that continued teduglutide treatment through STEPS, STEPS-2 and STEPS-3, the mean number of days per week reduced from 3.2 at the end of STEPS-2 to 2.7 at the end of STEPS-3. This shows there is continued improvement beyond 2.5 years, which is reflected in the scenario selected for the base case. Table 36 below shows that this is still a conservative modeling assumption. The 5-year extrapolation in the base case analysis can be changed in the 'controls' sheet of the Excel model.

Table 36 Average number of days PS is required in STEPS trials and modeled (without active stopping rules)

Outcome	Teduglutide		Standard care	
	STEPS - STEPS2 - STEPS3	Model	STEPS	Model
Average number of days PS is required at baseline	5.6 days	5.9 days	6.0 days	5.9 days
Average number of days PS is required after 24 weeks	4.6 days	4.9 days	5.5 days	5.4 days
Average number of days PS is required after 30 months	3.2 days	3.3 days	N/A	5.9 days
Average number of days PS is required after 42 months	2.7 days	3.0 days	N/A	5.9 days
Average number of days PS is required after 60 months	N/A	2.8 days	N/A	5.9 days

Key: N/A, not available; PS, parenteral support. **Sources**: STEPS; STEPS-2; STEPS-3

Following the observed 24 weeks of placebo data, patients in the standard care arm revert to their baseline PS requirement. This is achieved by redistributing the proportion of patients alive across the PS states according to the baseline distribution (see Table 27). This is a plausible assumption, as there is no reason that treatment with PS only should necessarily lead to a reduction in the need for PS itself. Any PS reductions observed in the placebo arm of the STEPS trial may represent the 'trial effect' of frequent follow-up visits and thorough monitoring, and these reductions may also be due to the 'fluid composite effect' seen in the trial, where placebo patients drank more and had an increased fluid intake that did not continue outside of the trial setting (weaning algorithms and placebo response are discussed in detail in **7.1.1**). While this may be seen as a controversial assumption, it would be expected that the same effect would be seen in the teduglutide arm, and therefore, this is not adjusted for in the model. This assumption was also backed by the clinical experts in the Delphi Panel (**Appendix K**).

The model allows for alternative extrapolation assumptions to be tested. For teduglutide, the user can select for patients to remain in the same PS health state following 30 months, or for the final set of transition probabilities to be applied until patients die. For standard care, the user can choose to have patients remain in the same PS state after the observed placebo data (i.e., beyond week 24) rather than revert to baseline (representing an equivalent extended effect for standard care patients). These assumptions are tested in scenario analyses presented in section **8.7.1**.

8.4 Documentation of health-related quality of life (HRQoL)

8.4.1 Overview of health state utility values (HSUV)

As per section 7.1.2 of the DMC methods guide, literature-based utility values can be applied in cases where *"… study data is not of sufficient quality or based a limited number of patients."* As described in more detail in **7.1.1**, the quality of the SBS-QoL data from the STEPS trial is of insufficient quality due to inherent problems with the instrument itself, and insufficient number of patients in the trial to power the detection of clinically meaningful differences.

Consequently, we decided to use literature-based utilities in the base case analysis instead. For completeness, we have also included a scenario where SBS-QoL, which is a non-preference-based instrument, from STEPS has been mapped to utility values with UK preference weights.

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Table 37 Summary of published studies reporting health-state utility values in SBS-IF

Reference	Population	Intervention & comparators	Method	Outcomes
Culkin *et al.* 2009[77]	Patients with chronic IF (n=48). The definition of chronic IF used in this study is unclear given not all patients receive PS	PS (33 patients out of 48 type 3 IF patients)	Quality of life was calculated using EQ-5D-3L VAS, EQ-5D Index & SF-36	**1.** Quality of Life EQ-5D Index; all patients (n=48): 0.75 ± 0.19, Patients on PS (n=33): 0.77 ± 0.16 **2.** Difference in quality of life indices for patients dependent & independent of PS EQ-5D Index (median, IQR); Not on PS (n=15): 0.00, -0.11 – 0.04, On PS (n=32): 0.07, 0.00 – 0.13.
Lachaine *et al.* 2016[78]	SBS patients and the Canadian general population (n=799)	Days and/or hours per day on PS	General population time trade-off survey to elicit health state utility values	PS0 = 0.74 PS1 = 0.70 PS2 = 0.65 PS3 = 0.61 PS4 = 0.57 PS5 = 0.52 PS6 = 0.48 PS7 Low = 0.44 PS7 High = 0.39
Ballinger *et al.* 2018[79]	UK general public (adults; n=100) rating SBS (not specific to type of IF) health states	Days of PS	Health state vignette study involving VAS and time trade-off technique	Health state: mean (SD) PS0: 0.82 (0.22) PS1: 0.78 (0.23) PS2: 0.72 (0.23) PS3: 0.65 (0.27) PS4: 0.58 (0.31) PS5: 0.51 (0.33) PS6: 0.41 (0.34) PS7: 0.36 (0.35)
Carey *et al.* 2019[80]	Australian patients on PS (n=19) rating health states of patients with type 3 IF receiving PS	PS, teduglutide, intestinal transplant	Treatment vignette study involving time trade-off technique	Median values by treatment (note these values are the inverse of utility): Teduglutide: 0.5 Intestinal transplant: 1.0 Reduction in line infections: 0.75 Optimisation of care: 0.5
Raghu *et al.* 2020a[81]	Simulated cohort of adults with SBS-IF	PS, teduglutide	Cost-effectiveness (Markov) model	Utilities obtained from Ballinger et al 2018 and subjected to age adjustment: PS0: 0.84 PS1: 0.77 PS2: 0.70 PS3: 0.63 PS4: 0.56 PS5: 0.49 PS6: 0.42 PS7: 0.35
Raghu *et al.* 2020b[82]	Simulated cohort of children with SBS-IF	PS, teduglutide	Cost-effectiveness (Markov) model	Utilities derived from Ballinger *et al*. 2018 Enteral autonomy/PS0: 0.82 PS7: 0.36

Key: EQ-5D(-3L), EuroQol five dimensions (3 levels); PS, parenteral support; PSx, x days per week of PS; SBS, short bowel syndrome; SBS-IF, short bowel syndrome with type 3 intestinal failure; SF-36, 36 item short form questionnaire; VAS, visual analogue scale. **Source**: Studies identified by quality of life SLR [77, 78, 79, 80, 81, 82]

Literature-based utilities

PS related

Several systematic literature reviews (SLRs) were performed to identify other relevant HRQoL or health state utility value (HSUV) studies. These were performed in line with NICE guidance in the methods of technology appraisal, using a pre-prepared search strategy and multiple reviewers assessing results (details can be found **Appendix H**). Most recently, a HRQoL and HSUV SLR, covering data for adults and children with SBS-IF, was performed on 21st May 2021. Of the 31 studies identified by the SLRs, six reported utility values for patients with SBS-IF; these are shown in Table 37, the remaining quality of life studies are summarized in **Appendix H**.

Complications

Liver complications

The health state utility value associated with liver disease was 0.596. This was informed by the UK catalogue of EuroQol 5 Dimension (EQ-5D) scores for a range of conditions reported by Sullivan 2011.[83] From this, the average utility decrement for liver disease is calculated per model cycle, based on the proportion of patients in the PS health states (excluding PS0). The utility decrement for liver disease is calculated as follows:

$$Udec_{IFALD} = \left(U(IFALD) * \left(\frac{Pr[PS_1]U(PS_1) + \cdots + Pr[PS_7]U(PS_7)}{Pr[PS_1] + \cdots + Pr[PS_7]} \right) \right) - \left(\frac{Pr[PS_1]U(PS_1) + \cdots + Pr[PS_7]U(PS_7)}{Pr[PS_1] + \cdots + Pr[PS_7]} \right)$$

Key: IFALD, intestinal failure related liver disease; Udec, utility decrement; Pr(), proportion in health state; U(), associated utility

This utility decrement multiplied by the proportion of patients in IFALD, adjusted for cycle length, and finally adjusted for age results in an estimated total per cycle QALY loss associated with IFALD, which is sensitive to PS state populations. In the base case, the values from Sullivan 2011 for 'Other liver disorders' are used for IFALD.

Chronic Kidney Disease

The health state utility value associated with CKD stage V was 0.710, taken from an article by Wyld 2012[84] for CKD and Dialysis. This value is used to apply the correct decrement to utility across states per the IFALD formula above.

Adverse Events

Many AEs and complications of teduglutide and/or PS affect patients' quality of life. For a given AE, the quality-of-life impact was assumed to be the same regardless of whether the patient received teduglutide or standard care. The impact on quality of life is measured in utility decrements, of which values are informed by the available literature and are combined with the relevant event rate to estimate a decrement per model cycle. See Table 39.

Mapping

Both STEPS and 004, randomized controlled trials of teduglutide versus placebo, collected data on HRQoL outcomes. Neither study was powered to detect differences in quality of life, either for comparing baseline versus week 24 within a treatment arm, or for comparing teduglutide versus placebo, and so use of the data is limited. 004 collected quality of life data using the SF-36, EQ-5D and IBDQ instruments (**7.1.1**). No difference in quality of life was reported for any of these instruments when comparing results for the teduglutide arm versus baseline or versus placebo at week 24 (see **Appendix R**). While EQ-5D is preferred by the DMC for generating utilities, the teduglutide EPAR[85] noted that the SF-36, EQ-5D and IBDQ instruments had not been developed to assess the quality of life of patients with SBS and were unlikely to be sensitive enough to detect quality of life changes in this population. We therefore decided that data from 004 were not appropriate to use within our model.

STEPS captured quality of life data using the SBS-QoL instrument. No statistically significant difference in SBS-QoL scores was observed between the teduglutide and placebo arms; potential reasons for this are discussed in section **7.1.1**. As a non-preference-based measure, utilities cannot be derived directly from SBS-QoL outcomes and therefore it cannot be directly used to inform the health state utility values in the model. However, a mapping algorithm from Lloyd 2014[86] provides a link between the SBS-QoL outcomes and utility values based on UK preferences derived using a time-trade-off technique in a similar fashion to the EQ-5D (see **Appendix I**).

The mapped utility values for each health state are presented below in Table 38. Results indicate that patients in the STEPS trial prefer receiving parenteral support for 4 days per week over any other health state, including health states that represent fewer PS days per week or even enteral autonomy. This is clearly not aligned with any other utility study or statement we have received from patients or clinical experts on quality of life; fewer PS days are associated with higher quality of life. While these mapped utilities are included as a scenario analysis, they are nonsensical, and the results should consequently be disregarded.

Table 38 Utilities mapped from the SBS-QoL data in STEPS (using the Lloyd algorithm presented in **Appendix I**)

	Results	From Instrument	To instrument	Comments
STEPS	PS0: 0.814 PS1: 0.814 PS2: 0.790 PS3: 0.812 PS4: 0.861 PS5: 0.782 PS6: 0.762 PS7: 0.745	SBS-QoL	Utility values with UK preference weights	*A mapping algorithm (Lloyd 2014) provides a link between the SBS-QoL outcomes and utility values derived using a time-trade-off technique in a similar fashion to the EQ-5D.*

Key: SBS-QoL, Short Bowel Syndrome Quality of Life; PS, Parenteral Support. **Source**: Lloyd 2014,[86] STEPS data

8.4.2 Health state utility values used in the health economic model

Of the six included studies that provide utilities relating to SBS-IF patients shown in Table 37, the key studies that can be used to directly inform the economic model are Ballinger 2018,[79] Lachaine 2016,[78] and Raghu 2020a.[81] These studies all provide utility estimates based on the number of days per week of PS required by patients; however, Raghu 2020a is an economic evaluation that reports age-adjusted values based on the Ballinger 2018 values. Therefore, there are two unique sources of utility values to consider informing the economic model.

Both Ballinger 2018 and Lachaine 2016 are vignette studies that use a time-trade off technique to elicit utility values, as used for the derivation of the EQ-5D UK valuation tariff. For this submission, it was decided to use utility values from the Ballinger 2018 study, as it provides utility estimates derived from a UK general population. Lacking utility estimates based on Danish preference weights, the use of UK preference weights has the advantage of being more comparable to health technology assessments by NICE, which is widely regarded as the gold standard for health technology assessments. The utilities reported by Ballinger 2018 are also in line with utilities reported in a previous study,[87] where the mean utility value for a patient on PS was 0.52, and reached as low as 0.28 in older patients. Therefore, given the limitations of the utility values derived from STEPS and 004, values from Ballinger 2018 have been used in the base case analyses of the model, and scenarios are provided using utility values derived from Lachaine 2016 and STEPS. Lachaine 2016 reported two utility values for the PS7 state based on high and low PS volume, so the midpoint between PS7 high and PS7 low was used in the Lachaine 2016 scenarios in the model. Utility values were age-adjusted based on the general danish population to account for decreasing utility with increasing age as per the DMC methods guide.[88] For application in the model, utilities were re-weighted to the starting

age of the model (50 years in the adult base case, 6 years in the pediatric base case). As no data were available for the ages 1-17 years, the utility value for all ages below 18 years were assumed to be identical to the utility value at 18 years.

Table 39 Summary of the HSUV used in the model

State	Utility value	Justification
PS0	0.82	*Ballinger 2018*[79]
PS1 disutility	-0.04	
PS2 disutility	-0.10	
PS3 disutility	-0.17	
PS4 disutility	-0.24	
PS5 disutility	-0.31	
PS6 disutility	-0.41	
PS7 disutility	-0.46	
Intestinal failure-associated liver disease (IFALD)	0.596	*Sullivan 2011*[83]
Chronic kidney disease (CKD)	0.71	*Wyld 2012*[84]
Abdominal distension	-0.0512	*Sullivan 2011,'Other gastrointestinal disorders'*[83]
Abdominal pain	-0.0512	
Arthralgia	-0.023	*Sullivan 2011,'Other bone disease and musculoskeletal disorders'*[83]
Bacteraemia	-0.52	*NICE TA352, vedolizumab for treating moderate to severely active Crohn's disease after prior therapy, 'serious infection'**
Catheter-related infection	-0.52	
Central line infection	-0.52	
Constipation	-0.0512	*Sullivan 2011,'Other gastrointestinal disorders'*[83]
Diarrhoea	-0.0512	
Injection site haematoma	-0.03	*NICE TA352, vedolizumab for treating moderate to severely active Crohn's disease after prior therapy, 'skin site reactions'*[89]*
Injection site pain	-0.03	
Peripheral oedema	-0.0508	*Sullivan 2011,'Aortic, peripheral and visceral artery disorders'*[83]
Bacterial overgrowth	-0.52	*NICE TA352, vedolizumab for treating moderate to severely active Crohn's disease after prior therapy, 'serious infection'**
Procedural site reactions	-0.03	*NICE TA352, vedolizumab for treating moderate to severely active Crohn's disease after prior therapy, 'skin site reactions'*[89]*
Small intestinal stenosis	-0.0512	*Sullivan 2011,'Other gastrointestinal disorders'*[83]
Upper respiratory tract infection	-0.52	*NICE TA352, vedolizumab for treating moderate to severely active Crohn's disease after prior therapy, 'serious infection'**
Urinary tract infection	-0.09	*Bermingham and Ashe 2012, 'Older adults with UTI'***
Vomiting	-0.0512	*Sullivan 2011,'Other gastrointestinal disorders'*[83]

Key: HSUV, health state utility value. Sources: *https://www.nice.org.uk/guidance/ta352/documents/crohns-disease-moderate-to-severe-vedolizumab-appraisal-consultation-document2; **NICE clinical guidelines No 139 Appendix K, Bermingham, S. L., & Ashe, J. F. (2012)[90].

Disutilities for adverse events are applied for the duration of one 28-day model cycle, as there was no information on duration of AEs available from STEPS and it seems reasonable to assume that most AEs evaluated would not last longer than this. Final utility values associated with AEs in our model are presented in Table 39.
Utility values for IFALD and CKD (also presented in Table 39) are also included in the model. However, these are chronic complications for which the per-cycle utility decrement is applied continuously from the onset of the complication. The average utility decrement for each complication is calculated per model cycle, based on the proportion of patients in each PS health state (ranging from 0 to 7 days of PS per week, noted as PS0 to PS7), as described in section **8.4.1**.

The quality of life of caregivers for people with SBS-IF may also be impacted by the PS burden of the SBS-IF patient in their care. As this is not recognized by the DMC, the base case analysis excludes caregiver utilities. However, caregiver utilities can be activated in the 'Controls' sheet of the Excel model. See **Appendix M** for more details.

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

8.5 Resource use and costs

8.5.1 Treatment cost and posology

Teduglutide dosing in the model follows the recommended posology in its SmPC: a daily dose of 0.05mg/kg body weight. A vial containing a 5mg dose covers a daily dose for patients weighing up to 100 kg. In the STEPS study, mean patient weight at baseline was 62.2 kg, with a maximum of 87.9 kg. The model therefore assumes that one vial of teduglutide is sufficient to cover a daily dose in all relevant patients. Vial sharing is not allowed in the model.
The list price of teduglutide is 121,998.27 kr. for 28 vials, corresponding to 4.357,08 kr. per administration. A scenario with a reduced price and an alternative pricing structure is provided in **Appendix N**.

Table 40 Cost of teduglutide

Drug	Pack size	Dose (mg)	Pack cost	Cost per dose	Source
Teduglutide	28	5	DKK 121,998.27	DKK 4,357.08	www.medicinpriser.dk

8.5.2 Treatment administration

Teduglutide is self-administered, and there are no teduglutide specific administrations costs except for an initial nurse-led appointment to instruct patients on how to self-administer the treatment. The training is assumed to take one hour with a unit cost of 580,81 kr., corresponding to the hourly wage of the nurse including overhead. This is calculated as per the DMC methods guide[8] based on a gross annual salary of 494,255 kr. (SIRKA,[91] Datasæt 00 2020), which is divided by 12 months, then divided by 141.83 hours per month, and then multiplied by 2 to account for overhead. The cost of nurse-led training can be switched off in the model.

Table 41 Treatment administration cost of teduglutide

Type of cost	Mean cost	Source
Self-injection training	DKK 581.81	DMC – Værdisætning af enhedsomkostninger[8] and SIRKA[91]

8.5.3 Treatment monitoring

As per its SmPC, teduglutide treatment requires a colonoscopy procedure at treatment initiation, after 1 and 2 years, and every 5 years thereafter.[72] The unit cost of these teduglutide-specific colonoscopies was sourced from DRG tariffs (DRG 2021: 06PR03 Koloskopi og polypektomi) with a unit cost of 5,485 kr. per colonoscopy.

Table 42 Monitoring costs of teduglutide

Type of cost	Mean cost	Source
Colonoscopy	DKK 5,485	DRG 2021: 06PR03 Koloskopi og polypektomi

Key: DRG, diagnose relaterede grupper. **Source**: https://sundhedsdatastyrelsen.dk/da/afregning-og-finansiering/takster-drg/takster-2021

8.5.4 Adverse Events

The rate of each adverse event, as presented in section **8.2.2.5**, is combined with the unit cost of managing that event to estimate the likely total cost of adverse events incurred in each model cycle. The unit cost of each adverse event included in the model is presented below in Table 43. Not all adverse events are assumed to be associated with a cost, because some events were judged to be largely transient, such that its management will not directly require health care resources. For example, 'headache' may typically be resolved by over-the-counter oral medication and is not associated with a cost in the model. Consequently, these are not listed in the below tables.

Table 43 Adverse events cost

Adverse event	Unit cost	Source (DRG 2021)
Abdominal distension	DKK 22,789	06MA14 Andre sygdomme i fordøjelsesorganerne, pat. mindst 18 år
Abdominal pain	DKK 22,789	06MA14 Andre sygdomme i fordøjelsesorganerne, pat. mindst 18 år
Arthralgia	DKK 9,602	21MA05 Forgiftning og toksisk virkning af lægemiddel, øvrige
Bacteraemia	DKK 42,770	18MA01 Sepsis
Catheter related infection	DKK 19,185	18MA09 Observation for infektion eller parasitær sygdom
Central line infection	DKK 19,185	18MA09 Observation for infektion eller parasitær sygdom
Constipation	DKK 2,673	06MA17 Observation for sygdom i fordøjelsesorganerne, u. endoskopi
Diarrhoea	DKK 5,130	06MA11 Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag.
Dizziness	DKK 285	70AK01 Lette akutte kontakter
Dyspnoea	DKK 285	70AK01 Lette akutte kontakter
Gastrointestinal stoma complication	DKK 5,130	06MA11 Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag.
Injection site haematoma	DKK 285	70AK01 Lette akutte kontakter
Injection site pain	DKK 285	70AK01 Lette akutte kontakter
Muscle spasms	DKK 285	70AK01 Lette akutte kontakter
Nausea	DKK 2,673	06MA17 Observation for sygdom i fordøjelsesorganerne, u. endoskopi
Peripheral oedema	DKK 1,529	40PR01 Lymfeødembehandling
Bacterial overgrowth	DKK 35,768	18MA08 Andre infektioner eller parasitære sygdomme
Pain	DKK 1,643	23PR01 Smertetilstande, kroniske, komplicerede
Procedural site reactions	DKK 285	70AK01 Lette akutte kontakter
Pyrexia	DKK 285	70AK01 Lette akutte kontakter
Renal colic	DKK 22,789	06MA14 Andre sygdomme i fordøjelsesorganerne, pat. mindst 18 år
Small intestinal stenosis	DKK 22,789	06MA14 Andre sygdomme i fordøjelsesorganerne, pat. mindst 18 år
Upper respiratory tract infection	DKK 15,166	03MA05 Mellemørebetændelse og øvre luftvejsinfektion, pat. mindst 18 år, u. kompl. bidiag.
Urinary tract infection	DKK 24,431	11MA07 Infektioner i nyrer og urinvej, pat. mindst 16 år
Vomiting	DKK 5,130	06MA11 Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag.

Key: DRG, diagnose relaterede grupper. **Source**: https://sundhedsdatastyrelsen.dk/da/afregning-og-finansiering/takster-drg/takster-2021

8.5.5 Complications

The unit cost of CKD is sourced from DRG tariff *DRG2021: 11MA02 Andre primære eller sekundære medicinske nyresygdomme uden dialyse*, reflecting the severity of the condition. The tariff of 34,245 kr. is applied for a full 28-day model cycle.

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Liver disease is divided into three stages: Non-progressed liver disease, fibrosis and cirrhosis. The unit cost of non-progressed liver disease is assumed to be low and is set to 0 in the model. The cost of fibrosis is sourced from the DRG tariff *DRG 2021: 18MA98, MDC18 1-dagsgruppe pat. mindst 7 år, Diagnosis: DK740: Leverfibrose* and is associated with a unit cost of 2,734 kr. The cost of cirrhosis is also sourced from DRG tariffs, *DRG 2021: 07MA05: Kronisk leversygdom uden komplikationer* with a unit cost of 30,893 kr. Analogously to CKD unit costs, these tariffs were chosen to reflect the severity of the condition and the unit costs are applied for a full 28-day model cycle.
When no progression of liver disease is modelled (base case), the average time spent in the three-liver disease sub-health states is used to calculate a weighted average of the cost per 28-day cycle, resulting in a cost of 24,802.98 kr. for overall liver disease per 28-day model cycle.

Table 44 Complication cost

Complication	Cost (DKK)	Source
Extensive fibrosis	2,734 kr.	DRG 2021, 18MA98: MDC18 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DK740: Leverfibrose
Cirrhosis	30,893 kr.	DRG 2021, 07MA05: Kronisk leversygdom uden komplikationer (trimpunkt 11)
Overall Liver Disease	24,802.98 kr.	Weighted average
Chronic Kidney Disease	34,245 kr.	DRG 2021, 11MA02: Andre primære eller sekundære medicinske nyresygdomme uden dialyse (trimpunkt 11)

Key: DRG, diagnose relaterede grupper. **Source**: https://sundhedsdatastyrelsen.dk/da/afregning-og-finansiering/takster-drg/takster-2021

8.5.6 Parenteral support-related costs

Finding an accurate estimate for PS-related costs has been challenging. One of the reasons for this is the fact that no two patients are alike, making it difficult to define a meaningful average cost for the PS-related health states. This issue with heterogeneity is particularly challenging due to the rarity of the disease, as no sufficient data source is available to provide us with accurate estimates. In the following, we provide our best estimates for the resource use and cost associated with each PS-related health state.

Initially, to identify accurate resource use estimates in the Danish healthcare system, we initiated a Delphi panel with Danish SBS-IF clinical experts. Unfortunately, after receiving the questions in the Delphi panel survey, Prof. Palle Jeppesen replied that it is his opinion that it is not possible to make accurate estimates for Denmark via a Delphi panel survey. Later, all but one of the other invited clinical experts provided similar feedback after being in dialogue with Prof. Jeppesen. Consequently, we only received input from one Danish clinical expert, Sine Obling (**List of experts**). Recognizing the uncertainty of our cost estimates, especially when based on the opinion of only one clinical expert, all PS cost inputs are manipulable in the 'PS cost' sheet of the Excel model, so the user can explore the impact of alternative cost inputs on the model results.

The resource use estimates for PS-related costs are consequently mainly based on a series of discussions with the NICE evidence review group (ERG), who conducted their own analysis of PS health state costs, along with the NICE appraisal committee (AC), for a previous NICE submission of teduglutide. We recognize that resource use may be different in Denmark compared to England, but we choose to utilize these foreign estimates anyway, because they are our best alternative source when lacking Danish data. When available, we have also applied estimates from the one Danish clinical expert that responded in the Danish Delphi panel survey[92]. Given the complexity of the resource use in the defined PS states, it is sought illustrated in Table 45, including pharmaceuticals, tests, complications, and healthcare provider time. Some cost elements related to treatment with parenteral support, such as parenteral support bags, will vary according to the level of parenteral support required. The majority of costs related to PS are sourced from the DMC cost catalogue[8] and DRG tariffs.[7] All unit costs for PS are presented in Table 46 followed by the aggregated costs for each PS state in Table 47.

Table 45 Resource use for PS-related health states

Cost item	Units	PS0	PS1	PS2	PS3	PS4	PS5	PS6	PS7	Cost group	Ressource use source
PN bag (≥8 ingredients) band A	day/ week	0	1	2	3	4	5	6	7	Hospital costs	UK Evidence Review Group (ERG)
Delivery	event/ month	0	2	2	2	2	2	2	2	Hospital costs	UK Evidence Review Group (ERG)
Nurse time (PS related, distinct from training costs)	hour/ week	0.0	0.8	1.6	2.4	3.2	4.0	4.8	5.6	Municipality costs	UK Evidence Review Group (ERG)
Taurolock	day/ week	0	1	2	3	4	5	6	7	Pharmaceuticals	UK Evidence Review Group (ERG)
Proton pump inhibitors	day	0	1	1	1	1	1	1	1	Pharmaceuticals	UK Evidence Review Group (ERG)
Antimotility agents	day	0	1	1	1	1	1	1	1	Pharmaceuticals	UK Evidence Review Group (ERG)
Fragmin 5	day	0	1	1	1	1	1	1	1	Pharmaceuticals	UK Evidence Review Group (ERG)
Ondansetron	day	0	1	1	1	1	1	1	1	Pharmaceuticals	UK Evidence Review Group (ERG)
Specialist visits (adults)	visit/ year	0	3	3	3	3	3	3	3	GP/Specialists	UK Evidence Review Group (ERG)
Specialist visits (paediatrics)	visit/ year	0	4	4	4	4	4	4	4	GP/Specialists	UK Evidence Review Group (ERG)
Haematology tests (paediatrics only)	tests/ year	0	4	4	4	4	4	4	4	Hospital costs	UK Evidence Review Group (ERG)
Inflammatory markers/Clinical biochemistry (paediatrics only)	tests/ year	0	4	4	4	4	4	4	4	Hospital costs	UK Evidence Review Group (ERG)
Line sepsis	episode/ year	0.00	0.23	0.26	0.30	0.33	0.38	0.44	0.51	Hospital costs	UK Evidence Review Group (ERG)
Line fracture occlusion (adult)	period/ year	0	1	1	1	1	1	1	1	Hospital costs	UK Evidence Review Group (ERG)
Line fracture occlusion (paediatric)	episode/ year	0	1	1	2	2	2	2	2	Hospital costs	UK Evidence Review Group (ERG)
PS administration time, patient	hour/ week	0	15	15	15	45	45	90	90	Patient/Relative	Danish clinical expert[92]
PS administration time, relative (adults)	hour/ week	0.00	2.50	2.50	2.50	15.00	15.00	25.00	25.00	Patient/Relative	Danish clinical expert[92]
PS administration time, relative (paediatrics)	hour/ week	0,00	3.75	3.75	3.75	22.50	22.50	37.50	37.50	Patient/Relative	Assumption: 30% more than adults
Support besides PS administration, doctor	hour/ month	0,50	0.50	0.50	0.50	1.00	1.00	2.00	2.00	Municipality costs	PS1-7: Danish clinical expert[92], PS0: Assumption
Support besides PS administration, nurse	hour/ month	0	2	2	2	2	2	4	4	Municipality costs	PS1-7: Danish clinical expert[92], PS0: Assumption
Hospitalisation (outpatient incl. visits to hepatologic clinic)	episode/ year	0	4	4	4	5	5	7	7	Hospital costs	PS1-7: Danish clinical expert[92], PS0: Assumption
Hospitalisation (outpatient incl. visits to hepatologic clinic)	episode/ year	0	4	4	4	5	5	7	7	Patient/Relative	PS1-7: Danish clinical expert[92], PS0: Assumption
Hospitalisation (inpatient) (avrg. inpatient stay: 7 days)	day/ year	0.00	2.33	2.33	2.33	7.00	7.00	14.00	14.00	Hospital costs	PS1-7: Danish clinical expert[92], PS0: Assumption
Hospitalisation (inpatient) transportation cost	episode/ year	0.00	0.33	0.33	0.33	1.00	1.00	2.00	2.00	Patient/Relative	PS1-7: Danish clinical expert[92], PS0: Assumption
General practitioner visits	episode/ year	1	2	2	2	4	4	6	6	GP/Specialists	PS1-7: Danish clinical expert[92], PS0: Assumption

Table 46 Unit cost of PS resources

Cost item	Units	Unit cost	Cost source
PN bag (≥8 ingredients) band A	day/ week	1,050.00 kr.	*Described in section* Parenteral support-related costs***8.5.6***
Delivery	event/ month	98.56 kr.	*Transport: 3.52 * 28 km*
Nurse time (PS related, distinct from training costs)	hour/ week	550.00 kr.	*Værdisætning af enhedsomkostninger v1.2 - Timeomkostning for ikke ledende sygeplejerske ansat i kommunen*
Taurolock	day/ week	- kr.	*Price could not be identified – assumed to be 0 kr.*
Proton pump inhibitors	day	0.10 kr.	*Medicinpriser.dk (Omestad 595964 - AIP 10,70kr)*
Antimotility agents	day	10.48 kr.	*Medicinpriser.dk (Imolope 154521 - AIP 125,74kr)*
Fragmin 5	day	17.45 kr.	*Medicinpriser.dk (Fragmin 513043 - AIP 524.00kr)*
Ondansetron	day	3.20 kr.	*Medicinpriser.dk (Ondansetron "Bluefish" 140709 - AIP 160.00kr)*
Specialist visits (adults)	visit/ year	646.87 kr.	*Værdisætning af enhedsomkostninger v1.2 - Konsultation hos speciallæge i intern medicin*
Specialist visits (paediatrics)	visit/ year	646.87 kr.	*Værdisætning af enhedsomkostninger v1.2 - Konsultation hos speciallæge i intern medicin*
Haematology tests (paediatrics only)	tests/ year	393.00 kr.	*Trombocytter - 214kr* https://labportal.rh.dk/LabPortal.asp?Mode=View&Id=5437 *Alanintransaminase - 24kr* https://labportal.rh.dk/LabPortal.asp?Mode=View&Id=3982 *Hæmoglobin; B - 31kr* https://labportal.rh.dk/LabPortal.asp?Mode=View&Id=2403 *Bilirubiner - 24kr* https://labportal.rh.dk/LabPortal.asp?Mode=View&Id=3996 *Fosfat - 24kr* https://labportal.rh.dk/LabPortal.asp?Mode=View&Id=6749 *Magnesium - 24kr* https://labportal.rh.dk/LabPortal.asp?Mode=View&Id=6755 *Kreatinin - 24kr* https://labportal.rh.dk/LabPortal.asp?Mode=View&Id=4000 *Natrium - 14kr* https://labportal.rh.dk/LabPortal.asp?Mode=View&Id=5242 *Kalium - 14kr* https://labportal.rh.dk/LabPortal.asp?Mode=View&Id=3947
Inflammatory markers/Clinical biochemistry (paediatrics only)	tests/ year	24.00 kr.	*C-reaktivt protein - 24kr* https://labportal.rh.dk/LabPortal.asp?Mode=View&Id=6803 *Sedimentationsreaktion - 10kr* https://labportal.rh.dk/LabPortal.asp?Mode=View&Id=6795
Line sepsis	episode/ year	42,770.00 kr.	*DRG 2021, 18MA01: Diagnosis: Sepsis (trimpunkt 15)*
Line fracture occlusion (adult)	period/ year	2,352.00 kr.	*01PR03 Kontrol af medicinpumpe*
Line fracture occlusion (paediatric)	episode/ year	2,352.00 kr.	*01PR03 Kontrol af medicinpumpe*
PS administration time, patient	hour/ week	179.00 kr.	*LONS20*
PS administration time, relative (adults)	hour/ week	179.00 kr.	*LONS20*
PS administration time, relative (paediatrics)	hour/ week	179.00 kr.	*LONS20*
Support besides PS administration, doctor	hour/ month	811.49 kr.	*Værdisætning af enhedsomkostninger v1.2 - Kommunernes og Regionernes Løndatakontor, SIRKA, Datasæt 00 2020, Kørsel 3.8.2021 12.43.34 - brutto årsløn =690,566 delt med 12 måneder delt med 141,83 timer gange 2 (overhead)*
Support besides PS administration, nurse	hour/ month	580.81 kr.	*Værdisætning af enhedsomkostninger v1.2 - Kommunernes og Regionernes Løndatakontor, SIRKA, Datasæt 00 2020, Kørsel 3.8.2021 12.43.34 - brutto årsløn =494.255 delt med 12 måneder delt med 141,83 timer gange 2 (overhead)*

Hospitalisation (outpatient incl. visits to hepatologic clinic)	episode/ year	2,343.00 kr.	*DRG 2021, 06MA98: MDC06 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DK912B Korttarmssyndrom*
Hospitalisation (outpatient incl. visits to hepatologic clinic)	episode/ year	98.56 kr.	*Transport: 3.52 * 28 km*
Hospitalisation (inpatient) (avrg. inpatient stay: 7 days)	day/ year	22,992.00 kr.	*DRG 2021, 06MA14: Andre sygdomme i fordøjelsesorganerne, pat. mindst 18 år, Diagnosis: DK912B Korttarmssyndrom (trimpunkt 6)* *For børn 3,825kr (DRG 2021, 06MA15: Andre sygdomme i fordøjelsesorganerne, ekskl. svulster, pat. 0-17 år, Diagnosis: DK912B Korttarmssyndrom (kontaktdage 2))*
Hospitalisation (inpatient) transportation cost	episode/ year	98.56 kr.	*Transport: 3.52 * 28 km*
General practitioner visits	episode/ year	143.44 kr.	*Konsultation*

Key: PS, parenteral support

Identifying a unit cost for PS bags per PS day was particularly challenging. For the model, we assumed that each patient needs 2200 kcal on average per PS day. We then identified SmofKabiven itemno. 154640 on www.medicinpriser.dk, which is a standard product for parenteral support, with a pharmacy purchasing price of 2,100 kr. for 4 x 1970 ml, corresponding to 4 x 2200 kcal. However, SmofKabiven is not suited for SBS-IF patients, who require specific combinations of nutrients based on their individual needs, which can change over time. To account for this, the price of SmofKabiven is multiplied by a factor of 2, resulting in a crude unit cost of (2,100 kr. / 4 bags) x 2 = 1,050 kr. per PS day, which is applied in the model. While this is currently our best estimate, we had originally aimed to elicit the unit cost via the Danish Delphi panel, and we recognize that the current estimate is associated with significant uncertainty.

Table 47 Cycle cost per PS health state

Health state	Cost per 28 days cycle *Adults*	Cost per 28 days cycle *Pediatrics*
PS7	162,670.59 kr.	171,978.35 kr.
PS6	156,481.08 kr.	165,788.84 kr.
PS5	93,598.61 kr.	99,326.37 kr.
PS4	87,474.67 kr.	93,202.43 kr.
PS3	41,600.07 kr.	42,852.84 kr.
PS2	35,508.93 kr.	36,581.38 kr.
PS1	29,450.56 kr.	30,523.02 kr.
PS0	957.74 kr.	957.74 kr.

8.5.7 Patient and transportation cost

Time spend by patients and relatives and transportation cost are included in the model in line with the DMC cost catalog.[8] The unit cost per patient hour is assumed to be 179 kr. and the transportation cost per visit was assumed to be 98.56 kr. See Table 48. These costs are integrated in the overall costs for the 8 PS states. We intended to source the time spent by patients and relatives on PS via a Delphi panel. However, as mentioned in section **8.5.6**, we received only one response to our initial Delphi questionnaire, which we have based our resource use estimate upon. For an overview of the time usage and transportation frequencies, see Table 46.

Table 48 Unit cost for estimation of patient and transportation cost

Resource	Unit cost	Source
Average hourly wage	179.00 kr.	DMC cost catalog[8]
Transportation cost per visit	98.58 kr.	DMC cost catalog[8]

8.6 Results

8.6.1 Base case overview

The base case, as described throughout the health economic section, is summarized, and presented in Table 49.

Table 49 Base case overview

	Variable	Base case setting
Model type	Markov model	*N/A*
Comparator	Standard care	*N/A*
Perspective	Limited societal perspective	*N/A*
Settings	Time horizon	40 years (lifetime for adults) 94 years (lifetime for pediatrics)
	Cycle length	28 days
	Discounting	0-35 years 3.5% 36-70 years 2.5% >70 years 1.5%
	Half-cycle correction	Included
	Clinical data	STEPS and STEPS-2
Population	Starting age	50 (adults) 6 (pediatrics)
	Female (%)	53.5%
Baseline distribution	PS7	52%
	PS6	18%
	PS5	6%
	PS4	13%
	PS3	11%
	PS2	0%
	PS1	0%
	PS0 (enteral autonomy)	0%
Assumptions	Adverse Events	All adverse events that occurred in more the 5% of patients in either arm of STEPS trial included
	Liver disease	Included
	Chronic Kidney Disease	Excluded
	Extrapolation of transition probabilities	**Teduglutide**: Last set of transition probabilities applied to patients continuing treatment beyond 30 months, until 5 years from baseline. Remain in same PS health state after that.
		Standard care: Patients revert to baseline PS requirement at the end of 24 weeks (no movement)
	Stopping rules	Teduglutide stopping rule at 24 weeks from baseline. Those failing to achieve a 20% volume reduction vs baseline or 1+ day per week reduction in PS dependency are discontinued, staying in the same PS health state afterwards
		No stopping rule for patients achieving PS-independence, continuing treatment for life
	Overall survival	Log-Logistic parametric survival curves fitted to data from Salazar (2021) for adults and Pironi (2011) for pediatrics.
	Teduglutide discount	0%
	Measurement and valuation of health effects	Age adjusted utilities based on UK Vignette study, Ballinger (2018)
	Nurse-led training cost	Included
Key: PS: parenteral support		

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

8.6.2 Base case results

The results of the base case analyses are presented in section **8.6.2.1**, Table 50 for adults, and in section **8.6.2.2**, Table 53 for pediatrics. The discounted total costs in each arm of the base case are split into the price of teduglutide, administration cost (nurse led administration training), monitoring cost (teduglutide related colonoscopies), disease specific costs (all PS-related costs except patient, relative and transportation costs), cost of adverse events, and Patient- and transportation cost (time and transportation by patient and relatives) in Table 51 for adults, and Table 54 for pediatrics. The discounted total QALYs in each arm of the base case analyses were split into each Markovian health state and presented in Table 52 for adults, and Table 55 for pediatrics. Finally, figures containing Markov traces for the PS0 health state, PS1-3 health states combined, PS4-5 health states combined and PS6-7 health states combined are presented for the teduglutide arm and standard care am for adults in Figure 29 and Figure 30, respectively, and for pediatrics in Figure 31 and Figure 32, respectively.

8.6.2.1 Adults

Table 50 Base case results, adults

	Total			Incremental			ICER
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Standard Care	22.986.574,39 kr.	12,73	5,14				
Teduglutide	26.483.343,01 kr.	12,73	6,53	3.496.768,61 kr.	0,00	1,39	**2.507.713,23 kr.**

Table 51 Base case results – cost breakdown, adults

	Teduglutide	Standard Care
Teduglutide costs	9.994.696,83 kr.	- kr.
Administration costs	580,81 kr.	- kr.
Monitoring costs	15.304,27 kr.	- kr.
Regional disease-specific costs	5.970.727,11 kr.	8.208.853,54 kr.
Municipal disease-specific costs	2.255.405,96 kr.	3.025.444,68 kr.
Costs of adverse events	481.868,22 kr.	616.133,66 kr.
Patient- and transportation costs	7.764.759,81 kr.	11.136.142,52 kr.
Total	**26.483.343,01 kr.**	**22.986.574,39 kr.**

Table 52 Base case results – QALY breakdown, adults

	Teduglutide	Standard Care
No PS	1,91	0,00
PS 1 day per week	0,03	0,00
PS 2 days per week	0,10	0,01
PS 3 days per week	1,27	0,86
PS 4 days per week	1,21	0,91
PS 5 days per week	0,21	0,37
PS 6 days per week	0,20	0,87
PS 7 days per week	1,67	2,17
Liver disease Utility decrement	-0,05	-0,06
CKD Utility decrement	0,00	0,00
Total	**6,53**	**5,14**

Figure 29 Markov trace, teduglutide arm, adults

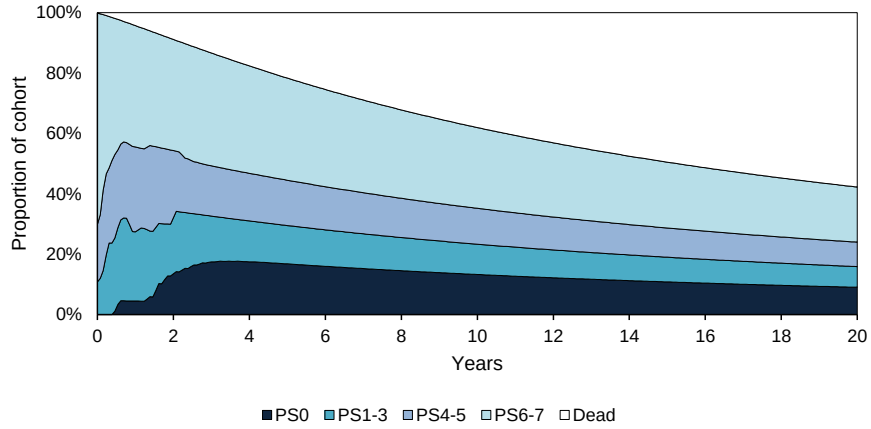
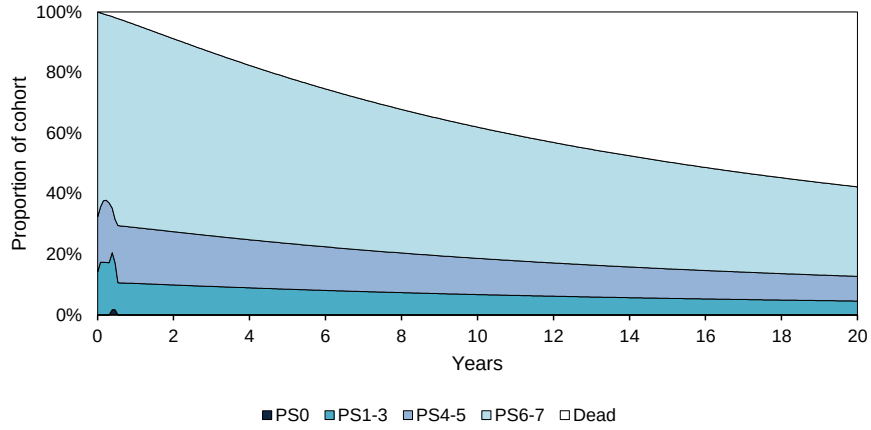


Figure 30 Markov trace, standard care arm, adults



8.6.2.2 Pediatrics

Table 53 Base case results, pediatrics

	Total			Incremental			ICER
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Standard Care	45.398.202,27 kr.	23,66	9,22				
Teduglutide	50.402.038,32 kr.	23,66	11,86	5.003.836,04 kr.	0,00	2,64	**1.894.267,81 kr.**

Table 54 Base case results – cost breakdown, pediatrics

	Teduglutide	Standard Care
Teduglutide costs	18.220.362,62 kr.	- kr.
Administration costs	580,81 kr.	- kr.
Monitoring costs	21.542,09 kr.	- kr.
Regional disease-specific costs	11.245.016,07 kr.	15.615.662,78 kr.
Municipal disease-specific costs	4.165.747,51 kr.	5.642.050,84 kr.
Costs of adverse events	875.022,65 kr.	1.144.969,75 kr.
Patient- and transportation costs	15.873.766,56 kr.	22.995.518,91 kr.
Total	**50.402.038,32 kr.**	**45.398.202,27 kr.**

Table 55 Base case results – QALY breakdown, pediatrics

	Teduglutide	Standard Care
No PS	3,70	0,00
PS 1 day per week	0,03	0,00
PS 2 days per week	0,11	0,01
PS 3 days per week	2,32	1,56
PS 4 days per week	2,19	1,67
PS 5 days per week	0,32	0,68
PS 6 days per week	0,34	1,59
PS 7 days per week	3,05	3,95
Liver disease Utility decrement	-0,19	-0,24
CKD Utility decrement	0,00	0,00
Total	**11,86**	**9,22**

Figure 31 Markov trace, teduglutide arm, pediatrics

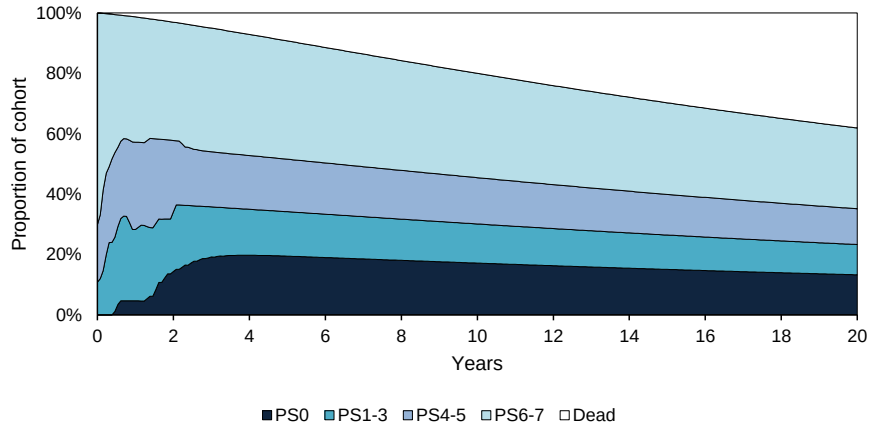
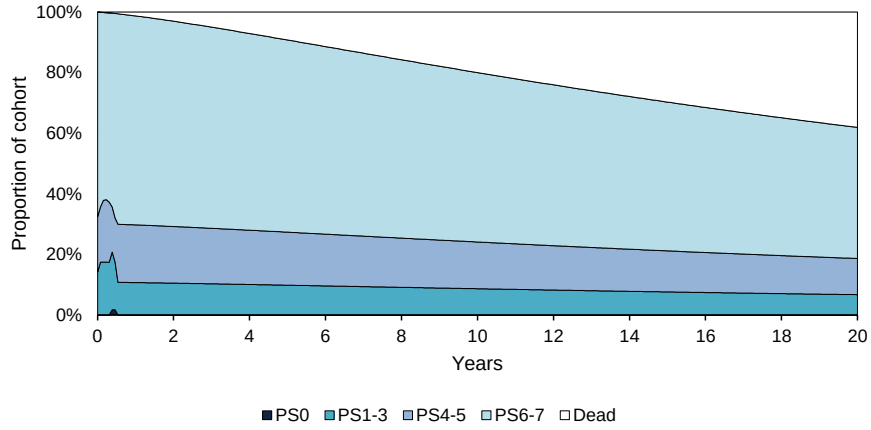


Figure 32 Markov trace, standard care arm, pediatrics



8.7 Sensitivity analyses

For the deterministic sensitivity analysis, both scenario analyses and one-way sensitivity analyses were conducted for adults (**8.7.1.1**), and pediatrics (**8.7.1.2)**. A number of relevant scenarios identified throughout the health-economic section are explored in the scenario analyses. All scenarios are listed in the 'Scenarios' sheet of the Excel model. Scenarios include alternative time horizons (5, 10, and 30 years plus 50 years for adults and 70 years for pediatrics),

alternative utilities (Lachaine 2016 and STEPS), exclusion of liver complications, inclusion of kidney disease, transition probabilities based on combined data from STEPS and 004, two alternative scenarios for extrapolating teduglutid effectiveness beyond the duration of the trials (last observed transition probability until death, and remain in same health state until death), an additional scenario for extrapolating standard care transition probabilities (remain in same PS health state until death), alternative stopping rules (no stopping rules, and stopping rule based on non-response after 24 weeks in terms of 20% PS volume reduction), as well as alternative survival models (Exponential, Gompertz, Weibull, Log-Normal, and, for adults, Generalized Gamma).

The 10 scenarios with the highest impact on the ICER are presented in horizontal bar charts as deviations from the base case ICER in Figure 33 for adults, and Figure 36 for pediatrics. The ICERS from all tested scenarios are included in Table 56 for adults and Table 58 for pediatrics.

For the one-way sensitivity analyses (OWSA), upper and lower bounds were identified by assuming a distribution around the base case value as a mean value with a standard error assumed to be 20% of the mean (unless empirical estimates exist for the parameter). The distributions applied are Gamma for cost inputs, Beta for utilities, probabilities, and rates, Normal for the exponential model, Multivariate Normal for other survival models, and Dirichlet with cumulative Gamma for the transition probabilities (to ensure that each row of the transition probability matrices sums to unity). Upper and lower bounds were set to 0.025 and 0.975. All parameters and distributions are listed in the 'Parameters' sheet of the Excel model. Results for adults are presented in a Tornado diagram showing the 10 parameters with highest impact on the net-monetary (NMB) in Figure 34, and the 20 parameters with highest impact on NMB are listed in Table 57. These results are presented for pediatrics in Figure 37 and Table 59, respectively. The NMB is calculated as follows, with an assumed willingness to pay of 500,000 kr.

$$NMB = \lambda \Delta Q - \Delta C$$

Where: NMB: net monetary benefit; λ: willingness to pay for a QALY; ΔQ: incremental QALYs; ΔC incremental costs

Finally, as per the DMC methods guide, analyses were conducted to explore the relationship between pack price and ICER in the base case analyses. These results are presented for adults and pediatrics in Figure 35 and

Figure 38, respectively.

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

8.7.1 Deterministic sensitivity analyses

8.7.1.1 Adults

Figure 33 Scenario analysis, adults

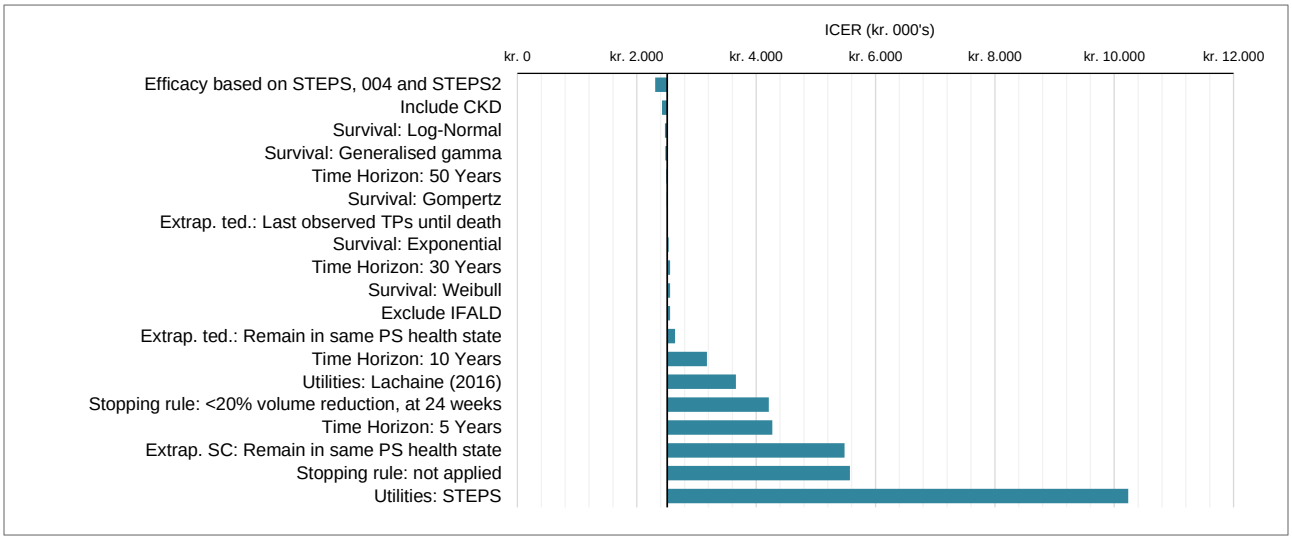


Table 56 Scenario analysis, adults

Scenario	ICER (kr. 000s)	*Explanation*
Efficacy based on STEPS, 004 and STEPS2	2.307 kr.	*Transition probabilities based on combined data from STEPS, STEPS-2 and 004*
Include CKD	2.423 kr.	*Include chronic kidney disease as complication*
Survival: Log-Normal	2.470 kr.	*Survival based on Log-Normal model*
Survival: Generalised gamma	2.479 kr.	*Survival based on Generalised gamma model*
Time Horizon: 50 Years	2.495 kr.	*Time horizon 50 years*
Survival: Gompertz	2.501 kr.	*Survival based on Gompertz model*
Extrap. ted.: Last observed TPs until death	2.506 kr.	*Teduglutide effectiveness extrapolated by applying the last observed transition probability until death*
Survival: Exponential	2.533 kr.	*Survival based on Exponential model*
Time Horizon: 30 Years	2.558 kr.	*Time horizon 30 years*
Survival: Weibull	2.559 kr.	*Survival based on Weibull model*
Exclude IFALD	2.559 kr.	*Exclude intestinal failure associated liver disease complication*
Extrap. ted.: Remain in same PS health state	2.642 kr.	*Teduglutide effectiveness extrapolated by patients remaining in same PS health state until death*
Time Horizon: 10 Years	3.174 kr.	*Time horizon 10 years*
Utilities: Lachaine (2016)	3.659 kr.	*Utility values from Lachaine (2016) applied*
Stopping rule: <20% volume reduction, at 24 weeks	4.213 kr.	*Patients in the teduglutide arm discontinue treatment if they do not achieve at least 20% reduction in PS volume at 24 weeks*
Time Horizon: 5 Years	4.272 kr.	*Time horizon 5 years*
Extrap. SC: Remain in same PS health state	5.482 kr.	*Standard care outcomes are extrapolated by patients remaining in the same PS health state until death*
Stopping rule: not applied	5.570 kr.	*All patients in the teduglutide arm remains on treatment until death*
Utilities: STEPS	10.233 kr.	*Utility values from STEPS applied*

Figure 34 One-way sensitivity analysis Tornado diagram, adults

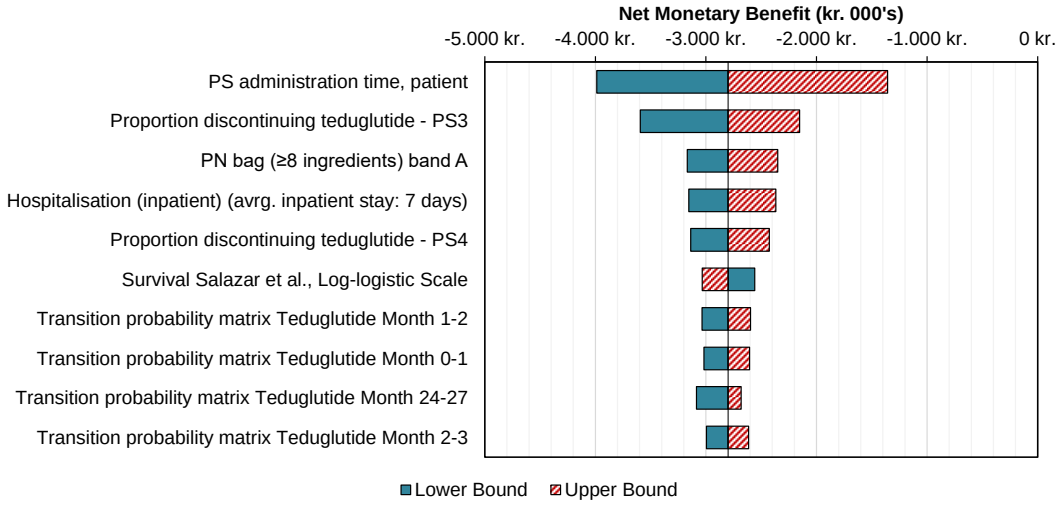
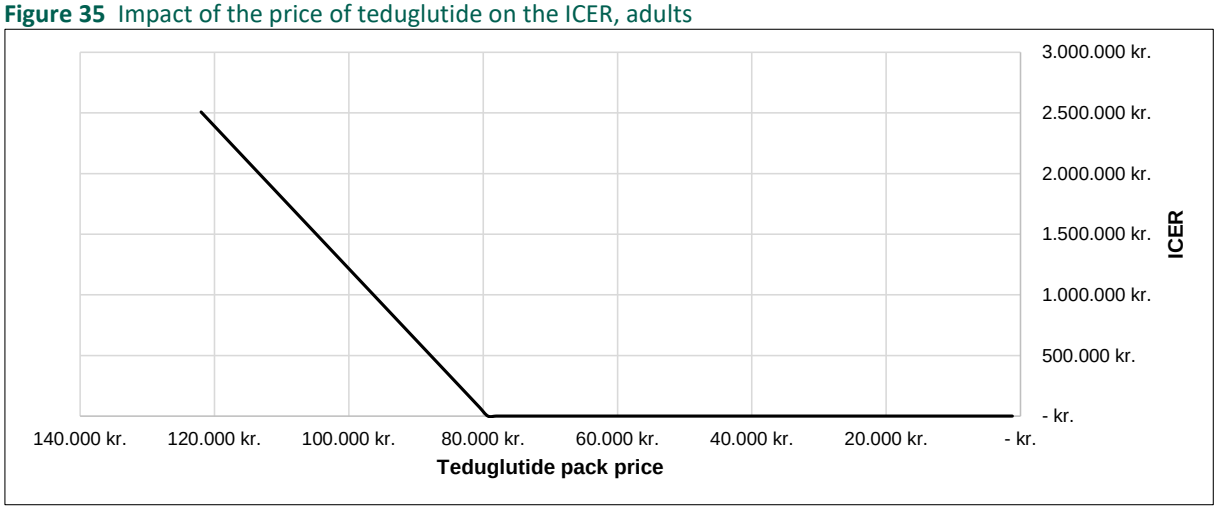


Table 57 One-way sensitivity analysis results, adults

Rank	Parameter	Lower Bound	Upper Bound	Difference
1	PS administration time, patient	-3.988.275,26 kr.	-1.356.335,80 kr.	2.631.939,46 kr.
2	Proportion discontinuing teduglutide - PS3	-3.594.509,66 kr.	-2.152.096,63 kr.	1.442.413,03 kr.
3	PN bag (≥8 ingredients) band A	-3.169.338,62 kr.	-2.350.619,32 kr.	818.719,30 kr.
4	Hospitalisation (inpatient) (avrg. inpatient stay: 7 days)	-3.154.848,10 kr.	-2.368.212,48 kr.	786.635,61 kr.
5	Proportion discontinuing teduglutide - PS4	-3.137.750,00 kr.	-2.426.482,81 kr.	711.267,19 kr.
6	Survival Salazar et al., Log-logistic Scale	-2.558.614,47 kr.	-3.033.209,20 kr.	474.594,73 kr.
7	Transition probability matrix Teduglutide Month 1-2	-3.036.199,58 kr.	-2.596.070,81 kr.	440.128,77 kr.
8	Transition probability matrix Teduglutide Month 0-1	-3.018.729,84 kr.	-2.605.722,77 kr.	413.007,07 kr.
9	Transition probability matrix Teduglutide Month 24-27	-3.085.684,33 kr.	-2.681.628,70 kr.	404.055,64 kr.
10	Transition probability matrix Teduglutide Month 2-3	-2.995.996,48 kr.	-2.614.088,12 kr.	381.908,36 kr.
11	Nurse time (PS related, distinct from training costs)	-2.954.518,32 kr.	-2.611.435,94 kr.	343.082,37 kr.
12	Transition probability matrix Teduglutide Month 18-21	-3.012.929,89 kr.	-2.702.575,47 kr.	310.354,42 kr.
13	Transition probability matrix Teduglutide Month 15-18	-2.955.973,23 kr.	-2.672.673,52 kr.	283.299,71 kr.
14	Utility decrement PS6	-2.931.974,51 kr.	-2.658.936,34 kr.	273.038,16 kr.
15	Utility decrement PS7	-2.931.446,90 kr.	-2.663.753,13 kr.	267.693,78 kr.
16	Transition probability matrix Teduglutide Month 5-6	-2.761.119,65 kr.	-3.007.807,71 kr.	246.688,06 kr.
17	Proportion discontinuing teduglutide - PS5	-2.915.680,72 kr.	-2.671.468,81 kr.	244.211,92 kr.
18	Transition probability matrix Teduglutide Month 4-5	-2.941.945,29 kr.	-2.720.019,35 kr.	221.925,94 kr.
19	Transition probability matrix Teduglutide Month 21-24	-2.956.006,86 kr.	-2.741.388,06 kr.	214.618,80 kr.
20	Proportion discontinuing teduglutide - PS6	-2.892.613,56 kr.	-2.690.814,59 kr.	201.798,97 kr.

Figure 35 Impact of the price of teduglutide on the ICER, adults



8.7.1.2 Pediatrics

Figure 36 Scenario analysis, pediatrics

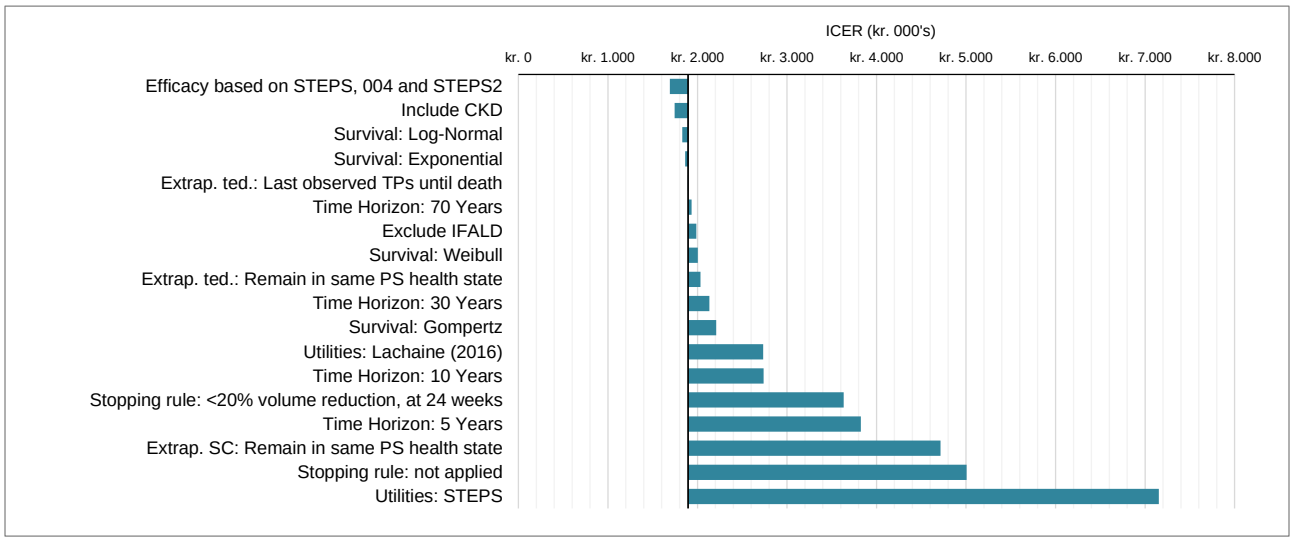


Table 58 Scenario analysis, pediatrics

Scenario	ICER (kr. 000s)	*Explanation*
Efficacy based on STEPS, 004 and STEPS2	1.693 kr.	*Transition probabilities based on combined data from STEPS, STEPS-2 and 004*
Include CKD	1.745 kr.	*Include chronic kidney disease as complication*
Survival: Log-Normal	1.830 kr.	*Survival based on Log-Normal model*
Survival: Exponential	1.863 kr.	*Survival based on Exponential model*
Extrap. ted.: Last observed TPs until death	1.892 kr.	*Teduglutide effectiveness extrapolated by applying the last observed transition probability until death*
Time Horizon: 70 Years	1.934 kr.	*Time horizon 70 years*
Exclude IFALD	1.988 kr.	*Exclude intestinal failure associated liver disease complication*
Survival: Weibull	2.003 kr.	*Survival based on Weibull model*
Extrap. ted.: Remain in same PS health state	2.033 kr.	*Teduglutide effectiveness extrapolated by patients remaining in same PS health state until death*

Time Horizon: 30 Years	2.133 kr.	*Time horizon 30 years*
Survival: Gompertz	2.209 kr.	*Survival based on Gompertz model*
Utilities: Lachaine (2016)	2.735 kr.	*Utility values from Lachaine (2016) applied*
Time Horizon: 10 Years	2.739 kr.	*Time horizon 10 years*
Stopping rule: <20% volume reduction, at 24 weeks	3.632 kr.	*Patients in the teduglutide arm discontinue treatment if they do not achieve at least 20% reduction in PS volume at 24 weeks*
Time Horizon: 5 Years	3.826 kr.	*Time horizon 5 years*
Extrap. SC: Remain in same PS health state	4.714 kr.	*Standard care outcomes are extrapolated by patients remaining in the same PS health state until death*
Stopping rule: not applied	5.007 kr.	*All patients in the teduglutide arm remains on treatment until death*
Utilities: STEPS	7.153 kr.	*Utility values from STEPS applied*

Figure 37 One-way sensitivity analysis Tornado diagram, pediatrics

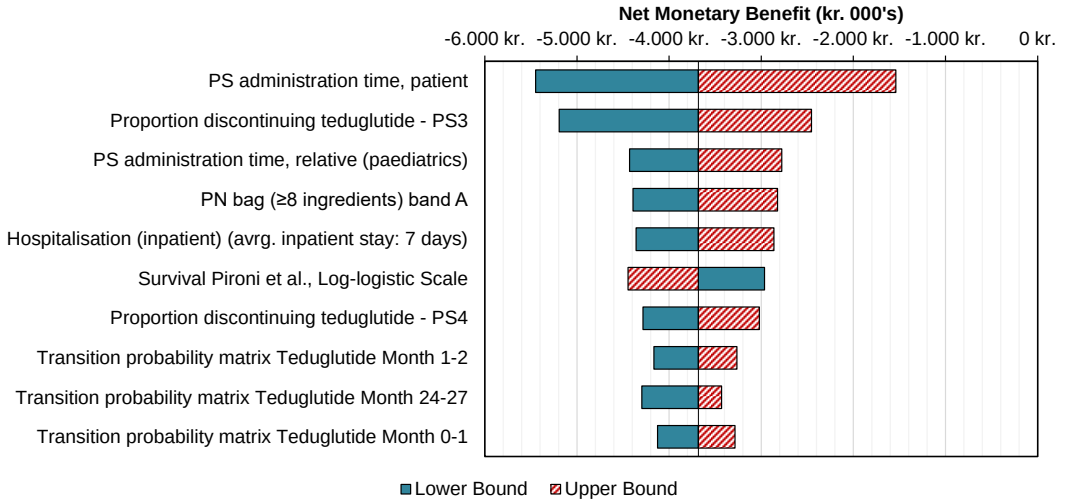


Table 59 One-way sensitivity analysis results, pediatrics

Rank	Parameter	Lower Bound	Upper Bound	Difference
1	PS administration time, patient	-5.448.798,71 kr.	-1.539.232,64 kr.	3.909.566,07 kr.
2	Proportion discontinuing teduglutide - PS3	-5.192.400,60 kr.	-2.453.680,13 kr.	2.738.720,46 kr.
3	PS administration time, relative (pediatrics)	-4.428.517,14 kr.	-2.777.972,13 kr.	1.650.545,01 kr.
4	PN bag (≥8 ingredients) band A	-4.391.798,25 kr.	-2.822.553,10 kr.	1.569.245,16 kr.
5	Hospitalisation (inpatient) (avrg. inpatient stay: 7 days)	-4.359.205,98 kr.	-2.862.123,88 kr.	1.497.082,10 kr.
6	Survival Pironi et al., Log-logistic Scale	-2.965.056,18 kr.	-4.445.799,71 kr.	1.480.743,53 kr.
7	Proportion discontinuing teduglutide - PS4	-4.282.853,33 kr.	-3.021.353,82 kr.	1.261.499,51 kr.
8	Transition probability matrix Teduglutide Month 1-2	-4.164.934,71 kr.	-3.262.863,81 kr.	902.070,90 kr.
9	Transition probability matrix Teduglutide Month 24-27	-4.296.857,18 kr.	-3.431.121,14 kr.	865.736,05 kr.
10	Transition probability matrix Teduglutide Month 0-1	-4.125.422,93 kr.	-3.285.169,45 kr.	840.253,48 kr.
11	Transition probability matrix Teduglutide Month 2-3	-4.093.460,92 kr.	-3.284.701,75 kr.	808.759,18 kr.
12	Nurse time (PS related, distinct from training costs)	-3.980.050,64 kr.	-3.322.462,19 kr.	657.588,45 kr.
13	Transition probability matrix Teduglutide Month 18-21	-4.132.210,74 kr.	-3.478.608,77 kr.	653.601,97 kr.
14	Transition probability matrix Teduglutide Month 15-18	-3.998.193,11 kr.	-3.423.297,78 kr.	574.895,32 kr.
15	Utility decrement PS6	-3.926.062,39 kr.	-3.424.954,13 kr.	501.108,26 kr.
16	Transition probability matrix Teduglutide Month 4-5	-3.976.227,77 kr.	-3.495.272,69 kr.	480.955,08 kr.
17	Utility decrement PS7	-3.917.824,13 kr.	-3.441.281,09 kr.	476.543,05 kr.
18	Transition probability matrix Teduglutide Month 21-24	-4.014.883,47 kr.	-3.559.389,26 kr.	455.494,21 kr.
19	Proportion discontinuing teduglutide - PS5	-3.895.777,89 kr.	-3.448.374,73 kr.	447.403,15 kr.
20	Proportion discontinuing teduglutide - PS6	-3.845.503,39 kr.	-3.493.183,45 kr.	352.319,94 kr.

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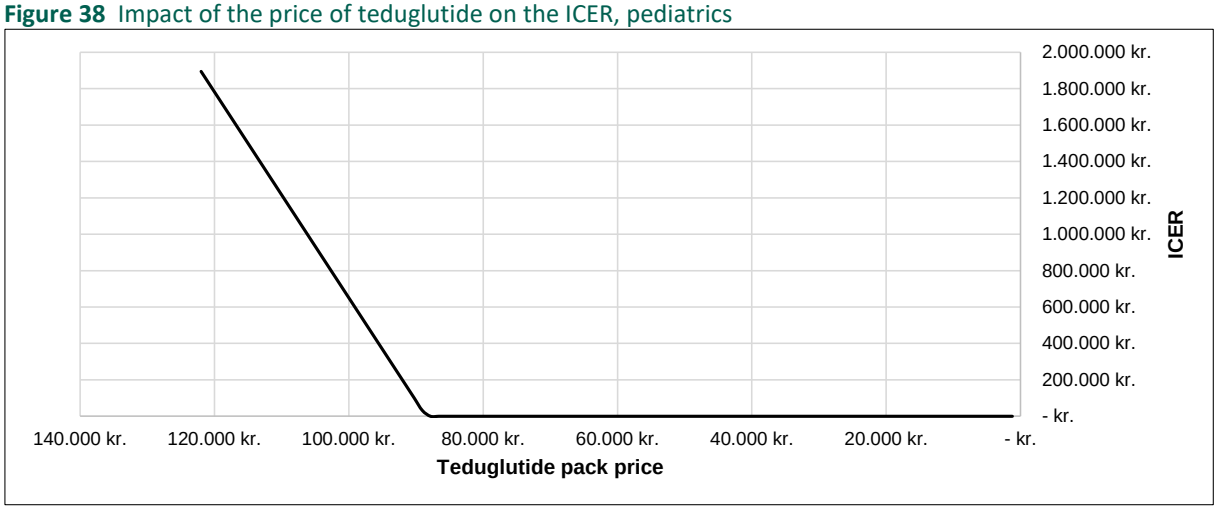
Figure 38 Impact of the price of teduglutide on the ICER, pediatrics



8.7.2 Probabilistic sensitivity analyses

A probabilistic sensitivity analysis (PSA) was performed to assess the overall parameter uncertainty in the model. This involved simultaneously sampling all input values from their underlying or estimated distributions. These are all shown in the 'Parameters' worksheet of the Excel model and in **Appendix J**. The parameter distributions are the same as described in section **8.7.1**.

Transition probabilities were included in the PSA by using a Dirichlet distribution, applying a set of Bayesian priors to the transition probabilities between states. In the primary PSA, the priors were all set to 0. Consequently, all transition probabilities larger than 0 were varied in the PSA, i.e., only transitions that were observed in STEPS. Setting the priors to 0 therefore does not allow transitions out of PS0. To assess the impact of this assumption, Bayesian priors were applied to the probability of staying in the same state (0.5), going up by 1 state (0.2), e.g., from PS0 to PS1, and going down by one state (0.3), e.g., from PS1 to PS0. The Dirichlet distribution of transition probabilities from one state to the other possible states are still determined primarily by the observed data, yet a distribution is created around each individual probability, given the other transition probabilities. Thus, each row of the transition probability matrix (i.e., a set of transitions from one state to all other states, including staying in that state) still sums to 1 in every PSA run, while the individual probabilities are varied in each PSA iteration.

A consequence of applying vague priors around each transition probability is that patients can have their need for PS both decline and escalate in every cycle. In the STEPS trial, only few patients in either relevant arm was seen to escalate their PS needs between any 4-week assessment points (as can be seen in the model in the 'Lists' sheet showing the patient-level data). This PSA therefore suggests the possibility of transitions between states which were only very rarely observed in the clinical trial, leading to, for instance, PS independent patients transitioning back to PS1 in the PSA (the extent of which is dependent on the individual random draw for the No PS -> PS1 probability). This leads to worse outcomes in the teduglutide arm in the PSA with alternative Bayesian priors compared to the deterministic model, where in the clinical trial PS independent patients remained PS independent until the end of the trial. Conversely, the placebo arm has better outcomes on average due to the high proportion of patients on PS7, for which the only transition out of that state possible in the PSA is to PS6. To summarize, in the PSA with informed priors greater than zero, patients in No PS can transition back to PS1, and patients on PS7 can transition to PS6, narrowing the QALY gap compared to the deterministic model, leading to a higher ICER for teduglutide.

The values used for the Bayesian informed priors are assumptions that have not been clinically validated, due to the difficulty to elicit Bayesian priors using expert clinician input, because of the technical nature of informed Bayesian priors. The 3 mentioned informed Bayesian priors can be changed in the 'Controls' sheet of the Excel model, or each individual prior can be updated in the 'Lists' sheet.

For adults, the probabilistic ICER (average ICER over 5.000 PSA iterations) in the base case is 2.549.496 kr. per QALY gained, and 2.517.611 kr. in the PSA with alternative priors, corresponding to an increase of 10.7% from allowing transitions out of PS0, and allowing more transitions to higher PS states than what was observed in the clinical trials. For pediatrics, the base case PSA ICER is 1.956.599 kr. compared to 2.121.747 kr. in the scenario with alternative priors, corresponding to an increase of 8.4%.

PSA scatter plots of 5.000 PSA runs for adults are presented in Figure 39 for adults, and Figure 43 for pediatrics. Cost-effectiveness acceptability curve (CEACs) for adults is presented in Figure 40, and for pediatrics in Figure 44. Probabilistic ICERs are presented with the base case deterministic ICERS in Table 60 for adults and Table 62 for pediatrics. Results of the PSAs with alternative informed Bayesian priors are presented for adults in Figure 41, Figure 42 and Table 61, and for pediatrics in Figure 45, Figure 46 and Table 63**.**

8.7.2.1 Adults

Figure 39 Probabilistic Sensitivity Analysis Scatter Plot, adults

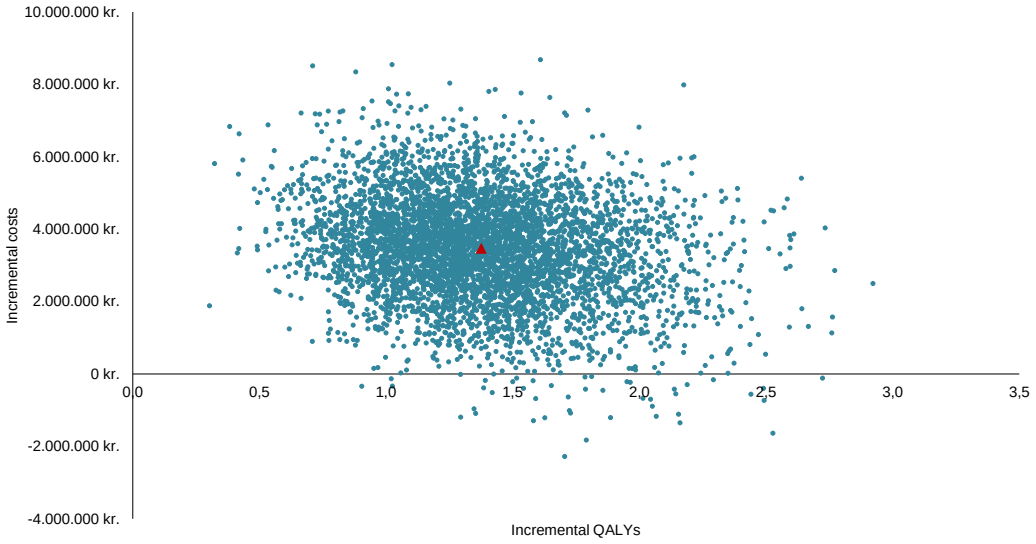


Figure 40 Probabilistic Sensitivity Analysis – Cost Effectiveness acceptability Curve, adults

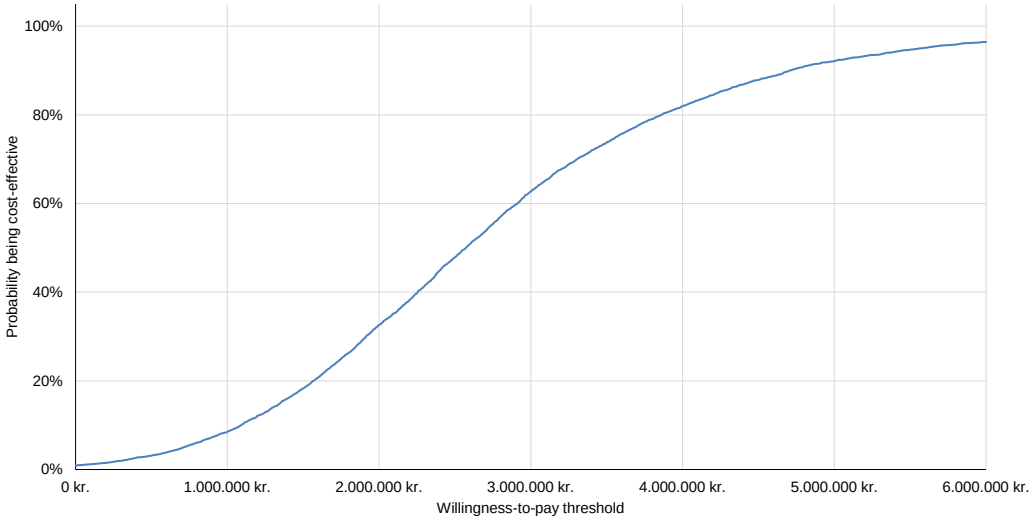


Table 60 Probabilistic Sensitivity Analysis results, adults

	Teduglutide		Standard Care				
	Costs	QALYs	Costs	QALYs	Δ Costs	Δ QALYs	ICER
Current Results:	26.483.343 kr.	6,53	22.986.574 kr.	5,14	3.496.769 kr.	1,39	**2.507.713 kr.**
Average:	26.315.328 kr.	6,53	22.850.995 kr.	5,16	3.464.333 kr.	1,38	**2.517.611 kr.**
St Dev:	3.040.467 kr.	2,03	3.175.218 kr.	2,00	1.405.646 kr.	0,37	1.589.843 kr.

Figure 41 PSA Scatter Plot, adults: Alternative informed Bayesian priors (stay: 0.5, up: 0.2, down: 0.3)

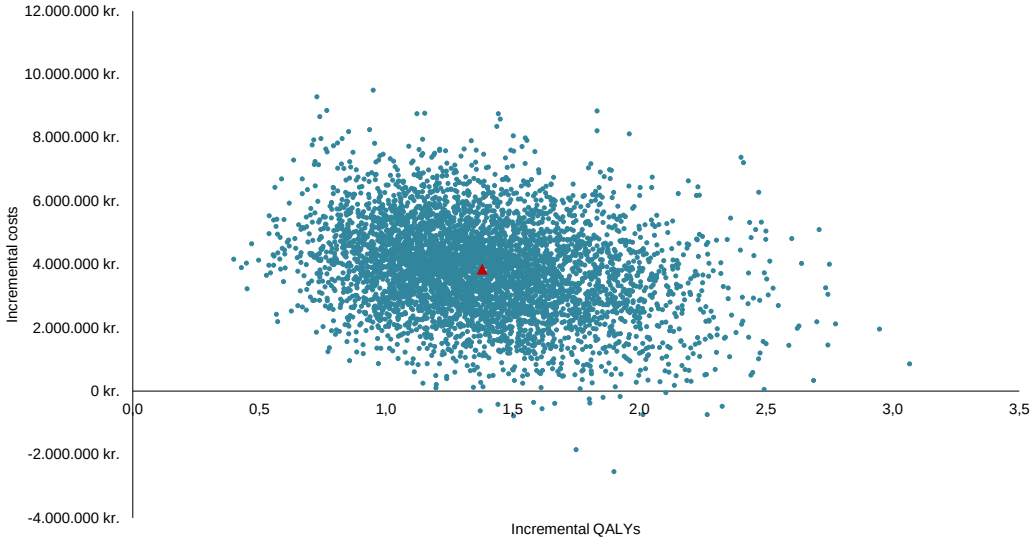


Figure 42 PSA – CEAC, adults: Alternative informed Bayesian priors (stay: 0.5, up: 0.2, down: 0.3)

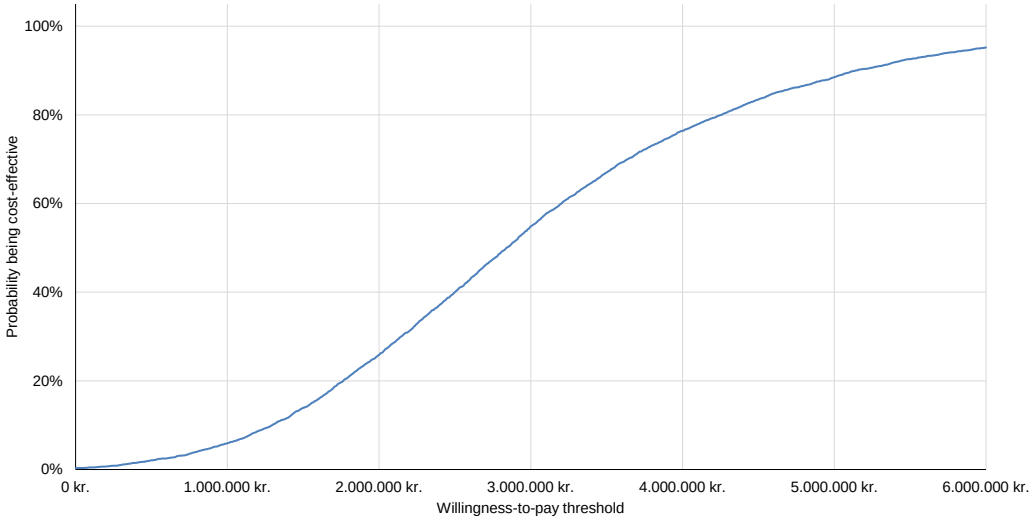


Table 61 PSA results, adults: Alternative informed Bayesian priors (stay: 0.5, up: 0.2, down: 0.3)

	Teduglutide		Standard Care				
	Costs	QALYs	Costs	QALYs	Δ Costs	Δ QALYs	ICER
Current Results:	26.483.343 kr.	6,53	22.986.574 kr.	5,14	3.496.769 kr.	1,39	**2.507.713 kr.**
Average:	26.714.450 kr.	6,51	22.868.499 kr.	5,13	3.845.951 kr.	1,38	**2.787.653 kr.**
St Dev:	3.050.807 kr.	2,00	3.170.052 kr.	1,98	1.436.557 kr.	0,36	1.610.334 kr.

8.7.2.2 Pediatrics

Figure 43 Probabilistic Sensitivity Analysis Scatter Plot, pediatrics

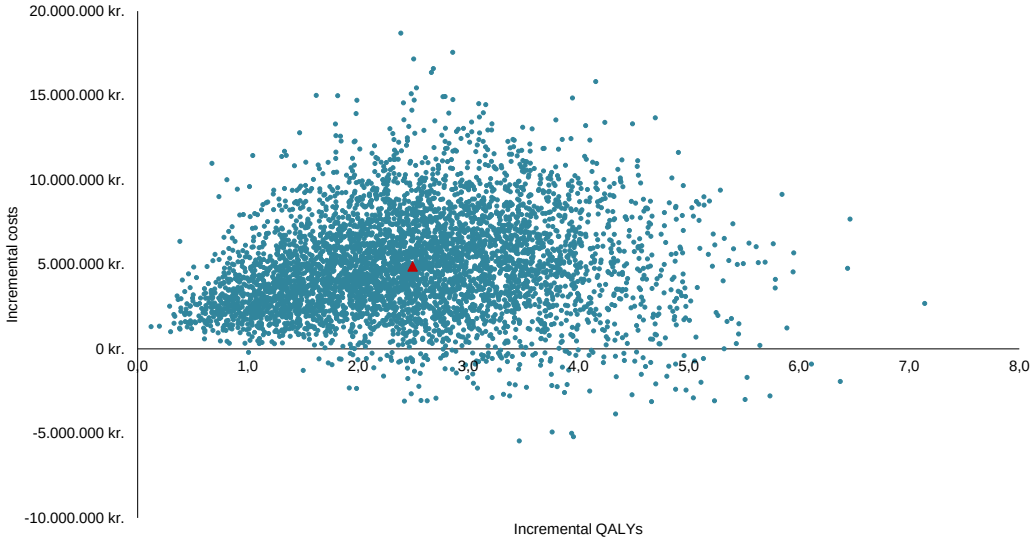


Figure 44 Probabilistic Sensitivity Analysis – Cost-Effectiveness Acceptability Curve, pediatrics

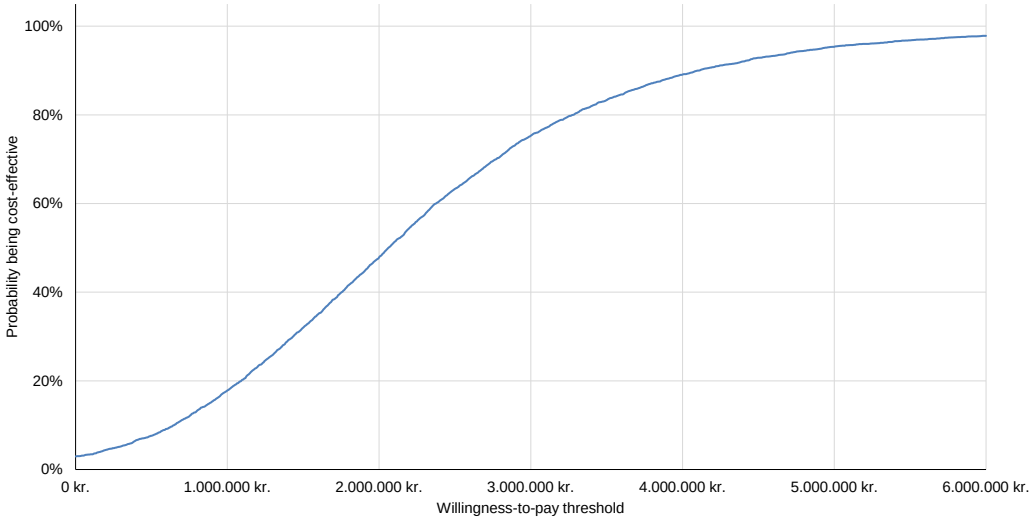


Table 62 Probabilistic Sensitivity Analysis results, pediatrics

	Teduglutide		Standard Care				
	Costs	QALYs	Costs	QALYs	Δ Costs	Δ QALYs	ICER
Current Results:	50.402.038 kr.	11,86	45.398.202 kr.	9,22	5.003.836 kr.	2,64	**1.894.268 kr.**
Average:	47.994.997 kr.	11,27	43.114.117 kr.	8,78	4.880.880 kr.	2,49	**1.956.599 kr.**
St Dev:	15.632.284 kr.	4,96	14.542.056 kr.	4,41	2.912.234 kr.	1,03	1.502.587 kr.

Figure 45 PSA Scatter Plot, pediatrics: Alternative informed Bayesian priors (stay: 0.5, up: 0.2, down: 0.3)

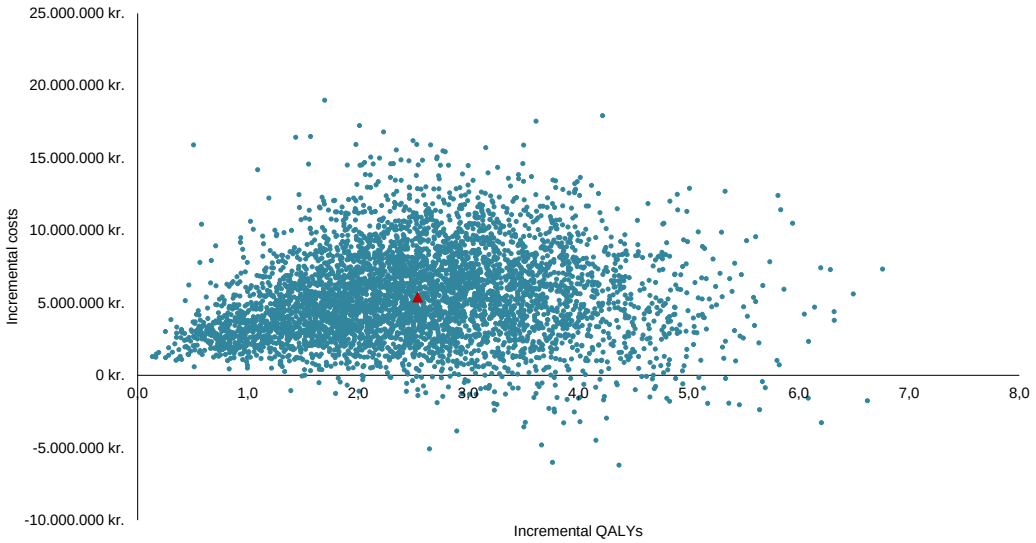


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Figure 46 PSA – CEAC, pediatrics: Alternative informed Bayesian priors (stay: 0.5, up: 0.2, down: 0.3)

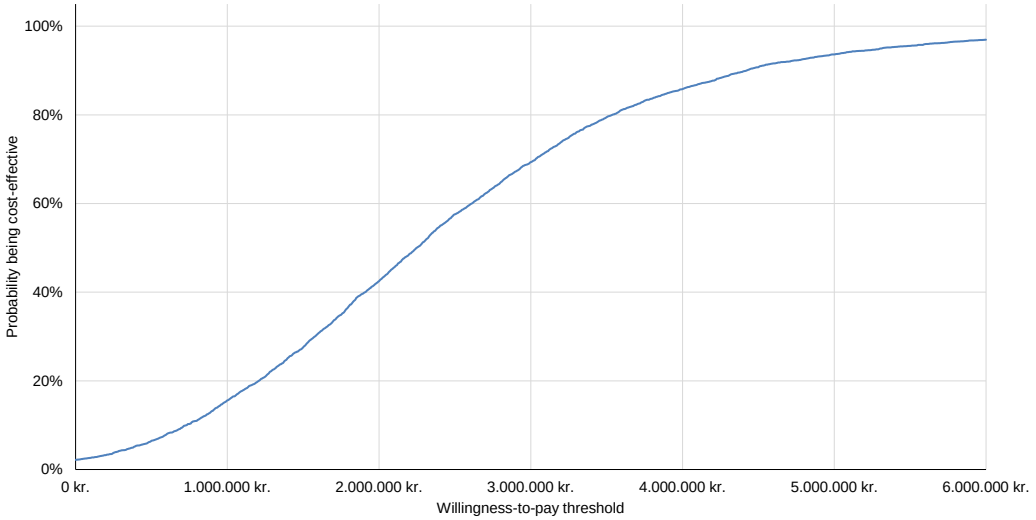

Table 63 PSA results, pediatrics: Alternative informed Bayesian priors (stay: 0.5, up: 0.2, down: 0.3)

	Teduglutide		Standard Care				
	Costs	QALYs	Costs	QALYs	Δ Costs	Δ QALYs	ICER
Current Results:	50.402.038 kr.	11,86	45.398.202 kr.	9,22	5.003.836 kr.	2,64	**1.894.268 kr.**
Average:	49.181.644 kr.	11,37	43.789.704 kr.	8,83	5.391.940 kr.	2,54	**2.121.747 kr.**
St Dev:	15.810.041 kr.	4,97	14.586.784 kr.	4,45	3.059.714 kr.	1,05	1.652.915 kr.

9. Budget impact analysis

The budget impact is calculated based on the cos-effectiveness model, and can be found in the 'Budget Impact' sheet of the Excel model, and is calculated separately for the adult indication **9.1** and the pediatric indication **0**. More information can be found in the 'Budget Impact' sheet of the Excel model.

As described in section **5.1**, we anticipate that around 100 adult SBS-IF patients are eligible for treatment with teduglutide. In addition to this, we anticipate that around 10 additional adult incident SBS-IF patients each year will be eligible for treatment with teduglutide. In the adult budget impact model, it is assumed that 10 of the 100 prevalent and eligible SBS-IF patients will initiate treatment in the first year, and that all the 10 incident and eligible patients each year will initiate treatment. Consequently, we anticipate that 20 adult SBS-IF patients will initiate treatment in year 1, and 10 in each of the following 4 years. See Table 64.

For pediatric patients, we anticipate that around 15 pediatric SBS-IF patients are eligible for treatment with teduglutide. In addition to this, we anticipate that around 3 additional pediatric incident SBS-IF patients each year will be eligible for treatment with teduglutide. In the teduglutide budget impact model, it is assumed that 3 of the 15 prevalent and eligible SBS-IF patients will initiate treatment in the first year, and that all the 3 incident and eligible patients each year will initiate treatment. Consequently, we anticipate that 6 pediatric SBS-IF patients will initiate treatment in year 1, and 3 in each of the following 4 years. See Table 68.

Only regional costs are included in the budget impact model, which have been split into the price of teduglutide, administration cost (nurse led administration training), monitoring cost (teduglutide related colonoscopies), disease specific costs (PS costs held by the Regions and cost of complications) and cost of adverse events.

9.1 Adults

Table 64 Number of adult patients expected to be treated over the next five-year period if teduglutide is introduced

Teduglutide is recommended	Year 1	Year 2	Year 3	Year 4	Year 5
SBS-IF patients on teduglutide (n)	20	30	40	50	60
SBS-IF patients not on teduglutide (n)	90	90	90	90	90
	110	**120**	**130**	**140**	**150**

Table 65 Number of adult patients expected to be treated over the next five-year period if teduglutide is NOT introduced

Teduglutide is NOT recommended	Year 1	Year 2	Year 3	Year 4	Year 5
SBS-IF patients on teduglutide (n)	0	0	0	0	0
SBS-IF patients not on teduglutide (n)	110	120	130	140	150
	110	**120**	**130**	**140**	**150**

Table 66 Costs per adult patient per year

Regional cost per patient	Year 1	Year 2	Year 3	Year 4	Year 5
initiating teduglutide	1.843.112 kr.	1.188.669 kr.	1.103.141 kr.	1.046.157 kr.	994.338 kr.
not initiating teduglutide	704.217 kr.	638.840 kr.	608.548 kr.	579.038 kr.	551.115 kr.

Table 67 Expected budget impact of recommending teduglutide for the current adult indication

	Year 1	Year 2	Year 3	Year 4	Year 5
Teduglutide is recommended	**100.241.751 kr.**	**99.700.118 kr.**	**107.150.000 kr.**	**114.385.764 kr.**	**121.297.900 kr.**
Of which: Teduglutide costs	24.103.906 kr.	26.043.830 kr.	32.356.579 kr.	38.352.714 kr.	44.055.758 kr.
Of which: Administration costs	11.616 kr.	5.808 kr.	5.808 kr.	5.808 kr.	5.808 kr.
Of which: Monitoring costs	159.431 kr.	127.372 kr.	103.544 kr.	103.544 kr.	103.544 kr.
Of which: Disease-specific costs	70.153.278 kr.	68.187.047 kr.	69.244.031 kr.	70.387.585 kr.	71.504.187 kr.
Of which: Costs of adverse events	5.813.519 kr.	5.336.060 kr.	5.440.038 kr.	5.536.113 kr.	5.628.604 kr.
Minus: Teduglutide is NOT recommended	**77.463.837 kr.**	**77.314.575 kr.**	**80.370.900 kr.**	**83.210.210 kr.**	**85.929.069 kr.**
Of which: Teduglutide costs	0 kr.	0 kr.	0 kr.	0 kr.	0 kr.
Of which: Administration costs	0 kr.	0 kr.	0 kr.	0 kr.	0 kr.
Of which: Monitoring costs	0 kr.	0 kr.	0 kr.	0 kr.	0 kr.
Of which: Disease-specific costs	71.869.191 kr.	71.856.796 kr.	74.704.851 kr.	77.349.025 kr.	79.881.175 kr.
Of which: Costs of adverse events	5.594.646 kr.	5.457.780 kr.	5.666.048 kr.	5.861.185 kr.	6.047.894 kr.
Budget impact if recommended:	**22.777.914 kr.**	**22.385.542 kr.**	**26.779.100 kr.**	**31.175.554 kr.**	**35.368.832 kr.**

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9.2 Pediatrics

Table 68 Number of pediatric patients expected to be treated over the next five-year period if teduglutide is introduced

Teduglutide is recommended	Year 1	Year 2	Year 3	Year 4	Year 5
SBS-IF patients on teduglutide (n)	6	9	12	15	18
SBS-IF patients not on teduglutide (n)	12	12	12	12	12
	18	**21**	**24**	**27**	**30**

Table 69 Number of pediatric patients expected to be treated over the next five-year period if teduglutide is NOT introduced

Teduglutide is NOT recommended	Year 1	Year 2	Year 3	Year 4	Year 5
SBS-IF patients on teduglutide (n)	0	0	0	0	0
SBS-IF patients not on teduglutide (n)	18	21	24	27	30
	18	**21**	**24**	**27**	**30**

Table 70 Costs per pediatric patient per year

Regional cost per patient	Year 1	Year 2	Year 3	Year 4	Year 5
initiating teduglutide	1.871.085 kr.	1.249.555 kr.	1.195.692 kr.	1.167.580 kr.	1.140.761 kr.
not initiating teduglutide	719.370 kr.	673.717 kr.	661.759 kr.	648.370 kr.	634.348 kr.

Table 71 Expected budget impact of recommending teduglutide for the current pediatric indication

	Year 1	Year 2	Year 3	Year 4	Year 5
Teduglutide is recommended	**19.858.951 kr.**	**21.195.183 kr.**	**24.477.173 kr.**	**27.734.910 kr.**	**30.908.478 kr.**
Of which: Teduglutide costs	7.320.236 kr.	8.061.074 kr.	10.177.083 kr.	12.243.738 kr.	14.260.671 kr.
Of which: Administration costs	3.485 kr.	1.742 kr.	1.742 kr.	1.742 kr.	1.742 kr.
Of which: Monitoring costs	48.285 kr.	39.278 kr.	31.710 kr.	31.710 kr.	31.710 kr.
Of which: Disease-specific costs	11.491.968 kr.	12.129.037 kr.	13.212.323 kr.	14.316.418 kr.	15.388.946 kr.
Of which: Costs of adverse events	994.977 kr.	964.051 kr.	1.054.314 kr.	1.141.302 kr.	1.225.409 kr.
Minus: Teduglutide is NOT recommended	**12.948.659 kr.**	**14.285.009 kr.**	**16.090.915 kr.**	**17.835.191 kr.**	**19.527.908 kr.**
Of which: Teduglutide costs	0 kr.	0 kr.	0 kr.	0 kr.	0 kr.
Of which: Administration costs	0 kr.	0 kr.	0 kr.	0 kr.	0 kr.
Of which: Monitoring costs	0 kr.	0 kr.	0 kr.	0 kr.	0 kr.
Of which: Disease-specific costs	12.019.148 kr.	13.280.984 kr.	14.961.668 kr.	16.584.814 kr.	18.160.103 kr.
Of which: Costs of adverse events	929.511 kr.	1.004.026 kr.	1.129.246 kr.	1.250.377 kr.	1.367.805 kr.
Budget impact if recommended:	**6.910.292 kr.**	**6.910.174 kr.**	**8.386.258 kr.**	**9.899.719 kr.**	**11.380.570 kr.**

10. Discussion on the submitted documentation

The rare nature of the disease and the drug being an orphan drug is an inherent overarching limitation in this application, which inevitably leads to uncertainty in the clinical documentation due to the paucity of data and the small sample sizes in the studies. The limitations of the included studies have been described in greater detail in section **7.1.1**.

Under normal circumstances, an application would rely on data from the registration studies only. However, because teduglutide was approved by EMA in 2012 (adults) and 2016 (pediatrics), a strength of the present application is the ability to leverage real world data based on several years of experience with teduglutide treatment in real-world clinical settings in neighboring- and European countries.

[redacted]

The health economic model assumes that patients in the same health state at a given cycle are similar in terms of cost, quality of life, and disease progression, which is a limiting assumption due to the heterogenous nature of the SBS-IF patient population. By using the STEPS studies as clinical input, this issue is partly mitigated, because patients needing PS for less than 3 days per week were not included in the trial. However, what is a gain in terms of reduced heterogeneity in the patient population is also a loss in terms of the external validity and transferability of the results.

The protocolled weaning algorithms used in the STEPS studies may also affect the transferability of the results to a Danish clinical setting, as we expect more aggressive weaning off PS, as indicated by published real-world studies. The health economic model structure is based on weekly PS days (see Figure 22). As a result of this, a reduction in PS volume alone will not have any impact on the cost or health outcomes in the model, unless the reduction in volume is associated with a reduction in days per week needing PS. Consequently, if a high volume PS7 patient achieves lower PS volume but not fewer PS days, any potential benefit from this in terms of reduced cost or improved quality of life will not be captured in the current cost-effectiveness model.

The data from the pediatric trials were not considered to be suitable for cost-effectiveness modeling due to the low patient numbers and the lack of randomization. Instead, we chose to modify the adult model to fit a pediatric population, but still using clinical input from adult trials. As further explained in section **8.1**, this is a conservative assumption in favor of the comparator, and not having clinical input of sufficient quality to drive a pediatric model is a limitation.

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[redacted]

Finally, according to the SmPC, response of teduglutide should not be evaluated until after 6 months. Combined with significant heterogeneity in the patient population leading to different expected time to response and different expected outcomes (reduced PS volume vs. fewer PS days vs. enteral autonomy), the introduction of teduglutide in Danish clinical practice may be associated with uncertainties in terms of realized value and budget impact. To address these uncertainties, we are open to discussing alternative payment schemes and value-based contracting (see an example in **Appendix N**).

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11. List of experts

Chief physician Med.Sc.D Palle Bekker Jeppesen
Chief physician Med.Sc.D. Lars Vinter-Jensen
Chief physician Henrik Højgaard Rasmussen
Chief physician Sine Obling

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Appendix A

Literature search for efficacy and safety of intervention and comparator(s)

Not applicable. See justification in Section **6**.

Appendix B

Main characteristics of included studies

Table 72 Main characteristics of study NCT00081458

Trial name: Safety and Efficacy Study of Teduglutide in Subjects With Short Bowel Syndrome	**NCT number: NCT00081458**
Publication title: Randomised placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome	
Objective	*Evaluate the efficacy, safety, tolerability, and pharmacokinetics (PK) of teduglutide compared with placebo in subjects with parenteral nutrition (PN)-dependent short bowel syndrome (SBS)*
Publications – title, author, journal, year	*Jeppesen PB, Gilroy R, Pertkiewicz M, Allard JP, Messing B, O'Keefe SJ. Randomised placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome. Gut. 2011 Jul;60(7):902-14. doi: 10.1136/gut.2010.218271. Epub 2011 Feb 11.*
Study type and design	*Double-blinded placebo-controlled study. Enrolled patients were randomly assigned 2:2:1 to one of three groups (teduglutide 0.05 mg/kg, teduglutide 0.01 mg/kg or placebo) using to a computer-generated interactive response system (Fisher Automated Clinical Trial Services. were masked during treatment assignment. Participant, Care Provider, Investigator were masked during the entire study.*

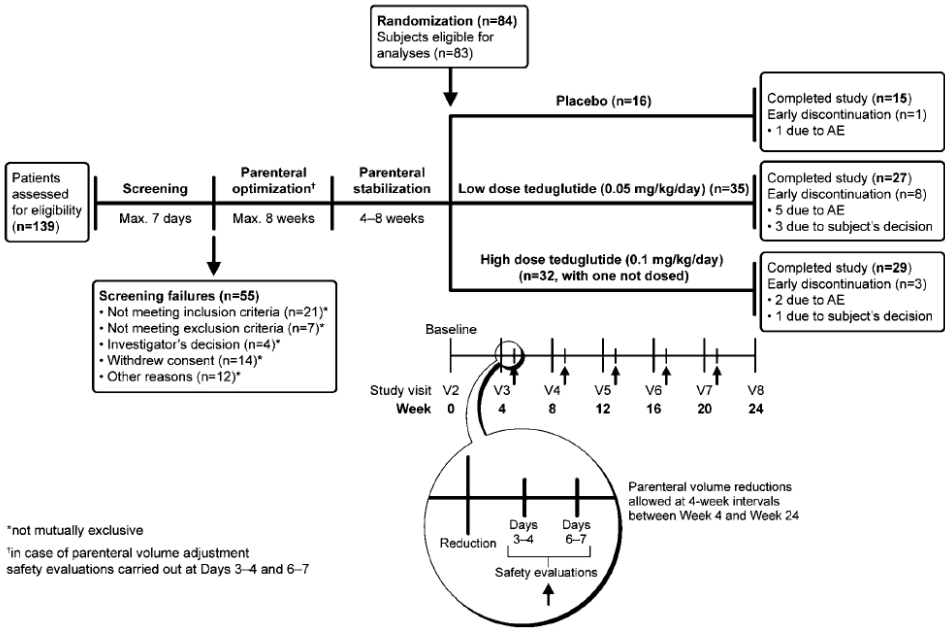

Figure 1 Basic study design. AE, adverse event.

Trial name: Safety and Efficacy Study of Teduglutide in Subjects With Short Bowel Syndrome	NCT number: NCT00081458
Publication title: Randomised placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome	

Sample size (n)	*83*
Main inclusion and exclusion criteria	*Inclusion Criteria:* • *Men and women, aged 18 years of age or older at the time of signing the informed consent form (ICF)* • *SBS as a result of major intestinal resection resulting in at least 12 months intravenous feeding* • *Body weight must be less than 90 kg* • *At baseline, subjects must require PN treatment to meet their caloric or electrolyte needs due to ongoing malabsorption at least 3 times weekly and to be on a stable PN regimen for 4 weeks before dosing* • *Body mass index (BMI) 18 to 27 kg/m2* • *Adequate hepatic and renal function* *Exclusion Criteria:* • *History of cancer or clinically significant lymphoproliferative disease with fewer than 5 years documented disease-free state* • *History of alcohol or drug abuse (within previous year)* • *Participation in a clinical study within 30 days prior to signing the ICF, or concurrent participation in any clinical study* • *Clinically significant laboratory abnormalities at the time of randomization* • *Previous use of teduglutide (ALX-0600)* • *Prior use of native GLP-2 within 3 months of screening visit* • *Hospital admission within 1 month prior to screening visit* • *Pregnant or lactating women* • *Any condition or circumstance, which in the investigator's opinion would put the subject at any undue risk, prevent completion of the study, or interfere with analysis of the study results.* • *Presence of excluded disease: Radiation enteritis, Scleroderma, Celiac disease, Refractory/Tropical sprue, Pseudo-obstruction, Active inflammatory bowel disease (IBD), Pre-malignant/malignant change in colonoscopy biopsy or polypectomy, Surgery scheduled within the time frame of the study, Human immunodeficiency virus (HIV) positive test, Immunological disorders, Possible allergies to teduglutide or its constituents, Significant, active, uncontrolled, untreated systemic diseases*
Intervention	• *Teduglutide 0.05 mg/kg/day subcutaneous injection (n=35)* • *Teduglutide 0.10 mg/kg/day subcutaneous injection (n=32)*
Comparator(s)	• *Placebo daily subcutaneous injection (n=16)*
Follow-up time	*6 months*

Trial name: Safety and Efficacy Study of Teduglutide in Subjects With Short Bowel Syndrome NCT number: NCT00081458 Publication title: Randomised placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome	
Is the study used in the health economic model?	*Yes*
Primary, secondary and exploratory endpoints	*State all primary, secondary and exploratory endpoints of the study, regardless of whether results are provided in this application. Definition of included outcomes and results are provided in appendix D.* *Primary:* • *A Graded Response Score in Parenteral Nutrition (PN) Reduction. The end point, took into account higher levels and earlier onset of response, leading to longerduration of response. The results were tested according to a step-down procedure starting with the 0.10 mg/kg/day dose.* *Secondary:* • *Secondary efficacy end points included the number and percentage of subjects who responded, the absolute reduction from baseline in parenteral volume and parenteral kilojoules; achievement of at least one day reduction in weekly parenteral administration or total weaning from parenteral support.* *Exploratory:* • *Exploratory end points included the change from baseline in oral fluid intake and urine production, body composition (evaluated by DEXA), plasma citrulline (an amino acid produced by enterocytes as a biomarker of a reduced enterocyte mass), bowel morphology (histopathological evaluation and villus height and crypt depth morphometrics, optionally taken via stomas or by colonoscopy) and health-related quality of life questionnaires (SF-36,the EuroQol EQ-5D and the IBDQ).*
Method of analysis	*All efficacy analyses were intention-to-treat analyses. All statistical tests were two-sided with an a level of 0.05. For the analysis of the primary efficacy end point (the GRS), pairwise treatment comparisons were made using a rank analysis of covariance (an extension of the Wilcoxon rank sum test) with strata for the baseline parenteral consumption level used for the stratification of the randomization and treatment groups, with the baseline weekly parenteral volume as a covariate and a step-down procedure for multiple comparisons. For the main secondary end point (responses maintained from week 20 and week 24), pairwise comparisons between treatment groups were made using the Fisher exact test.*
Subgroup analyses	*The small number of subjects in the study hindered meaningful subgroup analyses as the study was likely to be underpowered to detect clinically meaningful changes.*
Other relevant information	-

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Table 73 Main characteristics of study NCT00172185

Trial name: Safety and Efficacy Study of Teduglutide in Subjects With Short Bowel Syndrome Who Completed Protocol CL0600-004 (NCT00081458)	**NCT number: NCT00172185**
Publication title: Safety and efficacy of teduglutide after 52 weeks of treatment in patients with short bowel intestinal failure	
Objective	*Evaluate the long-term safety, tolerability, and efficacy of daily teduglutide administration for 52 weeks in subjects who received teduglutide or placebo in protocol CL0600-004 (NCT00081458)*
Publications – title, author, journal, year	*Jeppesen PB, Gilroy R, Pertkiewicz M, Allard JP, Messing B, O'Keefe SJ. Randomised placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome. Gut. 2011 Jul;60(7):902-14. doi: 10.1136/gut.2010.218271. Epub 2011 Feb 11.* *O'Keefe SJ, Jeppesen PB, Gilroy R, Pertkiewicz M, Allard JP, Messing B. Safety and efficacy of teduglutide after 52 weeks of treatment in patients with short bowel intestinal failure. Clin Gastroenterol Hepatol. 2013 Jul;11(7):815-23.e1-3. doi: 10.1016/j.cgh.2012.12.029. Epub 2013 Jan 17.* *Vipperla K, O'Keefe SJ. Study of teduglutide effectiveness in parenteral nutrition-dependent short-bowel syndrome subjects. Expert Rev Gastroenterol Hepatol. 2013 Nov;7(8):683-7. doi: 10.1586/17474124.2013.842894. Epub 2013 Oct 17. Review.*
Study type and design	*28 weeks double-blind extension study of the 24 week double-blinded placebo-controlled study (NCT00081458), for a total treatment period of 52 weeks. Patients who were randomized to teduglutide in the initial randomized controlled trial (NCT00081458) continued with the same teduglutide dose in the extension study (Figure 1). Patients who received placebo in the initial 24-week RCT also were eligible for randomized treatment in the extension study but they were excluded from this analysis because they did not receive teduglutide for the same length of time (ie, 52 weeks overall) as the patients who received teduglutide during the initial 24-week*
Sample size (n)	*65*

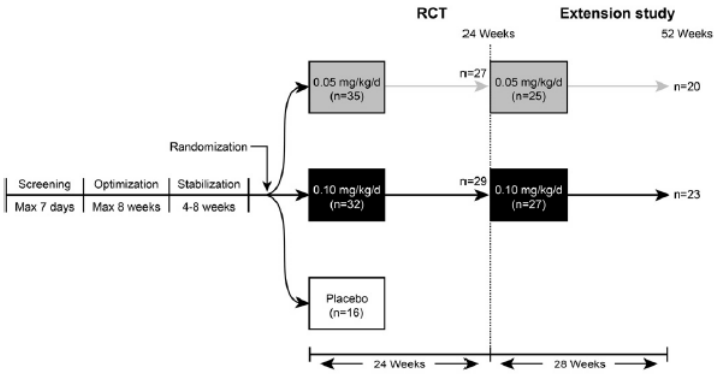

Figure 1. Flow chart for the 52-week efficacy and safety analysis. Patients who received placebo treatment in the initial 6-month RCT are not included in this report.

Trial name: Safety and Efficacy Study of Teduglutide in Subjects With Short Bowel Syndrome Who Completed Protocol CL0600-004 (NCT00081458)	NCT number: NCT00172185
Publication title: Safety and efficacy of teduglutide after 52 weeks of treatment in patients with short bowel intestinal failure	

Main inclusion and exclusion criteria	*Inclusion Criteria:* • *At dosing week 24 of protocol CL0600-004 (NCT00081458), subjects will be reviewed for their participation in this study. Subjects who meet all of the following criteria can be enrolled in this study:* *Signed and dated informed consent form (ICF) to participate before any study-related procedures are performed* *Completion of protocol CL0600-004 (NCT00081458)* *Exclusion criteria:* • *History of cancer or clinically significant lymphoproliferative disease with fewer than 5 years documented disease-free state* • *History of alcohol or drug abuse (within previous year)* • *Prior use of native glucagon-like peptide 2 (GLP-2) within 3 months of screening visit* • *Pregnant or lactating women* • *Any condition or circumstance, which in the investigator's opinion would put the subject at any undue risk, prevent completion of the study, or interfere with analysis of the study results*
Intervention	*Teduglutide 0.05 mg/kg/day (n=31)* • *Received placebo in NCT00081458 (n=6)* • *Received Teduglutide 0.05 mg/kg/d in NCT00081458 (n=25)* *Teduglutide 0.1 mg/kg/day (n=34)* • *Received placebo in NCT00081458 (n=7)* • *Received Teduglutide 0.1 mg/kg/d in NCT00081458 (n=27)*
Comparator(s)	*N/A*
Follow-up time	*52 weeks (24 weeks in the original study (NCT00081458) and 28 weeks in this extension study (NCT00172185)*
Is the study used in the health economic model?	*No*

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Trial name: Safety and Efficacy Study of Teduglutide in Subjects With Short Bowel Syndrome Who Completed Protocol CL0600-004 (NCT00081458) Publication title: Safety and efficacy of teduglutide after 52 weeks of treatment in patients with short bowel intestinal failure	NCT number: NCT00172185
Primary, secondary and exploratory endpoints	*Primary:* • *Assessments of safety included monitoring for AEs, laboratory tests (hematology, serum chemistries, and urinalysis with microscopic analysis), and clinical evaluations (vital signs, physical examination, and electrocardiograms). Safety assessments for all patients also included body weight, 48-hour oral fluid intake and urine output, IV catheter complications, colonoscopy (if colon was present), and antibodies to teduglutide and ECP.* • *Efficacy evaluations included PN volume and plasma citrulline levels at week 52.* *Secondary:* • *Fasting plasma citrulline levels*
Method of analysis	*The primary patient population for all analyses was the intent-to-treat population, defined as all patients who entered the study and received the study drug. The safety population consisted of all subjects who received at least one dose of study drug. Only observed data were analyzed; missing data were not imputed (e.g., last observation was not carried forward).*
Subgroup analyses	-
Other relevant information	-

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Table 74 Main characteristics of study NCT00798967 - STEPS

Trial name: Study of Teduglutide Effectiveness in Parenteral Nutrition (PN)-Dependent Short Bowel Syndrome (SBS) Subjects (STEPS) **NCT number: NCT00798967** **Publication title: Randomised placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome**	
Objective	*Evaluate whether teduglutide at the 0.05 mg/kg/d dosage and with a protocol allowing for earlier (ie, at second week of dosing) and more aggressive PS reductions of 10% to 30% of baseline levels of PN/IV fluid could reduce PS volume in patients with SBS-IF.*
Publications – title, author, journal, year	*Jeppesen, P. B., Pertkiewicz, M., Messing, B., Iyer, K., Seidner, D. L., O'keefe, S. J. D., Forbes, A., Heinze, H., & Joelsson, B. (2012). Teduglutide Reduces Need for Parenteral Support Among Patients With Short Bowel Syndrome With Intestinal Failure. Gastroenterology, 143(6), 1473-1481.e3. https://doi.org/10.1053/j.gastro.2012.09.007*
Study type and design	*Double-blinded placebo-controlled phase 3 study. Enrolled patients were randomly assigned 1:1 to teduglutide 0.05 mg/kg/d or placebo according to a computer-generated interactive response system and was stratified at 2 levels of baseline PS volume (≤6 or ≥6 L/wk.).Participant, Care Provider, Investigator were masked during the entire study.*

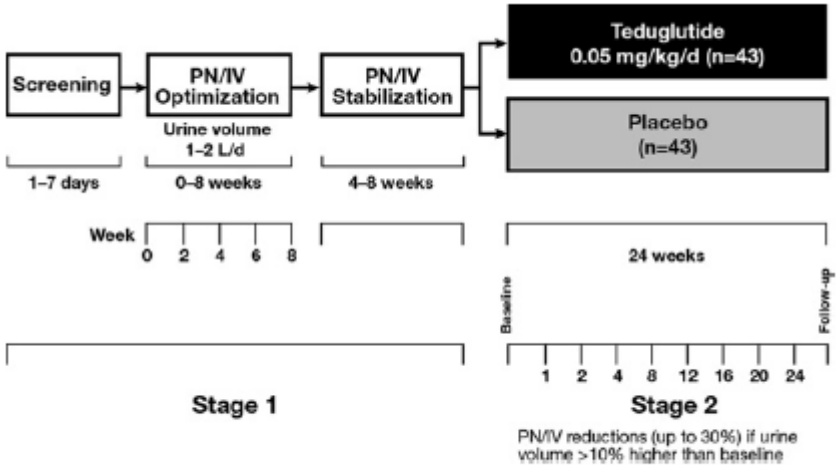

Figure 1. Study design.

Sample size (n)	*86*

Trial name: Study of Teduglutide Effectiveness in Parenteral Nutrition (PN)-Dependent Short Bowel Syndrome (SBS) Subjects (STEPS)	NCT number: NCT00798967
Publication title: Randomised placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome	

Main inclusion and exclusion criteria

Inclusion Criteria:

- *Signed and dated informed consent prior to any study-related procedures are performed*
- *Men and women 18 years of age or older at the time of informed consent signing*
- *Intestinal failure resulting in Short Bowel Syndrome*
- *At least 12 months of continuous PN dependency*
- *12 weeks of clinical remission of Crohn's disease (CD) prior to dosing*
- *PN required at least 3 times weekly*
- *A stable PN volume for four weeks prior to dosing*

Exclusion Criteria:

- *History of cancer or clinically significant lymphoproliferative disease with fewer than 5 years documented disease-free state*
- *Participation in clinical study within 30 days for drug or 90 days for antibody*
- *Use of native GLP-2 or human growth hormone (HGH) within 6 months of screening*
- *Use of iv glutamine within 30 days prior to screening*
- *Use of teduglutide*
- *CD patients who have been treated with biological therapy within 6 months of screening*
- *IBD patients who require chronic systemic immunosuppressant therapy*
- *More than 4 SBS- or PN-related hospitalizations within 12 months of screening*
- *Unplanned hospitalization within one month of screening*
- *Pregnant or lactating women*
- *Body weight > 88kg*
- *Body mass index (BMI) < 15 kg/m2*
- *Severe hepatic impairment or disturbed renal function*
- *Female subjects who are not surgically sterile or postmenopausal or who are not using medically acceptable methods of birth control during and for 30 days after the treatment period*
- *Not capable of understanding or not willing to adhere to the study visit schedules and other protocol requirements*
- *Any condition or circumstance that is the investigator's opinion would put the subject at any undue risk, prevent completion of the study, or interfere with the analysis of the study results*
- *Significant active, uncontrolled, untreated systemic diseases*

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Trial name: Study of Teduglutide Effectiveness in Parenteral Nutrition (PN)-Dependent Short Bowel Syndrome (SBS) Subjects (STEPS)	NCT number: NCT00798967
Publication title: Randomised placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome	

Intervention	• *Teduglutide 0.05 mg/kg/d subcutaneous injection (n=43)*
Comparator(s)	• *Placebo daily subcutaneous injection (n=43)*
Follow-up time	*24 weeks*
Is the study used in the health economic model?	*Yes*
Primary, secondary and exploratory endpoints	*State all primary, secondary and exploratory endpoints of the study, regardless of whether results are provided in this application. Definition of included outcomes and results are provided in appendix D.* *Primary:* • *Percentage of patients who demonstrated a response at week 20 and maintained that response at week 24 (responder). A response at a given visit was defined as the achievement of a 20% to 100% reduction from baseline in weekly PS volume.* *Secondary:* • *Secondary efficacy end points included the percentage and absolute change in PS and the number of patients who stopped PS and their time of discontinuation.* *Exploratory:* • *Exploratory end points included percentage of patients with response (20%-100% PS reduction vs baseline), response by visit, reduction in days on PS, change from baseline in plasma concentrations of citrulline (an amino acid produced by enterocytes and used here as a biomarker of remnant enterocyte mass),15 and change in the fluid composite effect (FCE).*
Method of analysis	*All efficacy analyses were intention-to-treat analyses. All statistical tests were two-sided with an a level of 0.05. The intent-to-treat analysis compared the event rates for the 2 treatment groups using the Cochran-Mantel-Haenszel test statistics adjusted for the randomization stratification variable (≤6 or ≥6 L/wk.) of PS volume at baseline. The percentage and absolute change in PS volume from baseline to the last dosing visit are presented by treatment group using descriptive statistics. Treatment group differences were compared using an analysis of covariance model with effects for treatment and baseline PS volume, with the potential for the interaction of the 2 variables also included as an effect. Safety analyses were descriptive.*
Subgroup analyses	*The small number of subjects in the study hindered meaningful subgroup analyses as the study was likely to be underpowered to detect clinically meaningful changes.*
Other relevant information	-

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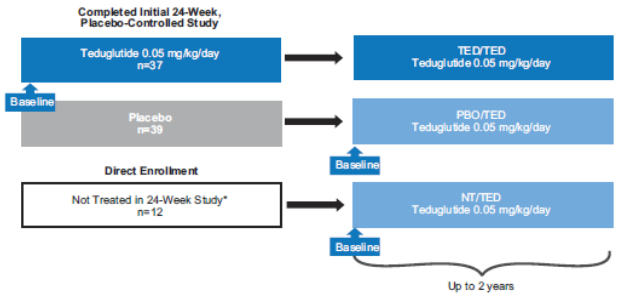
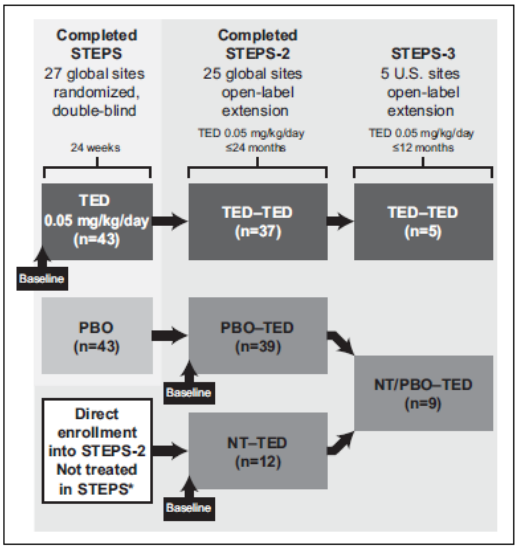
Table 75 Main characteristics of study NCT00930644 – STEPS-2

Trial name: A Long-Term, Open-Label Study With Teduglutide for Subjects With Parenteral Nutrition Dependent Short Bowel Syndrome **Publication title: Randomised placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome (STEPS-2)**	**NCT number: NCT00930644**
Objective	*Collect long term efficacy and safety data from patients who have completed the 24-weeks of study drug dosing in CL0600-020 (STEPS)*
Publications – title, author, journal, year	*Schwartz, L. K., O'Keefe, S. J. D., Fujioka, K., Gabe, S. M., Lamprecht, G., Pape, U.-F., Li, B., Youssef, N. N., & Jeppesen, P. B. (2016). Long-Term Teduglutide for the Treatment of Patients With Intestinal Failure Associated With Short Bowel Syndrome. Clinical and Translational Gastroenterology, 7(2), e142.*
Study type and design	*2-year, open-label extension study. All patients received a daily subcutaneous injection of 0.05 mg/kg/day teduglutide for up to 24 months. The study population included three patient subgroups as illustrated in the figure below.*  **Figure 1** STEPS-2 study design. All patients who completed 24 weeks of treatment in the initial placebo-controlled study with either teduglutide or placebo or who completed the fluid optimization and stabilization phases in the initial placebo-controlled study but were not randomized were eligible for enrollment. Baseline was considered to be the start of teduglutide treatment. *Patients who completed fluid optimization and stabilization but were not randomized in the initial 24-week placebo-controlled study because of full study enrollment were eligible for direct enrollment into STEPS-2. NT/TED, received no treatment in the initial placebo-controlled study and teduglutide in STEPS-2; PBO/TED, received placebo in the initial placebo-controlled study and teduglutide in STEPS-2; TED/TED, received teduglutide in the initial placebo-controlled study and in STEPS-2.
Sample size (n)	*88*
Main inclusion and exclusion criteria	*Inclusion Criteria:* • *must have completed 24 weeks of dosing of the CL0600-020 (STEPS) study* *Exclusion Criteria:* • *None*
Intervention	• *Teduglutide 0.05 mg/kg/day subcutaneous injection (n=88)*
Comparator(s)	• *N/A*
Follow-up time	*2 years*
Is the study used in the health economic model?	*Yes*

Trial name: A Long-Term, Open-Label Study With Teduglutide for Subjects With Parenteral Nutrition Dependent Short Bowel Syndrome	NCT number: NCT00930644
Publication title: Randomised placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome (STEPS-2)	

Primary, secondary and exploratory endpoints	*State all primary, secondary and exploratory endpoints of the study, regardless of whether results are provided in this application. Definition of included outcomes and results are provided in appendix D.* *Primary:* • *1) Percent Change in PN/IV Volume by Visit [Time Frame: 24 months] The mean change from baseline in weekly PN.IV volume in percent change is shown by visit.* • *2) Absolute Change in PN/IV Volume by Visit [Time Frame: 24 months]. The mean change from baseline in weekly PN.IV volume in Litres is shown by visit.* *Secondary:* • *Number of Subjects Achieving PN/IV Reduction [Time Frame: 24 Months or Last Dosing Visit]* • *The number of subjects who achieve at least 1-, 2-, and 3-day reductions in PN/IV per Week.*
Method of analysis	*The primary patient population for all analyses was the intent-to-treat population, defined as all patients who signed informed consent. The safety population included all patients who received at least one dose of study drug. For safety analyses, patients with no previous exposure to teduglutide (PBO/TED and NT/TED subgroups) were combined. For efficacy analyses, data for each subgroup were considered separately because patients in the NT/TED subgroup were not randomized in the initial 24-week placebo-controlled study and therefore did not participate in that study's regimented, regularly scheduled study visits, including the protocol-driven efforts at PS reduction. Treatment-emergent AEs (TEAEs) were coded using the Medical Dictionary for Regulatory Activities and summarized using descriptive statistics.*
Subgroup analyses	*For safety analyses, patients with no previous exposure to teduglutide (PBO/TED and NT/TED subgroups) were combined. For efficacy analyses, data for each subgroup were considered separately because patients in the NT/TED subgroup were not randomized in the initial 24-week placebo controlled study and therefore did not participate in that study's regimented, regularly scheduled study visits, including the protocol-driven efforts at PS reduction, see picture and abbreviation explanations below:*
Other relevant information	-

Table 76 Main characteristics of study NCT01560403 – STEPS-3

Trial name: A One-Year, Open-Label Study With Teduglutide for Subjects With Parenteral Nutrition-dependent Short Bowel Syndrome Who Completed Study CL0600-021 (STEPS-2) **Publication title: Randomised placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome (STEPS-3)**	**NCT number: NCT01560403**
Objective	*Collect long term efficacy and safety data from patients who have completed study CL0600-021 (STEPS-2)*
Publications – title, author, journal, year	*Seidner, D. L., Fujioka, K., Boullata, J. I., Iyer, K., Lee, H.-M., & Ziegler, T. R. (2018). Reduction of Parenteral Nutrition and Hydration Support and Safety With Long-Term Teduglutide Treatment in Patients With Short Bowel Syndrome–Associated Intestinal Failure: STEPS-3 Study. Nutrition in Clinical Practice, 33(4), 520–527.*
Study type and design	*1-year, open-label extension study. All patients received a daily subcutaneous injection of 0.05 mg/kg/day teduglutide for up to 12 months. The study population included two patient subgroups as illustrated in the figure below.*  **Figure 1.** Flow diagram of patients across the STEPS studies. NT/PBO–TED received NT or PBO in initial PBO-controlled trial (STEPS) and TED in STEPS-2. TED–TED received TED in initial PBO-controlled trial (STEPS) and in STEPS-2. *Patients who completed fluid optimization and stabilization but were not randomized in STEPS because of full study enrollment were eligible for direct enrollment into STEPS-2. NT, no teduglutide treatment; PBO, placebo; TED, teduglutide.
Sample size (n)	*14*

Trial name: A One-Year, Open-Label Study With Teduglutide for Subjects With Parenteral Nutrition-dependent Short Bowel Syndrome Who Completed Study CL0600-021 (STEPS-2) Publication title: Randomised placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome (STEPS-3)	NCT number: NCT01560403

Main inclusion and exclusion criteria	*Inclusion Criteria:* • *Completion of the 24-month study, CL0600-021, regardless if fully weaned from PN/I.V. supportExclusion Criteria:* • *Signed and dated informed consent form (ICF) to participate before any study-related procedures of Study TED-C11-001 are performed* *Exclusion Criteria:* • *None*
Intervention	• *Teduglutide 0.05 mg/kg/day subcutaneous injection (n=14)*
Comparator(s)	• *N/A*
Follow-up time	*1 year*
Is the study used in the health economic model?	*No*
Primary, secondary and exploratory endpoints	*State all primary, secondary and exploratory endpoints of the study, regardless of whether results are provided in this application. Definition of included outcomes and results are provided in appendix D.* *Primary:* • *Summary of Treatment-emergent Adverse Events [Time Frame: 12 months]* • *As the primary intent of this study was to collect additional safety data, this outcomes measure will provide a summary of the treatment emergent adverse events. Based on the start date of each subject in this study and the study end date, not all subjects reached 12 months.* *Secondary:* • *Prespecified efficacy parameters included absolute and relative change from baseline in actual PS volume received, reduction in days of PS infusions per week, and number of patients who achieved independence from PS in the STEPS-3 study. Prespecified safety parameters included duration of exposure to TED; incidence of treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TESAEs); physical examinations; vital signs; electrocardiogram results; colonoscopy evaluations; clinical laboratory testing (including serum chemistries for liver and kidney biochemical values, pancreatic enzymes, and electrolytes); and assessment of TED-specific antibody formation*
Method of analysis	*Descriptive statistics were used to summarize the baseline and demographic characteristics, efficacy endpoints, and TEAEs; the study was not designed or sufficiently powered to determine the statistical significance of safety or efficacy endpoints.*

Trial name: A One-Year, Open-Label Study With Teduglutide for Subjects With Parenteral Nutrition-dependent Short Bowel Syndrome Who Completed Study CL0600-021 (STEPS-2) Publication title: Randomised placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome (STEPS-3)	NCT number: NCT01560403
Subgroup analyses	*The STEPS-3 study population was stratified into 2 subgroups for the purpose of data analysis, depending on length of TED treatment, see picture below. The TED–TED subgroup was composed of patients who received TED in the initial PBO-controlled trial (STEPS) and in the open-label STEPS-2 study. The no teduglutide treatment (NT)/PBO–TED subgroup included patients who received NT (entered STEPS-2 directly) or PBO in the initial PBO controlled trial (STEPS) and TED in STEPS-2*
Other relevant information	-

Table 77 Main characteristics of study NCT01952080

Trial name: A 12-Week Pharmacokinetic, Safety, and Pharmacodynamic Study of Teduglutide in Pediatric Subjects Aged 1 Year Through 17 Years, With Short Bowel Syndrome Who Are Dependent on Parenteral Support Publication title: Outcomes from a 12-Week, Open-Label, Multicenter Clinical Trial of Teduglutide in Pediatric Short Bowel Syndrome	NCT number: NCT01952080
Objective	*Assess the short-term safety and pharmacodynamics (PD)/efficacy of teduglutide compared with SOC in pediatric patients (aged 1-17 years) with SBS who were dependent on PN for >1 year.*
Publications – title, author, journal, year	*Carter, B. A., Cohran, V. C., Cole, C. R., Corkins, M. R., Dimmitt, R. A., Duggan, C., Hill, S., Horslen, S., Lim, J. D., Mercer, D. F., Merritt, R. J., Nichol, P. F., Sigurdsson, L., Teitelbaum, D. H., Thompson, J., Vanderpool, C., Vaughan, J. F., Li, B., Youssef, N. N., … Kocoshis, S. A. (2017). Outcomes from a 12-Week, Open-Label, Multicenter Clinical Trial of Teduglutide in Pediatric Short Bowel Syndrome. The Journal of Pediatrics, 181, 102-111.e5. https://doi.org/10.1016/j.jpeds.2016.10.027*

Trial name: A 12-Week Pharmacokinetic, Safety, and Pharmacodynamic Study of Teduglutide in Pediatric Subjects Aged 1 Year Through 17 Years, With Short Bowel Syndrome Who Are Dependent on Parenteral Support

NCT number: NCT01952080

Publication title: Outcomes from a 12-Week, Open-Label, Multicenter Clinical Trial of Teduglutide in Pediatric Short Bowel Syndrome

Study type and design	*Open-label, non-randomized phase 3 study. Patients were enrolled in 3 temporally staggered escalating dose cohorts that received respective subcutaneous teduglutide doses of 0.0125 mg/kg/d, 0.025 mg/kg/d, and 0.05 mg/kg/d. In addition to the 3 dosing cohorts, a fourth observational cohort received SOC.*

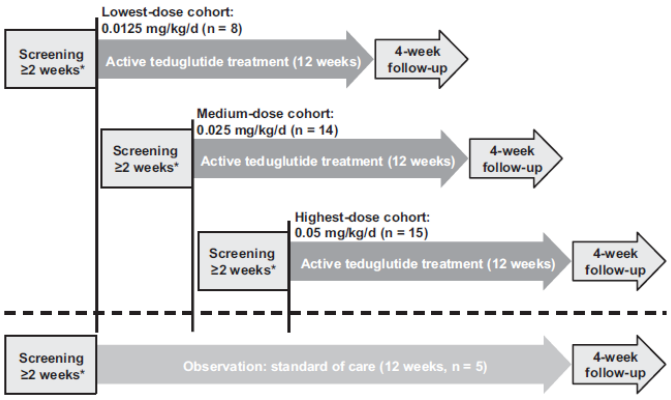


Figure 1. Study design. *Safety data were assessed after ≥28 days of teduglutide treatment before the next dosing cohort could proceed.

Sample size (n)	*42*
Main inclusion and exclusion criteria	*Inclusion Criteria:* • *Current history of SBS as a result of major intestinal resection, (eg, due to necrotizing enterocolitis, midgut volvulus, intestinal atresia, or gastroschisis) for at least 12 months prior to screening* • *Stable PN/IV support for at least 3 months prior to enrollment based upon the opinion of the investigator* *Exclusion Criteria:* • *Serial transverse enteroplasty or any other bowel lengthening procedure performed within the past 3 months* • *Unstable absorption due to cystic fibrosis, untreated Hirschsprung's disease or known DNA abnormalities (ie, Familial Adenomatous Polyposis, Fanconi syndrome)* • *Evidence of obstruction on upper gastrointestinal (GI) series done within 6 months prior to screening* • *Major gastrointestinal surgical intervention within 3 months prior to screening (insertion of feeding tube or endoscopic procedure is allowed)*

Trial name: A 12-Week Pharmacokinetic, Safety, and Pharmacodynamic Study of Teduglutide in Pediatric Subjects Aged 1 Year Through 17 Years, With Short Bowel Syndrome Who Are Dependent on Parenteral Support Publication title: Outcomes from a 12-Week, Open-Label, Multicenter Clinical Trial of Teduglutide in Pediatric Short Bowel Syndrome	NCT number: NCT01952080
Intervention	• *Teduglutide 0.025 mg/kg/d subcutaneous injection (n=8)* • *Teduglutide 0.025 mg/kg/d subcutaneous injection (n=14)* • *Teduglutide 0.05 mg/kg/d subcutaneous injection (n=15)*
Comparator(s)	• *Standard of Care (n=5)*
Follow-up time	*28 weeks*
Is the study used in the health economic model?	*No*
Primary, secondary and exploratory endpoints	*State all primary, secondary and exploratory endpoints of the study, regardless of whether results are provided in this application. Definition of included outcomes and results are provided in appendix D.* *Primary:* • *Percent Change in Parenteral Support [Parenteral Nutrition (PN)/Intravenous (IV)] Volume at Week 12* • *Percent Change in Parenteral Support (PN/IV) Volume at End of Treatment* • *Percent Change in Parenteral Support (PN/IV) Volume at Week 16* • *Absolute Change in Parenteral Support (PN/IV) Volume at Week 12* • *Absolute Change in Parenteral Support (PN/IV) Volume at End of Treatment* • *Absolute Change in Parenteral Support (PN/IV) Volume at Week 16* *Secondary:* • *Percent Change in Enteral Support (EN) Volume From Baseline at Week 12* • *Percent Change in Enteral Support (EN) Volume From Baseline at Week 16* • *Absolute Change in Enteral Support (EN) Volume From Baseline at Week 12* • *Change From Baseline in Parenteral Nutrition Intravenous (PN/IV) Caloric Intake at Week 24* • *Absolute Change in Enteral Support (EN) Volume From Baseline at Week 16* *Exploratory:* • *None*

Trial name: A 12-Week Pharmacokinetic, Safety, and Pharmacodynamic Study of Teduglutide in Pediatric Subjects Aged 1 Year Through 17 Years, With Short Bowel Syndrome Who Are Dependent on Parenteral Support Publication title: Outcomes from a 12-Week, Open-Label, Multicenter Clinical Trial of Teduglutide in Pediatric Short Bowel Syndrome	NCT number: NCT01952080
Method of analysis	*Because of the small pool of eligible patients, the study analysis was descriptive in nature and was not designed or sufficiently powered to determine the statistical significance of safety or PD/efficacy endpoints. The intent-to-treat (ITT) population consisted of all patients who enrolled in the trial. The safety population consisted of all patients in the ITT population who received at least 1 dose of teduglutide or SOC. The ITT population was analyzed for PD/efficacy endpoints except for analysis of percentage change from baseline in EN volume and calories (i.e., analysis did not include patients who did not receive EN at baseline [n = 10] or did not have EN volume/calorie data recorded at baseline [n = 1], because it is mathematically impossible to calculate a percentage change when the baseline is zero). Patients with no baseline EN intake were included in calculations of actual change in EN volume and calories.*
Subgroup analyses	*The small number of subjects in the study hindered meaningful subgroup analyses as the study was likely to be underpowered to detect clinically meaningful changes.*
Other relevant information	-

Table 78 Main characteristics of study NCT02682381

Trial name: A 24-Week Double-blind, Safety, Efficacy, and Pharmacodynamic Study Investigating Two Doses of Teduglutide in Pediatric Subjects Through 17 Years of Age With Short Bowel Syndrome Who Are Dependent on Parenteral Support Publication title: Safety and Efficacy of Teduglutide in Pediatric Patients With Intestinal Failure due to Short Bowel Syndrome: A 24-Week, Phase III Study	NCT number: NCT02682381
Objective	*Evaluate the safety and efficacy of teduglutide in children up to the age of 17 with SBS who are dependent on parenteral support. Subjects may choose whether to receive the study drug or to participate in a standard-of-care arm. All participants who complete the study may be eligible to receive the study drug in a long-term extension study.*
Publications – title, author, journal, year	*Kocoshis, S. A., Merritt, R. J., Hill, S., Protheroe, S., Carter, B. A., Horslen, S., Hu, S., Kaufman, S. S., Mercer, D. F., Pakarinen, M. P., Venick, R. S., Wales, P. W., & Grimm, A. A. (2019). Safety and Efficacy of Teduglutide in Pediatric Patients With Intestinal Failure due to Short Bowel Syndrome: A 24-Week, Phase III Study. Journal of Parenteral and Enteral Nutrition, 44(4), 621–631. https://doi.org/10.1002/jpen.1690*

Trial name: A 24-Week Double-blind, Safety, Efficacy, and Pharmacodynamic Study Investigating Two Doses of Teduglutide in Pediatric Subjects Through 17 Years of Age With Short Bowel Syndrome Who Are Dependent on Parenteral Support

NCT number: NCT02682381

Publication title: Safety and Efficacy of Teduglutide in Pediatric Patients With Intestinal Failure due to Short Bowel Syndrome: A 24-Week, Phase III Study

Study type and design	*Phase III trial with 2 randomized, double-blind teduglutide dose groups and a nonblinded standard of care (SOC) arm. Participant, Care Provider, Investigator were masked during the entire study.*

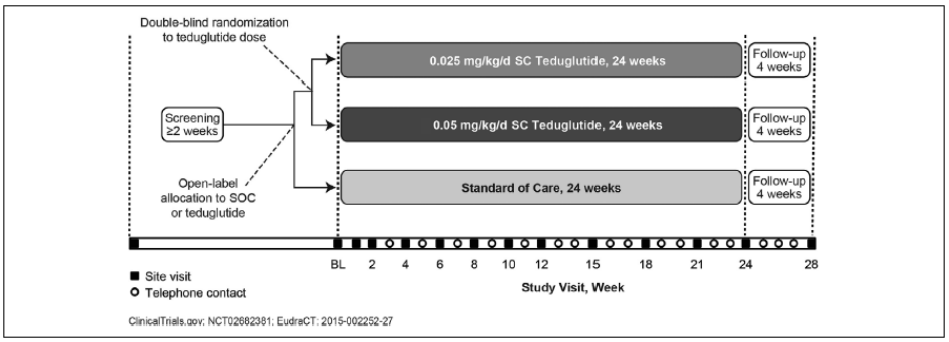


Figure 1. Study design. After screening, site visits occurred at baseline (day 0) and at the indicated study weeks. For all other study weeks, patients were contacted by telephone. BL, baseline; SC, subcutaneous; SOC, standard of care.

Sample size (n)	*59*

Main inclusion and exclusion criteria	*Inclusion Criteria:* • *Informed consent by a parent or guardian or emancipated minor prior to any study-related procedures* • *When applicable, an informed assent by the subject (as deemed appropriate by the Ethics Committee/Institutional Review Board) prior to any study-related procedures* • *Current history of SBS as a result of major intestinal resection, (e.g., due to necrotizing enterocolitis, midgut volvulus, intestinal atresia, or gastroschisis)* • *Short bowel syndrome that requires PN/IV support that provides at least 30% of caloric and/or fluid/electrolyte needs prior to screening* • *Stable PN/IV support, defined as inability to significantly reduce PN/IV support, usually associated with minimal or no advance in enteral feeds (i.e., 10% or less change in PN or advance in feeds) for at least 3 months prior to and during screening, as assessed by the investigator.* • *Sexually active female subjects of child-bearing potential (in the teduglutide treatment arm only) must use medically acceptable methods of birth control during and 4 weeks after the treatment period* *Exclusion Criteria:* • *Subjects who are not expected to be able to advance oral or tube feeding regimens* • *Serial transverse enteroplasty or any other bowel lengthening procedure performed within 3 months of screening* • *Known clinically significant untreated intestinal obstruction contributing to feeding intolerance and inability to reduce parenteral support* • *Unstable absorption due to cystic fibrosis or known DNA abnormalities* • *Severe, known dysmotility syndrome, such as pseudo-obstruction or persistent, severe, active gastroschisis-related dysmotility, that is the primary contributing factor to feeding intolerance and inability to reduce parenteral support, prior to screening. Dysmotility is defined as severe if it is expected to limit the advancement of enteral feeding.* • *Evidence of clinically significant obstruction on upper GI series done within 6 months prior to screening.* • *Major GI surgical intervention including significant intestinal resection within 3 months prior to the screening visit (insertion of feeding tube, anastomotic ulcer repair, minor intestinal resections ≤ 10 cm, or endoscopic procedure is allowed).* • *Unstable cardiac disease, congenital heart disease or cyanotic disease, with the exception of subjects who had undergone ventricular or atrial septal defect repair, and patent ductus arteriosus (PDA) ligation.* • *History of cancer or clinically significant lymphoproliferative disease, not including resected cutaneous basal or squamous cell carcinoma, or in situ non aggressive and surgically resected cancer.* • *Pregnant or lactating female subjects (in the teduglutide treatment arm only).* • *Participation in a clinical study using an experimental drug (other than glutamine or Omegaven) within 3 months or 5.5 half-lives of the experimental drug, whichever is longer, prior to screening, and for the duration of the study.* • *Previous use of teduglutide or native/synthetic glucagon-like peptide-2 (GLP-2)* • *Previous use of glucagon-like peptide-1 analog or human growth hormone within 3 months prior to screening*

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Trial name: A 24-Week Double-blind, Safety, Efficacy, and Pharmacodynamic Study Investigating Two Doses of Teduglutide in Pediatric Subjects Through 17 Years of Age With Short Bowel Syndrome Who Are Dependent on Parenteral Support Publication title: Safety and Efficacy of Teduglutide in Pediatric Patients With Intestinal Failure due to Short Bowel Syndrome: A 24-Week, Phase III Study	NCT number: NCT02682381

- *Previous use of octreotide, or dipeptidyl peptidase-4 (DPP-4) inhibitors within 3 months prior to screening*
- *Subjects with active Crohn's disease who had been treated with biological therapy (e.g., antitumor necrosis factor [anti-TNF]) within the 6 months prior to the screening visit*
- *Subjects with inflammatory bowel disease (IBD) who require chronic systemic immunosuppressant therapy that had been introduced or changed during the 3 months prior to screening*
- *More than 3 SBS-related or PN-related hospital admissions (e.g., documented infection-related catheter sepsis, clots, bowel obstruction, severe water-electrolyte disturbances) within 3 months prior to the screening visit*
- *Any major unscheduled hospital admission which affects parenteral support requirements within 1 month prior to or during screening, excluding uncomplicated treatment of bacteremia, central line replacement/repair, or issues of similar magnitude in an otherwise stable subject*
- *Body weight < 10 kg at the screening and baseline visits*
- *Signs of active severe or unstable, clinically significant hepatic impairment during the screening period, as indicated by any of the following laboratory test results :*
- *Total bilirubin (TBL) ≥ 2 x upper limit of normal (ULN)*
    - *Aspartate aminotransferase (AST) ≥ 7x ULN*
    - *Alanine aminotransferase (ALT) ≥ 7x ULN*

  For subjects with Gilbert's disease:

    - *Indirect (unconjugated) bilirubin ≥ 2x ULN*
- *Signs of known continuous active or unstable, clinically significant renal dysfunction shown by results of an estimated glomerular filtration rate (eGFR) below 50 mL/min/1.73 m2.*
- *Parent(s) and/or subjects who are not capable of understanding or not willing to adhere to the study visit schedule and other protocol requirements*
- *Unstable, clinically significant active, untreated pancreatic or biliary disease*
- *Any condition, disease, illness, or circumstance that in the investigator's opinion puts the subject at any undue risk, prevents completion of the study, or interferes with analysis of the study results.*

Intervention	• *Teduglutide 0.025 mg/kg/d subcutaneous injection (n=24)* • *Teduglutide 0.05 mg/kg/d subcutaneous injection (n=26)*
Comparator(s)	• *Standard of Care (n=9)*
Follow-up time	*28 weeks*

Trial name: A 24-Week Double-blind, Safety, Efficacy, and Pharmacodynamic Study Investigating Two Doses of Teduglutide in Pediatric Subjects Through 17 Years of Age With Short Bowel Syndrome Who Are Dependent on Parenteral Support Publication title: Safety and Efficacy of Teduglutide in Pediatric Patients With Intestinal Failure due to Short Bowel Syndrome: A 24-Week, Phase III Study	NCT number: NCT02682381

Is the study used in the health economic model?	*No*
Primary, secondary and exploratory endpoints	*State all primary, secondary and exploratory endpoints of the study, regardless of whether results are provided in this application. Definition of included outcomes and results are provided in appendix D.* *Primary:* • *Number of Participants Who Achieved at Least a 20 Percent (%) Reduction in Weight-Normalized Average Daily Parenteral Nutrition Intravenous (PN/IV) Volume at Week 24* *Secondary:* • *Number of Participants With Treatment-emergent Adverse Events (TEAEs)* • *Number of Participants Who Were Completely Weaned Off Parenteral Nutrition Intravenous (PN/IV) Support at Week 24* • *Change From Baseline in Parenteral Nutrition Intravenous (PN/IV) Volume at Week 24* • *Change From Baseline in Parenteral Nutrition Intravenous (PN/IV) Caloric Intake at Week 24* • *Change From Baseline in Plasma Citrulline Levels at Week 24* • *Change From Baseline in Enteral Nutrition Volume at Week 24* • *Change From Baseline in Enteral Nutrition Caloric Intake at Week 24* • *Change From Week 24 in Parenteral Nutrition Intravenous (PN/IV) Volume at Week 28* • *Change From Week 24 in Parenteral Nutrition Intravenous (PN/IV) Caloric Intake at Week 28* • *Change From Week 24 in Plasma Citrulline Levels at Week 28* • *Change From Week 24 in Enteral Nutrition Volume at Week 28* • *Change From Week 24 in Enteral Nutrition Caloric Intake at Week 28* • *Change From Baseline in Body Weight Z-score at Week 28* • *Change From Baseline in Body Height Z-score at Week 28* • *Change From Baseline in Head Circumference Z-score at Week 28* • *Change From Baseline in Body Mass Index (BMI) Z-score at Week 28* • *Change From Baseline in Participants' Stool Consistency at Week 28* • *Change From Baseline in Hours Per Day of Parenteral Nutrition Intravenous (PN/IV) Support at Week 24* • *Change From Baseline in Days Per Week of Parenteral Nutrition Intravenous (PN/IV) Support at Week 24*

Trial name: A 24-Week Double-blind, Safety, Efficacy, and Pharmacodynamic Study Investigating Two Doses of Teduglutide in Pediatric Subjects Through 17 Years of Age With Short Bowel Syndrome Who Are Dependent on Parenteral Support Publication title: Safety and Efficacy of Teduglutide in Pediatric Patients With Intestinal Failure due to Short Bowel Syndrome: A 24-Week, Phase III Study	NCT number: NCT02682381
Method of analysis	*All efficacy analyses were intention-to-treat analyses. Given the rarity of SBS, the planned sample size was based on the estimated feasibility of enrollment in the pediatric population with SBS rather than on power calculations, and no statistical hypothesis testing of efficacy was therefore prespecified in the protocol. However, because of unexpectedly high enrollment, post hoc statistical analysis of the primary end point and the mean reduction in PS volume was performed. Limited post hoc statistical comparison on the primary end point and the most relevant secondary efficacy end point, PS volume, was performed. Post hoc analysis of the primary end point between each teduglutide dose group and the SOC arm, and between each other, employed Fisher exact test and 95% CI of the difference using the Newcombe-Wilson method with continuity correction. Additionally, the percentage change in PS volume from baseline to EOT was compared between each teduglutide dose group and the SOC arm, and between each other, using the Wilcoxon rank sum test. The resulting P-values and CI were not adjusted for multiplicity..*
Subgroup analyses	*The small number of subjects in the study hindered meaningful subgroup analyses as the study was likely to be underpowered to detect clinically meaningful changes.*
Other relevant information	-

Appendix C

Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

Table 79 Baseline characteristics of patients in the adult studies included for the evaluation of efficacy and safety

Baseline characteristics of patients in the adult studies included for the evaluation of efficacy and safety		
	Safety and Efficacy Study of Teduglutide in Subjects With Short Bowel Syndrome	Study of Teduglutide Effectiveness in Parenteral Nutrition (PN)-Dependent Short Bowel Syndrome (SBS) Subjects (STEPS)
	Placebo (n=16) /Teduglutide (n=35)	Placebo (n=43)/Teduglutide 0.05 mg (n=43)
Age (years), mean (SD)	49.4 (15.1)/ 47.1 (14.2)	49.7 (15.6)/ 50.9 (12.6)
BMI (kg/m2, mean (SD)	22.0 (2.9)/21.2 (3.0)	22.3 (3.1)/ 22.5 (3.2)
Female sex, n (%)	9 (56.3%)/ 18 (51.4%)	24 (56)/ 22 (51)
Cause of major intestinal resection, n (%)		
Crohn's disease	7 (44%)/10 (29%)	8 (19)/10 (23)
Vascular disease	3 (19%)/14 (40%)	16 (37)/13 (30)
Injury	1 (6%)/3 (9%)	4 (9)/4 (9)
Volvulus	2 (13%)/5 (14%)	6 (14)/3 (7)
Other	3 (19%)/3 (9%)	7 (16)/12 (28)
Patients in whom the intestinal anatomy or remnant small bowel length was unknown	0/1	3/3

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Jejunostomy/ileostomy, n		
Ileostomy	1/2	9/6
Jejunostomy	4/6	5/11
Colon in continuity, n (%)	11 (69)/26 (74)	23 (54)/26 (61)
Overall remnant small bowel length, **Mean (SD), cm**	77 (53)/ 58 (44)	68.7 (63.9)/84.4 (64.6)
Remnant small bowel length in patients with jejunostomy/ileostomy, mean (SD), cm	144 (52)/ 105 (54)	122.8 (81.6)/ 137.7 (70.9)
Remnant small bowel length in patients with colon in continuity, mean (SD), cm	53 (26)/ 45 (29)	43.3 (31.5)/ 52.4 (31.8)
Remnant colon, n (%)		
>25-50% colon remnant	4 (36%)/7 (27%)	5 (12)/ 14 (33)
>50-75% colon remnant	4 (36%)/9 (35%)	8 (19)/ 6 (14)
>75-100% colon remnant	3 (27%)/10 (39%)	10 (23)/3(7)
Parenteral volume, ml/day Mean (SD)	1531 (874)/ 1374 (639)	1929 (1026)/ 1844 (1057)
Time on parenteral support, (Mean (SD), y	7.9 (7.5)/ 6.6 (6.5)	5.9 (5.7)/ 6.8 (6.3)
Concomitant medication		
Antidiarrhoeal agents, n (%)	8 (50%)/22 (63%)	16 (37)/ 22 (51)
Antisecretory agents, n (%)	7 (44%)/19 (54%)	22 (51)/ 25 (58)

Table 80 Baseline characteristics of patients in the paediatric studies included for the evaluation of efficacy and safety

Baseline characteristics of patients in the paediatric studies included for the evaluation of efficacy and safety		
	A 12-Week Pharmacokinetic, Safety, and Pharmacodynamic Study of Teduglutide in Pediatric Subjects Aged 1 Year Through 17 Years, With Short Bowel Syndrome Who Are Dependent on Parenteral Support	A 24-Week Double-blind, Safety, Efficacy, and Pharmacodynamic Study Investigating Two Doses of Teduglutide in Pediatric Subjects Through 17 Years of Age With Short Bowel Syndrome Who Are Dependent on Parenteral Support
	Placebo (SOC, n=5)/Teduglutide (n=15)	Placebo (SOC, n=9)/Teduglutide 0.05 mg/kg (n=26)
Age, mean (SD), y	2.2 (0.45)/ 4.5 (3.16)	6 (5)/ 6 (4)
Gender, male	3 (60)/8 (53)	6 (67)/ 19 (73)
Race		
White	3 (60)/ 13 (87)	2 (22)/ 21 (81)
Black	1 (20)/ 1 (7)	1 (11)/ 3 (11)
Asian	1 (20)/ 1 (7)	1 (11)/ 1 (4)
Other/Not applicable/Not allowed based on legal regulations	0/0	5(56)/ 1(4)
Reason for resection, n (%)*		
Necrotizing enterocolitis	2 (40)/ 2 (14)	2 (22)/ 3 (12)
Midgut volvulus	2 (40)/ 4 (29)	3 (33)/ 6 (23)
Intestinal atresia	1(20)/ 4 (29)	0/1(4)
Gastroschisis	0/7(50)	2 (22)/ 14 (54)
Other	0/0	2(22)/(2(8)
Patients with a stoma, n (%)	0/1(7)	3 (33)/ 5 (20)

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Jejunostomy	0/0	2 (67)/ 4 (80)
Ileostomy	0/1(110)	1 (33)/ 1 (20)
Colostomy	0/0	0/0
Estimated residual small intestine length, mean (SD), cm	37.4 (25.89)/ 32.8 (21.74)	45 (31)/ 47 (28)
Ileocecal valve present, n (%)	1 (20)/ 4 (27)	3 (100)/ 7 (78)
Intact colon, n (%)	5 (100)/ 14 (100)	25 (96)/6 (67)
Estimated colon remaining, mean (SD) %	66.6 (31.27)/ 75.4 (29.77)	69 (31)/60 (34)
Colon-in-continuity, n (%)†	5 (100)/ 14 (100)	6 (100)/ 22 (88)

*Patients may have had ≥1 reason for resection. Each reason has been accounted for and thus sums may not total the n listed in the header and percentages may not total 100%.
†Percentages are based on patients with remaining colon in each treatment arm.
‡Category includes only those patients who received EN at baseline.
§Use of probiotics in this patient population is controversial; listing of probiotics as a concomitant medication is not intended as an endorsement of this practice.

Comparability of the study populations with Danish patients eligible for treatment

Based on personal communication with Dr. Palle Jeppesen on the 04.10.2021 the following difference in the STEPS study population vs. the Danish patient population is suggested; percentage of patients with colon-in-continuity (61% vs. <20%), weekly PS volume (13L/wk. vs 17 L/wk.) and non-IBD etiology (77% vs 50%).

These changes are suggested by Dr. Jeppesen to result in a greater efficacy of teduglutide in terms of absolute PS volume reduction, but due to a higher baseline PS need also a lower probability for days of PN and complete parenteral autonomy.[93] However, meta-analysis of 8 published real-world data has demonstrated that the efficacy of teduglutide in a real world clinical setting is on par with was seen in the pivotal STEPS study, and the proportion of patients who achieve complete weaning is actually higher compared to STEPS.[64] Thus, the external validity of the clinical data set of STEPS must be seen as high and the effect estimate is most likely conservative.

Additional study details on the adult and paediatric extension studies and SBS-registry (not used in the comparative analysis)

STEPS-2

Baseline demographics and characteristics of the study population are summarized in Table 81 below.

Table 81 Baseline demographics and characteristics of the overall study population in STEPS-2.

AE preferred term, n (%)	TED/TED (n = 37)	PBO/TED (n = 39)	NT/TED (n = 12)	All Patients (N = 88)
Mean (s.d.) age, years	51.8 (12.5)	50.4 (15.9)	50.0 (13.9)	50.9 (14.2)
Mean (s.d.) body weight, kg	62.7 (12.1)	61.1 (13.2)	65.8 (12.9)	62.4 (12.6)
Mean (s.d.) BMI, kg/m^2	22.3 (3.3)	22.0 (3.2)	22.9 (3.9)	22.3 (3.3)
Men, n (%)	18 (49)	17 (44)	41 (47)6 (50)	6 (50)
Reason for resection, n (%)				
Vascular disease	12 (32)	15 (38)	2 (17)	29 (33)
Crohn's disease	8 (22)	7 (18)	1 (8)	16 (18)
Volvulus	3 (8)	6 (15)	2 (17)	11 (13)
Injury	4 (11)	3 (8)	0	7 (8)
Cancer	1 (3)	2 (5)	0	3 (3)
Other	9 (24)	6 (15)	7 (58)	22 (25)
Colon-in-continuity, n (%)	24 (65)	23 (59)	7 (58)	54 (61)
Mean (s.d.) percentage of colon remaining	55 (21)	70 (27)	60 (37)	63 (27)
Median (range) estimated remaining small intestine,[a] cm	60.0 (20–250)	43.0 (5–170)	45.0 (15–150)	50.0 (5–250)
Stoma, n (%)	17 (46)	14 (36)	5 (42)	36 (41)
Mean (range) time since start of PS dependence, years	7.0 (1.0–24.7)	6.0 (1.0–25.8)	6.2 (1.1–20.8)	6.4 (1.0–25.8)

BMI, body mass index; NT/TED, received no treatment in the initial placebo-controlled study and teduglutide in STEPS-2; PBO/TED, received placebo in the initial placebo-controlled study and teduglutide in STEPS-2; PS, parenteral support (parenteral nutrition and/or intravenous fluids); TED/TED, received teduglutide in the initial placebo-controlled study and in STEPS-2. [a] Includes only patients with known residual small intestine length.

The primary patient population for all analyses was the intent-to-treat population, defined as all patients who signed informed consent. Descriptive statistics summarized the change from baseline in efficacy variables at each time point. The study was not sufficiently powered to determine the statistical significance of safety or efficacy end points.

Of the 78 patients who completed the initial placebo-controlled study and were eligible for STEPS-2, 76

enrolled in the extension (n=37 TED/TED; n=39 PBO/TED). An additional 12 patients who were screened and optimized in the placebo-controlled study but not randomized were enrolled directly in STEPS-2. Of the 88 patients enrolled in STEPS-2, 65 (74%) completed the study (n=30/37 TED/TED; n=29/39 PBO/TED; n=6/12 NT/TED).

STEPS-3

Though STEPS-3 was designed primarily to assess the long-term safety of TED in patients with SBS–IF, efficacy outcome data were collected using measures from the original STEPS study. Eligible adult participants in STEPS-3 had completed 24 months of TED treatment in STEPS-2, regardless of whether they had been weaned from PS All patients received TED 0.05 mg/kg/day by subcutaneous injection. The STEPS-3 study population was stratified into 2 subgroups for the purpose of data analysis, depending on length of TED treatment (Figure 1). The TED–TED subgroup was composed of patients who received TED in the initial PBO-controlled trial (STEPS) and in the open-label STEPS-2 study. The no teduglutide treatment (NT)/PBO–TED subgroup included patients who received NT (entered STEPS-2 directly) or PBO in the initial PBO-controlled trial (STEPS) and TED in STEPS-2. Prespecified efficacy parameters included absolute and relative change from baseline in actual PS volume received, reduction in days of PS infusions per week, and number of patients who achieved independence from PS in the STEPS-3 study.

Of the 14 patients who completed treatment with TED in STEPS-2 and enrolled in STEPS-3 (ITT population), 13 patients completed the study. One patient was lost to follow-up after being treated with TED for 8 months; however, available data from this patient were included in the analysis. The confluence of the rolling start dates and the study end date meant that all patients did not receive 12 months of TED treatment. The mean (SD) duration of exposure to TED during STEPS-3 was 38.9 (9.8) weeks for the overall population, 41.5 (8.4) weeks for NT/PBO–TED, and 34.3 (11.3) weeks for TED–TED. Combined with the TED treatment in the STEPS-2 study, the total TED exposure time was ≤36 months for NT/PBO–TED and ≤42 months for TED–TED.

Baseline demographics and characteristics of the study population are summarized in Table 82 below.

Table 82 Baseline demographics and characteristics of the overall study population in STEPS-3.

Characteristic	NT/PBO–TED[a] (n = 9)	TED–TED[b] (n = 5)	All Patients (n = 14)
Mean (SD) age,[c] years	55.9 (12.2)	55.8 (10.7)	55.9 (11.3)
Age range, n (%)			
<45 years	2 (22)	1 (20)	3 (21)
45–<65 years	6 (67)	3 (60)	9 (64)
>65 years	1 (11)	1 (20)	2 (14)
Women, n (%)	6 (67)	4 (80)	10 (71)
Race, n (%)			
White	7 (78)	5 (100)	12 (86)
Black	2 (22)	0	2 (14)
Ethnicity, n (%)			
Not Hispanic or Latino	9 (100)	5 (100)	14 (100)

Mean (SD) body weight, kg	68.5 (14.2)	58.4 (14.2)	64.9 (14.5)
Mean (SD) BMI, kg/m^2	24.4 (4.2)	21.8 (3.2)	23.5 (3.9)
Reason for resection, n (%)			
Vascular disease	1 (11)	3 (60)	4 (29)
Crohn's disease	2 (22)	0	2 (14)
Injury	1 (11)	1 (20)	2 (14)
Volvulus	1 (11)	0	1 (7)
Cancer	0	0	0
Other	4 (44)	1 (20)	5 (36)
Colon remaining, n (%)	7 (78)	3 (60)	10 (71)
Colon-in-continuity, n (%)	5 (56)	3 (60)	8 (57)
Mean (SD) percentage of colon remaining[d]	52.6 (39.9)	50.0 (0.0)	51.8 (32.6)
Median (range) estimated remaining small intestine,[e] cm	55 (17–100)	76 (30–190)	66 (17–190)
Stoma, n (%)	2 (22)	3 (60)	5 (36)
Mean (SD) time since start of PS dependence, years	6.5 (9.1)	5.0 (3.5)	6.0 (7.4)

BMI, body mass index; NT, no teduglutide treatment; PBO, placebo; PS, parenteral support (parenteral nutrition and/or intravenous hydration); TED, teduglutide.

[a]NT/PBO–TED received NT or PBO in initial PBO-controlled trial (STEPS) and TED in STEPS-2.

[b]TED–TED received TED in initial PBO-controlled trial (STEPS) and in STEPS-2.

[c]Age at informed consent in initial PBO-controlled trial (STEPS).

[d]Includes only patients with a colon (NT/PBO−TED, n = 7; TED−TED, n = 3; all patients, n = 10).

[e]Includes only patients with known residual small intestine length (NT/PBO−TED, n = 7; TED−TED, n = 5; all patients, n = 12).

From study baseline to the final dosing visit, mean (SD) total PS volume was reduced during the STEPS-3 study period by 9.8 (14.4) and 3.9 (2.8) L/week for patients in the TED–TED and NT/PBO–TED subgroups, respectively. The mean (SD) percentage reduction from baseline in PS volume was 49.7% (72.4%) for the TED−TED subgroup and 47.8% (42.9%) for the NT/PBO−TED subgroup. In addition to the mean volume reduction with time during STEPS-3 compared with baseline, patients reduced the frequency of required PS infusions. For patients in the TED–TED subgroup, the reduction from baseline in mean (SD) days per week receiving PS at the last dosing study visit in this extension study was 3.0 (4.6) days. Patients in the NT/PBO–TED subgroup had a reduction of 2.1 (2.2) days per week receiving PS. Eight of 14 patients had a ≥1-day reduction in PS, and 6 of 14 patients had a ≥3-day reduction. At the completion of the STEP-3 study, 4 patients were independent from PS. Two patients with no stoma, colon-in-continuity, and baseline PS volumes of 4.5 and 4.7 L/week achieved enteral autonomy after 126 and 130 weeks, respectively, with TED treatment. The other 2 patients had achieved independence from PS during the STEPS-2 study and maintained long-term enteral autonomy in STEPS-3. These 2 patients had no stoma and baseline PS volumes of 4.1 and 6.3 L/week, respectively.

Paediatric safety analysis

Patients were eligible for inclusion in the extension studies if they completed the 12-week or 24-week core study in either the teduglutide or SoC arm. All patients who enrolled in the extension study following the 12-week core study experienced a gap of 2.4–3.3 years between studies due to a lag in study setup; patient safety data from this interstudy gap period were not included in this analysis. There was no gap in follow-up between the 24-week study and the respective extension study. The data cutoff for the interim analysis of prospective safety data included here was July 24, 2018.

In the ongoing extension studies, teduglutide is provided to children with SBS–IF in treatment cycles consisting of 24 weeks of 0.05 mg/kg teduglutide once daily followed by a 4-week follow-up period. After a teduglutide treatment period, teduglutide is only reinitiated if a patient's PS plateaus or deteriorates. At the end of the 4-week follow-up, patients who have not reinitiated teduglutide can enter a "no-teduglutide treatment" period of observation with safety and clinical data collection approximately every 12 weeks.

Table 83 Patient Demographics and Baseline Characteristics.

	N = 89
Parameter	**n (%)**
Age, mean (SD), years	5.6 (3.64)
Median (min, max), years	5.0 (1, 15)
Age group, n (%), years	
1 to <12	82 (92.1)
Infants, <2	5 (5.6)
Children, 2 to <12	77 (86.5)
12 to <18	7 (7.9)
Sex, n (%)	
Boys	61 (68.5)
Race, n (%)	
White	67 (75.3)
Black or African American	10 (11.2)
Asian	3 (3.4)
Other	3 (3.4)
Not available	6 (6.7)
Growth parameter at baseline	
Weight z-score,[a] mean (SD)	–0.8 (1.02)
Median (min, max)	–0.8 (–3.4, 1.0)
Height z-score,[a] mean (SD)	–1.2 (1.18)
Median (min, max)	1.0 (–4.3, 1.9)
BMI z-score,a mean (SD)	–0.03 (1.023)
Median (min, max)	-0.05 (-3.6, 2.4)
Primary reason for SBS diagnosis, n (%)	
Gastroschisis	30 (33.7)
Midgut volvulus	25 (28.1)
Necrotizing enterocolitis	15 (16.9)
Intestinal atresia	10 (11.2)
Hirschsprung disease	7 (7.9)
Multiple	2 (2.2)
Patients with a stoma, n (%)	17 (19.1)

Type of stoma	
Jejunostomy	11 (12.4)
Ileostomy	4 (4.5)
Colostomy	2 (2.2)
Total remaining small-intestine length, mean (SD),[b] cm	45.9 (33.94)
Min, max	0, 147.0
Distal/terminal ileum present, n (%)[c]	27 (31.4)
Ileocecal valve present, n (%)[d]	22 (25.6)
Patients with remaining colon, n (%)	82 (92.1)
Estimated percentage of colon remaining, mean (SD)[e]	66.9 (32.99)
Colon in continuity, n (%)	76 (85.4)
Colon present but not in continuity, n (%)	6 (6.7)
Duration of prior PS dependence, mean (SD), years	5.0 (3.2)
Baseline PS volume requirements, mean (SD),[f,g] mL/kg/day	62.7 (27.77)
Baseline PS calories, mean (SD),[f,h] kcal/kg/day	45.1 (18.41)
Baseline days per week of PS infusion, mean (SD)[f,i]	6.7 (0.82)
Baseline hours per day of PS infusion, mean (SD)[f,i]	12.0 (3.37)

BMI, body mass index; max, maximum; min, minimum; PS, parenteral support; SBS, short-bowel syndrome.

[a] Computer programs. Centers for Disease Control and Prevention. May 16, 2014. Accessed November 20, 2020. https://www.cdc.gov/growthcharts/computer_programs.htm

[b] n = 80.

[c] n = 86.

[d] Percentage based on total number of patients with data available on presence of distal/terminal ileum (n = 86).

[e] n = 70.

[f] Based on patients' diary data. PS volume and PS calories were calculated on a weekly basis and divided by the number of days (ie, 7) to provide values in mL/kg/day or kcal/kg/day.

[g] n = 82.

[h] n = 76.

[i] n = 85.

A Prospective, Multicenter Registry for Patients with Short Bowel Syndrome and Intestinal Failure (SBS-IF Registry)

Registry participants

- The SBS-IF registry (NCT01990040; EUPAS7973) was initiated in 2014 and enrollment is planned for 7 years with at least 10 years of follow-up for each patient.
- The SBS-IF registry includes teduglutide-exposed and teduglutide-unexposed patients with SBS-IF of any age.
- Patients cannot be included in the registry if they meet any of the following criteria:
  - current participation in a blinded clinical trial or its extension study
  - never treated with PS
  - current or previous exposure to any GLP-2 analogs other than teduglutide.

Table 84 Patient Demographics and Baseline Characteristics

	Teduglutide ever-treated (N=328)	Teduglutide never-treated (N=675)
Age, years, mean (SD)	54.1 (14.85)	57.4 (15.08)
Male, n (%)	139 (42.4)	265 (39.3)
Body mass index, kg/m^2, mean (SD)	n=295 22.88 (5.04)	n=610 23.02 (4.70)
Age at onset/diagnosis of SBS, years, mean (SD)	n=313 45.4 (17.52)	n=633 49.2 (18.22)
Duration between onset/diagnosis of SBS and enrollment, years, mean (SD)	n=317 8.4 (9.17)	n=634 8.3 (9.91)
Cause of major intestinal resection, n (%)	n=320	n=641
Crohn's disease	114 (35.6)	148 (23.1)
Intestinal ischemia	39 (12.2)	75 (11.7)
Mesenteric infarction	28 (8.8)	47 (7.3)
Intestinal volvulus	25 (7.8)	33 (5.1)
Motility disorder	6 (1.9)	49 (7.6)
Cancer	37 (5.8)	5 (1.6)
Length of remaining small intestine, cm, mean (SD)	n=270 80.01 (51.92)	n=533 107.51 (84.84)
Presence of stoma, n (%)	n=318 173 (54.4)	n=638 360 (56.4)
Type of stoma, n (%)[a]	n=173	n=360
Ileostomy	100 (57.8)	178 (49.4)
Jejunostomy	50 (28.9)	129 (35.8)
Colostomy	35 (20.2)	67 (18.6)
Other[b]	5 (2.9)	26 (7.2)
Colon status, n (%)	n=319	n=641
Intact	59 (18.5)	150 (23.4)
Remnant	166 (52.0)	338 (52.7)
No colon	94 (29.5)	153 (23.9)
Percentage of colon remaining, mean (SD)	n=100 48.38 (25.19)	n=161 55.43 (22.78)
Volume of PS, L/week, mean (SD)	n=218 9.687 (5.928)	n=547 11.981 (7.812)[c]
Number of days of PS, days/week, mean (SD)	n=223 5.215 (1.820)	n=551 5.612 (1.791)

[a]Among patients with stoma, patients may have multiple specified stoma types.

[b]Other included gastrostomy, duodenostomy, gastroduodenostomy and cecostomy.

[c]PS volumes for four patients were judged to be clinically unrealistic (>50 L/week) so were excluded from the calculation. PS, parenteral support; SBS, short bowel syndrome; SD, standard deviation.

[redacted]

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Appendix D

Efficacy and safety results per study

Definition, validity and clinical relevance of included outcome measures

Table 86 Definition, validity and clinical relevance of included outcome measures

Outcome measure	Definition	Validity	Clinical relevance
Graded Response Score	Achieving at least a 20% reduction from Baseline in weekly PN volume with a maximum reduction of 100% from Baseline. The criterion accounted for both intensity and duration of a response at the end of the 24-week period. The intensity of the response relied on a reduction from baseline in weekly parenteral volume (from 20% to 100%). The duration of the response considered the responses at weeks 16 and 20, as well as weeks 20 and 24. The analysis of this expanded end point took into account higher levels of response and earlier onset of response coupled with a longer duration of response. Thus, the score arose from the concept that, optimally, a graded change could be seen at the earlier time point and still observed at the later time point.	The outcome measure is not validated	This magnitude of response was deemed to be clinically relevant based on expert opinion.[94] PN volume reductions are associated with improvements in SBS-QoL.[16] For further details, please see below.
Clinical response	Percentage of patients who demonstrated a response at week 20 and maintained that response at week 24 (responder) A response at a given visit was defined as the achievement of a 20% to 100% reduction from baseline in weekly PS volume.	The outcome measure is not validated	PN volume reductions are associated with improvements in SBS-QoL.[16] The magnitude of response was deemed to be clinically relevant based on expert opinion.[94] This opinion was further supported by the CHMP during European regulatory review and is also in agreement based on discussions with the FDA.[85,95] In the STEPS study mean (SD) time receiving PS was 5.9 (1.5) and 5.6 (1.7) d/wk. with a median of 7.0 days for placebo and teduglutide 0.05 mg/kg, respectively. Thus a reduction of ≥20% in absolute PS volume was chosen because it would translate to the average home parenteral nutrition patient being able to eliminate 1 day of PN per week.

Outcome measure	Definition	Validity	Clinical relevance
Number and percentage of subjects who achieved at least a 1-day reduction in weekly PN	N/A	See above	See above
Absolute reduction from Baseline in weekly PN kilojoules (transformed from kilocalories)	N/A	N/A	The MCID has not been established
Absolute reduction from Baseline in weekly volume of PN	N/A	N/A	The MCID has not been established
Change from Baseline in plasma citrulline at Dosing Week 24	N/A	The outcome measure is not validated	Citrulline is an amino acid produced by enterocytes and used as a biomarker of remnant mucosal mass.[96] The MCID has not been established.
Duration of response, The percentage of subjects with a duration of response for ≥3 consecutive visits	N/A	The outcome measure is not validated	The MCID has not been established
The percentage and absolute change in PS PN/I.V. volume between baseline and last dosing visit	N/A	N/A	The MCID has not been established
Change in PN/I.V. volume by visit	N/A	N/A	The MCID has not been established

Outcome measure	Definition	Validity	Clinical relevance
≥ 10% reduction in PN/IV support	N/A	The outcome measure is not validated	The clinical relevance of ≥ 10% reduction in PN/IV support has not been established
Change in hours per day and days per week of PN/IV support	N/A	N/A	The MCID has not been established
SBS health-related QoL	The SBS-QoL contains 17 items regarding the influence of SBS on different aspects of QoL: general well-being, everyday activities, working life/ability to work, leisure activities, social life, energy level, physical health, mobility and self-care activities, emotional life, sleep, fatigue/weakness, pain, diet, eating and drinking habits, gastrointestinal symptoms, diarrhea/stomal output, skeleton/muscle symptoms and other symptoms/discomfort.	The outcome measure is validated[97]	The MCID has been set to a positive change above 18.4 point. This is based on clinical experts who had taken a conservative approach, defining a positive change above the 2-fold measurement error (9.2) as clinically important. The measurement error of 9.2 was determined during the validation process of the SBS-QoL. This MCID has been debated as the threshold is not anchored on a change that has been proven to be clinical meaningful to patients, which is the preferred methodology recommended by the FDA.[16,48] In a cross-sectional study from 2018 by Nordsten et al it was found that PS volume (L/day) was significantly correlated with SBS-QoL score with an estimate of 7 QoL points per L/day (95% CI:1 to 13; P = 0.044).[50] As of today, no clinical consensus has been reached on what the MCID is, and the benchmark is developing as more research is conducted on the QoL of patients with SBS.[6] The Medicines Council has previously, in the protocol for the evaluation of ustekinumab for the treatment of moderate to severe ulcerative colitis, established a “guiding” MCID and “adjusted” MCID for the absolute percentage change between intervention and comparator at ≥10% and ≥5%, respectively.[98]

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Outcome measure	Definition	Validity	Clinical relevance
Adverse events	Any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical/medicinal product. An AE did not necessarily have to have a causal relationship with the treatment	The outcome measure is not validated	The MCID has not been established
Serious adverse events	SAE was defined as an AE that resulted in any of the following outcomes: Death, was life-threatening, persistent or significant incapacity or substantial disruption of ability to conduct normal life functions , hospitalization or prolongation of existing hospitalization, congenital anomaly/birth defect, important medical events that did not result in death, were life-threatening, or require hospitalization were considered as an SAE when, based upon appropriate medical judgment, they jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed in this definition. Examples of such medical events included allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that did not result in hospitalization, or the d development of drug dependency or drug abuse.	The outcome measure is not validated	The Medicines Council has previously, in the protocol for the evaluation of ustekinumab for the treatment of moderate to severe ulcerative colitis, established a "guiding" MCID and "adjusted" MCID for the absolute percentage change between intervention and comparator at ≥5% and ≥2.5%, respectively.[98]

Results per study

Please see results per study in the tables below.

Table 87 Results of study NCT00081458

Trial name: Safety and Efficacy Study of Teduglutide in Subjects With Short Bowel Syndrome										**NCT number: NCT00081458**	
Publication title: Randomised placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome (Jeppesen_2011 Study 004)											
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		

Trial name: Safety and Efficacy Study of Teduglutide in Subjects With Short Bowel Syndrome Publication title: Randomised placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome (Jeppesen_2011 Study 004)										NCT number: NCT00081458
A graded response score (a scoring algorithm that takes both response intensity and duration between Weeks 16 and 24 into account)	Teduglutide 0.05 mg/kg/d	35	Response Score>0 (responders)*: 16/35 (45.7%)	39.46%	0.37% to 309.25%	0.0089**	Relative risk estimate = 7.31	1.06 to 50.48	0.0089**	*Calculated post hoc from the Clinical study report data to obtain an estimate of the absolute difference **Fisher's Exact Test *The graded response score (GRS) criterion accounted for both intensity and duration of a response at the end of the 24-week period. The intensity of the response relied on a reduction from baseline in weekly parenteral volume (from 20% to 100%). The duration of the response considered the responses at weeks 16 and 20, as well as weeks 20 and 24. The analysis of this expanded end point took into account higher levels of response and earlier onset of response coupled with a longer duration of response as shown in table 1. Thus, the score arose from the concept that, optimally, a graded change could be seen at the earlier time point and still observed at the later time point.*	
	Placebo	16	Response Score>0 (responders)*: 1/16 (6.3%)							

Trial name: Safety and Efficacy Study of Teduglutide in Subjects With Short Bowel Syndrome Publication title: Randomised placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome (Jeppesen_2011 Study 004)										NCT number: NCT00081458
The proportion of subjects achieving a 20% reduction of PN at both Week 20 and Week 24	Teduglutide 0.05 mg/kg/d	35	16/35 (45.7%)	39.46%	0.37% to 309.27%	0.0089	RR: 7.31	1.06 to 50.48	0.0089	*Fisher's Exact Test*
	Placebo	16	1/16 (6.3%)							

Trial name: Safety and Efficacy Study of Teduglutide in Subjects With Short Bowel Syndrome Publication title: Randomised placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome (Jeppesen_2011 Study 004)										NCT number: NCT00081458
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Number and percentage of subjects who achieved at least a 1-day reduction in weekly PN (week 24)	Teduglutide 0.05 mg/kg/d	35	11/35 (31.4%)	6.43	-13.20% to 58.71%	0.7485	RR: 1.26	0.47 to 3.35	0.7485	*Fisher's Exact Test*	
	Placebo	16	4/16 (25.0%)								
				Estimated absolute difference in effect			**Estimated relative difference in effect**			**Description of methods used for estimation**	**References**

Trial name: Safety and Efficacy Study of Teduglutide in Subjects With Short Bowel Syndrome **NCT number: NCT00081458**

Publication title: Randomised placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome (Jeppesen_2011 Study 004)

Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value	
Absolute reduction from Baseline in weekly volume of PN (Weekly PN Kilojoules) (w24)	Teduglutide 0.05 mg/kg/d	28	-6993.9 (-9681.1 to -4306.7)	-3449.30	-7878.45 to 979.85	0.1235	NA	NA	NA	*The absolute difference in effect is estimated using a two-sided t-test.*
	Placebo	15	-3544.6 (-7317.6 to 228.5)							
Absolute reduction from Baseline in weekly volume of PN (L) (w24)	Teduglutide 0.05 mg/kg/d	27	-2.2757 (-3.1972 to -1.3541	-1.41	-2.91 to 0.09	0.0650	NA	NA	NA	*The absolute difference in effect is estimated using a two-sided t-test.*
	Placebo	15	-0.8681 (-2.1356 to 0.3993							
Change from Baseline in plasma citrulline	Teduglutide 0.05 mg/kg/d	27	6.75 (-1.4 to 39.4	5.80	-16.33 to 27.93	0.5994	NA	NA	NA	*The absolute difference in effect is estimated using a two-sided t-test.*

Trial name: Safety and Efficacy Study of Teduglutide in Subjects With Short Bowel Syndrome Publication title: Randomised placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome (Jeppesen_2011 Study 004)										NCT number: NCT00081458	
((µmol/) (W24)	Placebo	15	0.95 (-9.3 to 10.5)								
Adverse Events	Teduglutide 0.05 mg/kg/d	35	94.3% (33/35)	0.54%	-12.64% to 15.85%	0.9399	1.01	0.87 to 1.17	0.9399	*Chi square test*	
	Placebo	16	93.8% (15/16)								
Serious Adverse Events	Teduglutide 0.05 mg/kg/d	35	37.14% (13/35)	5.89%	-15.29% to 55.21%	0.6828	1.19	0.51 to 2.77	0.6828	*Chi square test*	
	Placebo	16	31.25% (5/16)								

Table 88 Results of study NCT000798967

Trial name: Study of Teduglutide Effectiveness in Parenteral Nutrition (PN)-Dependent Short Bowel Syndrome (SBS) Subjects (STEPS)	NCT number: NCT00798967
Publication title: Randomised placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome (Jeppesen_2012 STEPS)	

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
The percentage of subjects who responded at Week 20 and week 24 (responder)	Teduglutide 0.05 mg/kg/d	43*	27/43 (62.8%)	32.56%	7.51% to 74.23%	0.0025	RR: 2.08	1.25 to 3.46	0.0025	Chi square test	*ITT
	Placebo	43*	13/43 (30.2%)								*ITT
The percentage of subjects with a duration of response for ≥3 consecutive visits (Duration of response)	Teduglutide 0.05 mg/kg/d	43*	24/43 (55.8%)	27.91%	4.32% to 68.75%	0.005	RR: 2.00	1.15 to 3.46	0.005	Chi square test	*ITT
	Placebo	43*	12/43 (27.9%)								*ITT

Trial name: Study of Teduglutide Effectiveness in Parenteral Nutrition (PN)-Dependent Short Bowel Syndrome (SBS) Subjects (STEPS) **NCT number: NCT00798967**

Publication title: Randomised placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome (Jeppesen_2012 STEPS)

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Reduction in days on PN/I.V. (the percentage of subjects with at least a 1-day reduction in weekly actual PN/I.V. use at Week 24)	Teduglutide 0.05 mg/kg/d	39**	21/39 (53.8%)	30.77%	5.25% to 79.29%	0.0052	RR: 2.33	1.23 to 4.44	0.005	Chi square test	** ITT with 4 missing at w24
	Placebo	39**	9/39 (23.1%)								** ITT with 4 missing at w24
The absolute change in PS PN/I.V. volume between baseline and last dosing visit (L/week) (w24)	Teduglutide 0.05 mg/kg/d	39**	-4.37 (-5.25 to -3.6)	-2.08	-3.23 to -0.93	<0.001	NA	NA	NA	The absolute difference in effect is estimated using a two-sided t-test.	** ITT with 4 missing at w24
	Placebo	39**	-2.29 (-3.11 to -1.45)								** ITT with 4 missing at w24
The percentage change in PS PN/I.V. volume between	Teduglutide 0.05 mg/kg/d	39**	-32.42 (-39.48 to -25.45)	-11.09	-20.85 to -1.33	0.0265	NA	NA	NA	The absolute difference in effect is estimated using a two-sided t-test.	** ITT with 4 missing at w24

Trial name: Study of Teduglutide Effectiveness in Parenteral Nutrition (PN)-Dependent Short Bowel Syndrome (SBS) Subjects (STEPS) Publication title: Randomised placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome (Jeppesen_2012 STEPS)											NCT number: NCT00798967
baseline and last dosing visit (percentage) (w24)	Placebo	39**	-21.33 (-28.49 to -14.45)								** ITT with 4 missing at w24
Adverse events (Safety population, patients who received ≥1 doses of study drug)	Teduglutide 0.05 mg/kg/d	42***	83.3% (35/42)	4.26%	-11.17% to 23.20%	0.6151	1.05	0.86 to 1.29	0.6151	*Chi square test*	*** Safety population
	Placebo	43	79.1% (34/43)								
Serious Adverse Events (Safety population, patients who received ≥1 doses of study drug)	Teduglutide 0.05 mg/kg/d	42***	35.7% (15/42)	7.81%	-8.86% to 39.07%	0.4395	1.28	0.68 to 2.40	0.4395	*Chi square test.*	*** Safety population (1 not taken drug)
	Placebo	43	27.9% (12/43)								
SBS Quality-of-Life	Teduglutide 0.05 mg/kg/d	35¤	-14.35 (SD= 28.110)	-7.76	-21.33 to 5.81	0.2579	NA	NA	NA	*Student's t-test*	¤ITT with 8 missing
	Placebo	35¤	-6.59 (SD= 28.789)								¤ITT with 8 missing

Trial name: Study of Teduglutide Effectiveness in Parenteral Nutrition (PN)-Dependent Short Bowel Syndrome (SBS) Subjects (STEPS)										NCT number: NCT00798967	
Publication title: Randomised placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome (Jeppesen_2012 STEPS)											
The number of subjects who were weaned off PN/I.V	Teduglutide 0.05 mg/kg/d	43*	0.00% (0/43) 95%-CI 0.00 to 8.22	-1.55	-2.29 to 16.19	1.000	0.3333	0.014 to 7.9614**	1.000	*The absolute difference in effect is estimated using Fisher's Exact Test, absolute difference is calculated using (RR-1)*2.30%* *** These logit estimators use a correction of 0.5 in every cell of those tables that contain a zero.*	*ITT
	Placebo	43*	2.33% (1/43) 95%-CI 0.06 to 12.29								

Table 89 Results of study NCT00930644

Trial name: Open-Label Study of Teduglutide for Subjects With PN-Dependent Short Bowel Syndrome (SBS) (STEPS-2)										NCT number: NCT00930644	
Publication title: Long-Term Teduglutide for the Treatment of Patients With Intestinal Failure Associated With Short Bowel Syndrome											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Clinical response (All patients), 20–100% PS volume reduction from baseline	TED/TED	37	33/37 (89%)	-	-	-	-	-	-	Descriptive statistics	
	PBO/TED	39	18/39 (46%)								

Trial name: Open-Label Study of Teduglutide for Subjects With PN-Dependent Short Bowel Syndrome (SBS) (STEPS-2)											NCT number: NCT00930644
Publication title: Long-Term Teduglutide for the Treatment of Patients With Intestinal Failure Associated With Short Bowel Syndrome											
	NT/TED	12	6/12 (50%)								
Mean PS reduction from baseline, l/week (s.d.)	TED/TED	36	6.79 (4.856)	-	-	-	-	-	-	Descriptive statistics	
	PBO/TED	36	2.85 (3.898)								
	NT/TED	10	3.34 (3.669)								
Percentage reduction in parenteral support volume, last dosing visit ITT population is n =36, n=36, n=10, respectively. (SD)	TED/TED	36	59.16% (34.269)	-	-	-	-	-	-	Descriptive statistics	
	PBO/TED	36	24.75% (33.458%)								
	NT/TED	10	18.50% (54.396%)								
Enteral autonomy and independence from PS (All patients)	TED/TED	37	10/37 (27%)	-	-	-	-	-	-	Descriptive statistics	
	PBO/TED	39	2/39 (5%)								

Trial name: Open-Label Study of Teduglutide for Subjects With PN-Dependent Short Bowel Syndrome (SBS) (STEPS-2)	NCT number: NCT00930644
Publication title: Long-Term Teduglutide for the Treatment of Patients With Intestinal Failure Associated With Short Bowel Syndrome	

	NT/TED	12	1/12 (8%)

Table 90 Results of study NCT01560403

Trial name: A One-Year, Open-Label Study With Teduglutide for Subjects Who Completed Study CL0600-021 (STEPS3)	NCT number: NCT01560403
Publication title: Reduction of Parenteral Nutrition and Hydration Support and Safety With Long-Term Teduglutide Treatment in Patients With Short Bowel Syndrome–Associated Intestinal Failure: STEPS-3 Study	

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Mean total PS reduction from baseline, l/week (s.d.)	TED-TED	5	9.8 (14.4)	-	-	-	-	-	-	Descriptive statistics	
	NT/PBO-TED	9	3.9 (2.8)								
Mean (SD) percentage reduction from baseline in PS volume	TED-TED	5	49.7% (72.4%)	-	-	-	-	-	-		
	NT/PBO-TED	9	47.8% (42.9%)								
	TED-TED	5	3.0 (4.6)	-	-	-	-	-	-		

Trial name: A One-Year, Open-Label Study With Teduglutide for Subjects Who Completed Study CL0600-021 (STEPS3)	NCT number: NCT01560403
Publication title: Reduction of Parenteral Nutrition and Hydration Support and Safety With Long-Term Teduglutide Treatment in Patients With Short Bowel Syndrome–Associated Intestinal Failure: STEPS-3 Study	

Outcome	Study arm	N	Result (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Reduction from baseline in mean (SD) days per week receiving PS at the last dosing study visit	NT/PBO -TED	9	2.1 (2.2)								
Proportion of patients who obtained enteral autonomy and independence from PS during STEPS-3	TED-TED	5	0 (0%)	-	-	-	-	-	-		
	NT/PBO -TED	9	2 (22%)								

Table 91 Results of study NCT01952080

Trial name: A 12-Week Pharmacokinetic, Safety, and Pharmacodynamic Study of Teduglutide in Pediatric Subjects Aged 1 Year Through 17 Years, With Short Bowel Syndrome Who Are Dependent on Parenteral Support	NCT number: NCT01952080
Publication title: Outcomes from a 12-Week, Open-Label, Multicenter Clinical Trial of Teduglutide in Pediatric Short Bowel Syndrome (Carter_2017)	

Outcome	Study arm	N	Result (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	*P* value	Difference	95% CI	*P* value		

Trial name: A 12-Week Pharmacokinetic, Safety, and Pharmacodynamic Study of Teduglutide in Pediatric Subjects Aged 1 Year Through 17 Years, With Short Bowel Syndrome Who Are Dependent on Parenteral Support Publication title: Outcomes from a 12-Week, Open-Label, Multicenter Clinical Trial of Teduglutide in Pediatric Short Bowel Syndrome (Carter_2017)												
NCT number: NCT01952080												
≥ 10% reduction in PN/IV support (week 12)	Teduglutide 0.05 mg/kg/d	15		9/15 (60.0%)	60.0%	35.21% to 84.79%	0.0379 *	RR: 7.125	0.4863 to 104.395 **	0.0379 *	*Fisher's Exact Test ** These logit estimators use a correction of 0.5 in every cell of those tables that contain a zero.	
	Standard of care	5		0/5 (0%)								
≥ 20% reduction in PN/IV support (week 12)	Teduglutide 0.05 mg/kg/d	15		8/15 (53.3%)	53.33%	28.09% to 78.58%	0.0547 *	RR: 6.375	0.4313 to 94.2363 **	0.0547 *	*Fisher's Exact Test ** These logit estimators use a correction of 0.5 in every cell of those tables that contain a zero.	
	Standard of care	5		0/5 (0%)								
Adverse Events	Teduglutide 0.05 mg/kg/d	15	100.0% (15/15)	0.0%		NA	NA	1.0	NA	NA	*Chi square test*	
	Standard of care	5	100.0% (15/15)									
Serious Adverse Events	Teduglutide 0.05 mg/kg/d	15	53.3% (8/15)	-6.67%		-37.39% to 65.79%	0.7952	0.89	0.38 to 2.1	0.7952	*Chi square test*	

Trial name: A 12-Week Pharmacokinetic, Safety, and Pharmacodynamic Study of Teduglutide in Pediatric Subjects Aged 1 Year Through 17 Years, With Short Bowel Syndrome Who Are Dependent on Parenteral Support Publication title: Outcomes from a 12-Week, Open-Label, Multicenter Clinical Trial of Teduglutide in Pediatric Short Bowel Syndrome (Carter_2017)	NCT number: NCT01952080

	Standard of care	5	60.0% (3/5)

Table 92 **Results of study NCT02682381**

Trial name: A 24-Week Double-blind, Safety, Efficacy, and Pharmacodynamic Study Investigating Two Doses of Teduglutide in Pediatric Subjects Through 17 Years of Age With Short Bowel Syndrome Who Are Dependent on Parenteral Support Publication title: Safety and Efficacy of Teduglutide in Pediatric Patients With Intestinal Failure due to Short Bowel Syndrome: A 24-Week, Phase III Study (Kocoshis_2019)	NCT number: NCT02682381

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Reduction in weight-normalized PS volume of at least 20% at Week 24/EOT from baseline	Teduglutide 0.05 mg/kg/d	26	18/26 (69.2%)	58.12%	-0.4% to 436.1%	0.0049	RR: 6.23	0.96 to 40.25	0.0049	Fisher's Exact Test absolute difference is calculated using (RR-1)*11.1%	
	Standard of care	9	1/9 (11.1%)								
"100% reduction in PN/IV volume	Teduglutide 0.05	26	3/26 (11.5%)	11.54%	-0.74% to 23.82%	0.5531*	RR: 2.5926	0.1466 to 45.8624**	0.5531*	*Fisher's Exact Test	

Trial name: A 24-Week Double-blind, Safety, Efficacy, and Pharmacodynamic Study Investigating Two Doses of Teduglutide in Pediatric Subjects Through 17 Years of Age With Short Bowel Syndrome Who Are Dependent on Parenteral Support Publication title: Safety and Efficacy of Teduglutide in Pediatric Patients With Intestinal Failure due to Short Bowel Syndrome: A 24-Week, Phase III Study (Kocoshis_2019)										NCT number: NCT02682381	
(complete weaning of PN/IV support) at Week 24 (or EOT) compared to baseline"	mg/kg/d Standard of care	9	0/9 (0.0%)							** These logit estimators use a correction of 0.5 in every cell of those tables that contain a zero.	

Trial name: A 24-Week Double-blind, Safety, Efficacy, and Pharmacodynamic Study Investigating Two Doses of Teduglutide in Pediatric Subjects Through 17 Years of Age With Short Bowel Syndrome Who Are Dependent on Parenteral Support Publication title: Safety and Efficacy of Teduglutide in Pediatric Patients With Intestinal Failure due to Short Bowel Syndrome: A 24-Week, Phase III Study (Kocoshis_2019)										NCT number: NCT02682381	
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Change from Baseline in PN/IV Volume (based on Diary Data) (absolute) (mL/kg/day)	Teduglutide 0.05 mg/kg/d	25	-23.3 (-30.16 to -16.44)	-17.27	-25.04 to -9.50	0.0001	NA	NA	NA	The absolute difference in effect is estimated using a two-sided t-test.	
	Standard of care	9	-6.026 (-9.00 to -3.05)								

Trial name: A 24-Week Double-blind, Safety, Efficacy, and Pharmacodynamic Study Investigating Two Doses of Teduglutide in Pediatric Subjects Through 17 Years of Age With Short Bowel Syndrome Who Are Dependent on Parenteral Support Publication title: Safety and Efficacy of Teduglutide in Pediatric Patients With Intestinal Failure due to Short Bowel Syndrome: A 24-Week, Phase III Study (Kocoshis_2019)										NCT number: NCT02682381	
Change from Baseline in PN/IV Volume (based on Diary Data)(percentage)	Teduglutide 0.05 mg/kg/d	25	-41.571 (-52.90 to -30.24)	-31.36	-46.32 to -16.40	0.0002	NA	NA	NA	The absolute difference in effect is estimated using a two-sided t-test.	
	Standard of care	9	-10.212 (-19.09 to -1.33)								
Change in hours per day of PN/IV support (change in hours per day)	Teduglutide 0.05 mg/kg/d	26	-3.03 (-4.50 to -1.56)	-2.82	-4.42 to -1.22	0.0011	NA	NA	NA	The absolute difference in effect is estimated using a two-sided t-test.	
	Standard of care	9	-0.21 (-0.66 to 0.24)								
Change in hours per day of PN/IV support (percentage)	Teduglutide 0.05 mg/kg/d	26	-26.09 (-39.98 to -12.20)	-24.34	-39.30 to -9.38	0.0023	NA	NA	NA	The absolute difference in effect is estimated using a two-sided t-test.	
	Standard of care	9	-1.75 (-5.60 to 2.10)								
Adverse Events	Teduglutide 0.05 mg/kg/d	26	96.2% (25/26)	-3.85%,	-10.96% to 3.84%	1.00	0.96	0.8904 to 1.0384	1.00	*Fisher's Exact TestChi square test*	
	Standard of Care	9	100.0% (9/9)								

Trial name: A 24-Week Double-blind, Safety, Efficacy, and Pharmacodynamic Study Investigating Two Doses of Teduglutide in Pediatric Subjects Through 17 Years of Age With Short Bowel Syndrome Who Are Dependent on Parenteral Support Publication title: Safety and Efficacy of Teduglutide in Pediatric Patients With Intestinal Failure due to Short Bowel Syndrome: A 24-Week, Phase III Study (Kocoshis_2019)											
NCT number: NCT02682381											
Serious Adverse Events	Teduglutide 0.05 mg/kg/d	26	76.9% (20/26)	32.48%	-8.48% to 120.07%	0.0705	1.73	0.81 to 3.7	0.0705	*Chi square test*	
	Standard of Care	9	44.4% (4/9)								

Appendix E

Safety data for intervention and comparator(s)

Table 93 NCT00081458

Trial name: Safety and Efficacy Study of Teduglutide in Subjects With Short Bowel Syndrome **Publication title: Randomized placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome**	**Placebo (n[16)**	**Teduglutide (0.05 mg/kg/d) (n[35)**	**NCT number: NCT00081458**
Subjects with AE, n (%)	15 (94%)	33 (94%)	
Subjects with SAE, n(%)	5 (31%)	13 (37%)	
Subjects with any AE or SAE leading to study discontinuation, n (%)	1* (6%)	6 (17%)	
Event description by system organ class			
Cardiac disorders	0	1	
Cardiac failure congestive	0	1	
Gastrointestinal disorders	0	6	
Abdominal distension	0	1	
Constipation	0	2	
Haemorrhoidal haemorrhage	0	1*	
Nausea	0	1	
Pancreatitis	0	0	
Small intestinal obstruction	0	0	
Vomiting	0	1	
General disorders and administration site conditions	0	1	
Asthenia	0	1	
Infections and infestations	1*	0	
Catheter sepsis	1*	0	
Investigations	0	1	
Drug level increased	0	1	
Nervous system disorders	0	3*	
Coma	0	1*	
Dysgeusia	0	1*	
Hypersomnia	0	1*	

If a subject experienced more than one adverse event in a category, the subject was counted only once in that category. Each event was counted. *Serious adverse event. Coma, dysgeusia and hypersomnia were all found in one patient.

Table 94 NCT00798967

Trial name: Study of Teduglutide Effectiveness in Parenteral Nutrition (PN)-Dependent Short Bowel Syndrome (SBS) Subjects (STEPS) Publication title: Teduglutide Reduces Need for Parenteral Support Among Patients With Short Bowel Syndrome With Intestinal Failure		NCT number: NCT00798967
	Placebo (n=43)	Teduglutide (0.05 mg/kg/d) (n=42)
Subjects with AE, n (%)	34 (79.1)	35 (83.3)
Subjects with SAE, n(%)	12 (27.9)	15 (35.7)
Subjects with any AE or SAE leading to study discontinuation, n (%)	3 (7.0)	2 (4.8)
Event description by system organ class		
Cardiac disorders	3 (7.0%)	2 (4.8%)
Eye Disorders	4 (9.3%)	0
Gastrointestinal disorders	21 (48.8)	27 (64.3)
Abdominal distension	1 (2.3)	9 (21.4)
Abdominal pain	10 (23.3)	13 (31.0)
Diarrhea	5 (11.6)	3 (7.1)
Nausea	8 (18.6)	12 (28.6)
Flatulence	3 (7.0)	5 (11.9)
Vomiting	4 (9.3)	5 (11.9)
General disorders and administration site conditions	15 (34.9)	17 (40.5)
Edema peripheral	2 (4.7)	7 (16.7)
Fatigue	3 (7.0),	4 (9.5)
Pyrexia	4 (9.3)	4 (9.5)
Infections and infestations	21 (48.8)	21 (50.0)
Urinary tract infection	4 (9.3	6 (14.3),
Catheter-related infection	1 (2.3),	5 (11.9),
Nasopharyngitis	0	3 (7.1),
Central line infection	3 (7.0),	2 (4.8),
Bacteremia	3 (7.0),	0
Investigations	10 (23.3	7 (16.7
Weight increased	3 (7.0	3 (7.1),
Weight decreased	6 (14.0),	1 (2.4),
Injury, Poisoning and Procedural Complications	10 (23.3),	14 (33.3),
Gastrointestinal stoma complication	3 (7.0),	10 (23.8),
Metabolism and Nutrition Disorders	11 (25.6),	6 (14.3),
Dehydration	3 (7.0),	2 (4.8),
Nervous system disorders	8 (18.6),	4 (9.5),
Headache	7 (16.3),	2 (4.8),
Musculoskeletal and Connective Tissue Disorders	10 (23.3),	6 (14.3),
Muscle spasms	4 (9.3),	1 (2.4),
Psychiatric Disorders	1 (2.3%),	3 (7.1%),
Respiratory, Thoracic and Mediastinal Disorders	5 (11.6),	6 (14.3),
Dyspnea	0	3 (7.1),
Skin and Subcutaneous Tissue Disorders	4 (9.3),	3 (7.1),
Vascular Disorders	4 (9.3),	8 (19.0),

Table 95 NCT00930644

Trial name: Open-Label Study of Teduglutide for Subjects With PN-Dependent Short Bowel Syndrome (SBS) (STEPS-2) Publication title: Long-Term Teduglutide for the Treatment of Patients With Intestinal Failure Associated With Short Bowel Syndrome	NCT number: NCT00930644
	Teduglutide (0.05 mg/kg/d) (n=88)
Subjects with AE, n (%)	84 (95%)
Subjects with SAE, n(%)	56 (64%)
Subjects with any AE or SAE leading to study discontinuation, n (%)	23 (26%)
Treatment-emergent adverse events occurring in ≥10% of study patients	
Abdominal pain	30 (34)
Catheter sepsis	25 (28)
Episodes of weight decrease	22 (25)
Asthenic conditions	20 (23)
Febrile disorders	18 (20)
Nausea	17 (19)
Urinary tract infections	16 (18)
Catheter site-related reactions	15 (17)
Upper respiratory tract infection	15 (17)
Abdominal distension	14 (16)
Diarrhea	13 (15)
Musculoskeletal pain	13 (15)
Gastrointestinal stomaa complications	12 (33)
Dehydration	12 (14)
Fluid overload	12 (14)
Headaches	10 (11)
Hypersensitivity	9 (10)
Muscle spasms	9 (10)
Flatulence	9 (10)
Vomiting	9 (10)
Treatment-emergent serious adverse events by system organ class and preferred term occurring in ≥2 patients	
Infections and infestations	34 (39)
Central line infection	8 (9)
Catheter bacteremia	4 (5)
Catheter sepsis	4 (5)
Sepsis	4 (5)
Catheter-related infection	3 (3)
Pneumonia	3 (3)
Urinary tract infection	3 (3)
Catheter site infection	2 (2)
Gastroenteritis	2 (2)
Gastrointestinal disorders	9 (10)
Crohn's disease	2 (2)
General disorders and administration site conditions	8 (9)
Pyrexia	5 (6)
Injury, poisoning, and procedural complications	8 (9)
Gastrointestinal stoma complicationb	2 (6)

	Teduglutide (0.05 mg/kg/d) (n=88)
Vascular disorders	6 (7)
Subclavian vein thrombosis	2 (2)
Investigations	2 (2)
Blood bilirubin increased	2 (2)

[a]Intent-to-treat population.

[b]Only among patients with stoma (n =36).

Table 96 NCT01560403

Trial name: A One-Year, Open-Label Study With Teduglutide for Subjects Who Completed Study CL0600-021 (STEPS3) **Publication title: Reduction of Parenteral Nutrition and Hydration Support and Safety With Long-Term Teduglutide Treatment in Patients With Short Bowel Syndrome–Associated Intestinal Failure: STEPS-3 Study**	**NCT number: NCT01560403**
	Teduglutide (0.05 mg/kg/d) (n=14)
Subjects with AE, n (%)	14 (100%)
Subjects with SAE, n(%)	5 (36%)
Subjects with any AE or SAE leading to study discontinuation, n (%)	0 (0%)
Treatment-emergent adverse events occurring in ≥2% of study patients	
Asthenic conditions	3 (21%)
Diarrhea	3 (21%)
Abdominal pain	2 (14%)
Benign neoplasms gastrointestinal	2 (14%)
Cognition and attention disorders and disturbances	2 (14%)
Dyspnea	2 (14%)
Hypersensitivity	2 (14%)
Viral infection	2 (14%)
Weight decreased	2 (14%)

[a]Intent-to-treat population.
[b]Only among patients with stoma (n =36).

Table 97 NCT01952080

Trial name: A 12-Week Pharmacokinetic, Safety, and Pharmacodynamic Study of Teduglutide in Pediatric Subjects Aged 1 Year Through 17 Years, With Short Bowel Syndrome Who Are Dependent on Parenteral Support Publication title: Outcomes from a 12-Week, Open-Label, Multicenter Clinical Trial of Teduglutide in Pediatric Short Bowel Syndrome		NCT number: NCT01952080
	Placebo (n=5)	Teduglutide (0.05 mg/kg/d) (n=15)
Subjects with AE, n (%)	5 (100.0)	15 (100.0)
Subjects with SAE, n(%)	3 (60.0)	8 (53.3)
Subjects with any AE or SAE leading to study discontinuation, n (%)	0	0
Vomiting	0	7 (47)
Upper respiratory tract infection	2 (40)	4 (27)
Catheter-related complication	1 (20)	2 (13)
Pyrexia	2 (40)	7 (47)
Cough	1 (20)	4 (27)
Abdominal pain	1 (20)	4 (27)
Headache	0	2 (13)
Nausea	0	2 (13)
Fatigue	0	4 (27
Blood bicarbonate decreased	2 (40)	3 (20)
Diarrhea	1 (20)	3 (20)
Fecal volume increased	0	2 (13)
Central line infection	0	1 (7)
Abdominal distension	0	1 (7)
Flatulence	0	0
Hematochezia	0	0
Injection-site hemorrhage	0	3 (20)
Viral gastroenteritis	1 (20)	2 (13)
Nasopharyngitis	0	1 (7)
Weight decreased	0	1 (7)
Dizziness	0	2 (13)
Rash	0	2 (13)
GI stoma complication†	0	1 (100)

*Percentages are based on the number of patients in each treatment group.

†Percentages are based on the number of patients with a stoma in each treatment group.

Table 98 NCT02682381

Trial name: A 24-Week Double-blind, Safety, Efficacy, and Pharmacodynamic Study Investigating Two Doses of Teduglutide in Pediatric Subjects Through 17 Years of Age With Short Bowel Syndrome Who Are Dependent on Parenteral Support Publication title: Safety and Efficacy of Teduglutide in Pediatric Patients With Intestinal Failure due to Short Bowel Syndrome: A 24-Week, Phase III Study		NCT number: NCT02682381
	Standard of Care (n=9)	Teduglutide (0.05 mg/kg/d) (n=26)
Subjects with AE, n (%)	9 (100.0)	25 (98)
Subjects with SAE, n(%)	4 (44.4)	20 (76.9)
Subjects with any AE or SAE leading to study discontinuation, n (%)	0	0
Pyrexia	4 (44)	11 (42)
Vomiting	5 (56)	8 (31)
Cough	3 (33)	10 (39)
Diarrhea	1 (11)	3 (12)
Dehydration	0	1 (4)
Upper respiratory tract infection	4 (44)	8 (31)
Alanine aminotransferase increased	0	2 (8)
Nasopharyngitis	2 (22)	6 (23)
Abdominal pain	0	6 (23)
Aspartate aminotransferase increased	0	0
Headache	5 (19)	1 (11)
Device-related infection	0	5 (19)
Rhinitis 1 (4)	0	5 (19)
Blood bicarbonate decreased	0	0
Abdominal pain upper	1 (11)	3 (12)
Nausea 3 (13) 3 (12)	1 (11)	3 (13)
Viral infection 3 (13) 3 (12) 1 (11)	1 (11)	3 (12)
Device breakage 3 (13) 3 (12) 0	0	3 (12)
Conjunctivitis 3 (13) 1 (4) 0	0	1 (4)
Device occlusion 3 (13) 1 (4) 0	0	1 (4)
Injection site bruising 3 (13) 1 (4) 0	0	1 (4)
Rhinorrhea	1 (11)	0
Gastroenteritis viral	0	0
Influenza	0	3 (12)
Ear infection	1 (11)	3 (12)
Catheter site infection	0	3 (12)
Urinary tract infection	1 (11)	1 (4)
Acidosis	0	1 (4)
Blood triglycerides increased	0	1 (4)

Device dislocation	0	1 (4)
Metabolic acidosis	0	1 (4)
Pain	0	1 (4)
Lymph node palpable	1 (11)	0
Cellulitis	0	0
Gastrointestinal bacterial overgrowth	0	0
Abdominal pain lower	0	0
Dermatitis diaper	0	0
γ -Glutamyltransferase increased	0	0
Pain in extremity	0	0
Seasonal allergy	0	2 (8)
Pharyngitis	0	2 (8)
Respiratory tract infection	0	2 (8)
Stoma site erythema	0	2 (8)
Abdominal distension	0	2 (8)

Pooled Safety Data

The safety analysis for adults is based on the pooled safety data from four prospective clinical trials of teduglutide in patients with SBS-IF conducted from May 2004 through January 2013

Table 99 Overall summary of TEAEs and TESAEs according to severity and discontinuation of treatment.

Parameter	RCT teduglutide *n*=109		RCT/extension teduglutide *n* = 173		RCT placebo group *n* = 59	
	n (%)	Number of events	*n* (%)	Number of events	*n* (%)	Number of events
Any TEAE	99 (90.8)	778	167 (96.5)	2235	49 (83.1)	372
TEAE severity						
Mild	84 (77.1)	441	151 (87.3)	1179	45 (76.3)	184
Moderate	74 (67.9)	268	140 (80.0)	849	34 (57.6)	145
Severe	31 (28.4)	69	83 (48.0)	207	16 (27.1)	43
Any TESAE	39 (35.8)	80	101 (58.4)	259	17 (28.8)	34
TESAE severity						
Mild	13 (11.9)	17	29 (16.8)	47	5 (8.5)	6
Moderate	18 (16.5)	28	59 (34.1)	114	7 (11.9)	9
Severe	16 (14.7)	35	56 (32.4)	98	8 (13.6)	19
TEAE leading to discontinuation	10 (9.2)	17	34 (19.7)	52	4 (6.8)	5
AEs leading to death	0	0	3 (1.7)	3	0	0

AE, adverse event; RCT, randomized controlled trial; TEAE, treatment-emergent AE; TESAE, treatment-emergent serious AE.

Table 100 TEAEs leading to discontinuation in more than one patient.

AE preferred term, *n* (%)	RCT teduglutide group, *n* = 109	RCT/extension teduglutide group, *n* = 173	RCT placebo group, *n* = 59
Any TEAE leading to discontinuation	10 (9.2)	34 (19.7)	4 (6.8)
Abdominal pain	1 (0.9)	8 (4.6)	0
Gastrointestinal stoma complication†	0	3 (4.4)	0
Nausea	1 (0.9)	3 (1.7)	0
Vomiting	1 (0.9)	3 (1.7)	0
Abdominal distension	2 (1.8)	2 (1.2)	0
Asthenia	1 (0.9)	2 (1.2)	0
Constipation	2 (1.8)	2 (1.2)	0

RCT, randomized controlled trial; TEAE, treatment-emergent adverse event.

†Percentages calculated based on number of patients with a stoma (*n*=68 for the RCT/extension teduglutide group).

Table 101 Frequency of TEAEs reported in at least 5.0% of patients in the RCT/extension teduglutide group.

AE grouping† or AE preferred term, *n* (%)	RCT teduglutide group, *n* = 109	RCT/extension teduglutide group, *n* = 173	RCT placebo group, *n* = 59
Gastrointestinal stoma complications‡	17 (37.8)	31 (45.6)	3 (13.6)
Abdominal pain†	42 (38.5)	72 (41.6)	16 (27.1)
Upper respiratory tract infection†	30 (27.5)	50 (28.9)	8 (13.6)
Catheter sepsis events†	17 (15.6)	47 (27.2)	10 (16.9)
Nausea†	29 (26.6)	46 (26.6)	12 (20.3)
Headaches†	18 (16.5)	35 (20.2)	9 (15.3)
Asthenic conditions†	14 (12.8)	35 (20.2)	7 (11.9)
Injection site reactions†	22 (20.2)	33 (19.1)	7 (11.9)
Abdominal distension	18 (16.5)	32 (18.5)	1 (1.7)
Urinary tract infections†	17 (15.6)	32 (18.5)	10 (16.9)
Catheter site–related reactions†	9 (8.3)	29 (16.8)	8 (13.6)
Febrile disorders†	10 (9.2)	29 (16.8)	7 (11.9)
Vomiting	15 (13.8)	26 (15.0)	6 (10.2)
Weight decreased†	2 (1.8)	26 (15.0)	6 (10.2)
Musculoskeletal pain†	8 (7.3)	25 (14.5)	6 (10.2)
Diarrhea†	7 (6.4)	24 (13.9)	7 (11.9)
Fluid overload†	11 (10.1)	23 (13.3)	4 (6.8)
Hypersensitivity†	9 (8.3)	21 (12.1)	3 (5.1)
Flatulence	9 (8.3)	19 (11.0)	4 (6.8)

Cognition and attention disorders and disturbances[†]	5 (4.6)	17 (9.8)	4 (6.8)
Dehydration	4 (3.7)	17 (9.8)	5 (8.5)
Arthralgia	7 (6.4)	15 (8.7)	3 (5.1)
Muscle spasms	4 (3.7)	15 (8.7)	4 (6.8)
Appetite disorders[†]	8 (7.3)	14 (8.1)	2 (3.4)
Biliary tract disorders[†]	4 (3.7)	14 (8.1)	1 (1.7)
Lower respiratory tract infection[†]	6 (5.5)	13 (7.5)	3 (5.1)
Skin hemorrhage[†]	5 (4.6)	13 (7.5)	1 (1.7)
Gastrointestinal stenosis and obstruction[†]	6 (5.5)	12 (6.9)	0
Sleep disturbances[†]	6 (5.5)	10 (5.8)	0
Depressive disorders[†]	2 (1.8)	10 (5.8)	1 (1.7)
Coughing and associated symptoms[†]	5 (4.6)	9 (5.2)	0
Hepatic enzyme increased[†]	4 (3.7)	9 (5.2)	2 (3.4)
Pancreatic disorders NEC[†]	3 (2.8)	9 (5.2)	1 (1.7)
Contusion	2 (1.8)	9 (5.2)	0
Peripheral embolism and thrombosis[†]	1 (0.9)	9 (5.2)	2 (3.4)
Hot flush	1 (0.9)	9 (5.2)	0
Blood bicarbonate decreased	0	9 (5.2)	0

AE, adverse event; NEC, not elsewhere classified; RCT, randomized controlled trial; TEAE, treatment-emergent AE.
[†]The preferred terms in the AE groupings represent medically similar terms.
[‡]Percentages calculated based on number of patients with a stoma (*n*=45 for the RCT teduglutide group; *n*=68 for the RCT/extension teduglutidegroup; *n*=22 for the RCT placebo group).

Table 102 Frequency of TESAEs occurring in ⩾1.5% of patients in the RCT/extension teduglutide group.

AE grouping[†] or AE preferred term, *n* (%)	RCT teduglutide group, *n* = 109	RCT/extension teduglutide group, *n* = 173	RCT placebo group, *n* = 59
Catheter sepsis events[†]	15 (13.8)	43 (24.9)	9 (15.3)
Gastrointestinal stenosis and obstruction[†]	5 (4.6)	8 (4.6)	0
Biliary tract disorder[†]	3 (2.8)	8 (4.6)	0
Gastrointestinal stoma complication[‡]	1 (2.2)	3 (4.4)	0
Catheter site–related reaction[†]	2 (1.8)	7 (4.0)	1 (1.7)
Febrile disorders[†]	2 (1.8)	7 (4.0)	0
Lower respiratory tract infection[†]	3 (2.8)	7 (4.0)	1 (1.7)
Peripheral embolism and thrombosis[†]	1 (0.9)	6 (3.5)	0
Urinary tract infections[†]	3 (2.8)	6 (3.5)	1 (1.7)
Abdominal pain[†]	1 (0.9)	3 (1.7)	0
Cognition and attention disorders and disturbances[†]	2 (1.8)	3 (1.7)	0

Cholestasis and jaundice[†]	0	3 (1.7)	1 (1.7)
Device dislocation	2 (1.8)	3 (1.7)	2 (3.4)
Intestinal haemorrhages[†]	1 (0.9)	3 (1.7)	0
Pancreatic disorders NEC[†]	1 (0.9)	3 (1.7)	0

AE, adverse event; NEC, not elsewhere classified; RCT, randomized controlled trial; TESAE, treatment-emergent serious AE.
[†]The AE preferred terms in the AE groupings represent medically similar terms.
[‡]Percentages calculated based on number of patients with a stoma (*n*=45 for the RCT teduglutide group; *n*=68 for the RCT/extension teduglutidegroup; *n*=22 for the RCT placebo group).

The safety analysis for pediatrics is based on the pooled safety data from four prospective clinical trials of teduglutide in children with SBS-IF

Table 103 AEs Occurring in ≥5.0% of Patients.

	N = 89	
Parameter (preferred terms)	**n (%)**	**Number of events**
Any AE	89 (100.0)	1717
Vomiting	46 (51.7)	145
Pyrexia	39 (43.8)	67
Upper respiratory tract infection	37 (41.6)	62
Cough	30 (33.7)	50
Device-related infection[a]	26 (29.2)	41
Abdominal pain	23 (25.8)	65
Diarrhea	23 (25.8)	40
Headache	18 (20.2)	43
Nasopharyngitis	18 (20.2)	27
Viral infection	18 (20.2)	27
Alanine aminotransferase increased	18 (20.2)	24
Nausea	15 (16.9)	25
Rash	15 (16.9)	22
Influenza	14 (15.7)	16
Dehydration	13(14.6)	23
C-reactive protein increased	13 (14.6)	17
Device breakage[a]	13 (14.6)	16
Abdominal pain upper	12 (13.5)	21
Blood bicarbonate decreased	12 (13.5)	15
Abdominal distension	11 (12.4)	13
Device occlusion[a]	10 (11.2)	18
Fatigue	10 (11.2)	18
Rhinorrhea	10 (11.2)	16
Rhinitis	9 (10.1)	12
Gastroenteritis viral	9 (10.1)	10
Device dislocation	9 (10.1)	9
Aspartate aminotransferase increased	8 (9.0)	10
Nasal congestion	8 (9.0)	10
Anemia	7 (7.9)	13
Oropharyngeal pain	7 (7.9)	8
Flatulence	7 (7.9)	8

Hematochezia	7 (7.9)	8
Ear infection	7 (7.9)	8
Lymphadenopathy	7 (7.9)	7
Epistaxis	6 (6.7)	9
γ -Glutamyl transferase increased	6 (6.7)	7
White blood cell–positive urine	6 (6.7)	7
Acidosis	6 (6.7)	7
Pain in extremity	6 (6.7)	7
Decreased appetite	6 (6.7)	7
Hemoglobin decreased	6 (6.7)	6
Urinary tract infection	5 (5.6)	14
Metabolic acidosis	5 (5.6)	13
Gastrointestinal bacterial overgrowth	5 (5.6)	13
Device malfunction[a]	5 (5.6)	9
Gastrostomy tube site complication	5 (5.6)	8
Injection-site bruising	5 (5.6)	8
Respiratory tract infection	5 (5.6)	7
Dizziness	5 (5.6)	6
Ear pain	5 (5.6)	6
Otitis media	5 (5.6)	6
Weight decreased	5 (5.6)	6
Constipation	5 (5.6)	5
Fecal volume increased	5 (5.6)	5
Device-related sepsis[a]	5 (5.6)	5
Hypoglycemia	5 (5.6)	5

AE, adverse event.

[a]All device-related events were related to central venous catheters used to administer parenteral support, not to the teduglutide injection device.

Table 104 SAEs Occurring in ≥5.0% of patients

	N = 89	
Parameter (preferred terms)	**n (%)**	**Number of events**
Any SAE	69 (77.5)	254
Pyrexia	25 (28.1)	36
Device-related infection[a]	24 (27.0)	36
Influenza	9 (10.1)	9
Device breakage[a]	8 (9.0)	9
Dehydration	7 (7.9)	12
Upper respiratory tract infection	6 (6.7)	6

AE, adverse event.

[a]All device-related events were related to central venous catheters used to administer parenteral support, not to the teduglutide injection device.

Table 105 AE and SAE relationship occurring in ≥5.0% of patients

Parameter (preferred terms)	N = 89	
	n (%)	Number of events
Any AE	89 (100.0)	1717
Leading to treatment discontinuation	2 (2.2)	2
Death[a]	1 (1.1)	1
AE severity[b]		
Mild	17 (19.1)	
Moderate	36 (40.4)	
Severe	36 (40.4)	
AE relationship[c]		
Not related	89 (100.0)	1605
Related	35 (39.3)	112
Any SAE	69 (77.5)	254
SAE relationship[c]		
Not related	69 (77.5)	251
Related	3 (3.4)	3

AE, adverse event; SAE, serious AE.

[a] Teduglutide treatment was discontinued, and the family electively withdrew enteral and parenteral fluid and nutrition support; death was considered by the investigator to be unrelated to teduglutide treatment.

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

[c] An individual patient may have had both an AE that was related to teduglutide and a separate AE that was not related to teduglutide.

Appendix F

Comparative analysis of efficacy and safety

See Rationale for not conducting a meta-analysis in adults and pediatrics in section 7.1.7 and 7.1.8, respectively.

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Appendix G

Extrapolation

Not applicable, as no data on efficacy was extrapolated. Extrapolation of survival is explained in detail in section **8.2.2.6**.

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Appendix H

Literature search for HRQoL data

SLRs were also conducted to identify any previous quality of life publications. As with the clinical SLRs original searches were conducted in 2015 and updated in December 2016. Two SLR updates were later performed, the first in January 2021 and the second in May 2021, to ensure that no new and relevant literature was left out.

The SLR was conducted to identify studies reporting HRQoL and/or HSUV data relevant to the decision problem from the published literature. Specifically, the aim was to capture:

- Published HRQoL data relating to adult or paediatric patients with SBS and IF Type III, receiving any or no intervention
- Published HSUV data relating to adult or paediatric patients with SBS and IF Type III, receiving any or no intervention.

The electronic databases, which are used as standard evidence sources are presented in Table 106.

Table 106 Bibliographic databases included in the literature search

Database	Platform	Span of search	Date searched
Embase	Ovid	• *January 2021 update*: November 10th 2016 to date of search • *May 2021 update*: January 22nd 2021 to date of search	• *January 2021 update*: January 22nd 2021 • *May 2021 update*: May 12th 2021
MEDLINE Daily, In-Process & Other Non-indexed citations, and e-pub ahead-of-print		• *January 2021 update*: November 10th 2016 to date of search • *May 2021 update*: January 22nd 2021 to date of search	
Centre for Reviews and Dissemination (CRD) - Health Technology Assessment Database (HTAD)		• *January 2021 update*: 2016[a] to 4th Quarter 2016[b] • *May 2021 update*: Not searched; no coverage beyond 4th Quarter 2016[b]	
Centre for Reviews and Dissemination (CRD) - NHS Economic Evaluation Database (EED)		• *January 2021 update*: 2016[a] to 1st Quarter 2016[b] • *May 2021 update*: Not searched; no coverage beyond 1st Quarter 2016[b]	

Hand-searching

Hand-searching was used as a supplementary measure to ensure all relevant studies were captured by the review. The sources for the hand-searching were conference proceedings and reference list, as specified below.

Conference proceedings

Only conference abstracts from the past two years (January 1st 2019–May 12th 2021) were eligible. Five specific conferences, listed below, were deemed particularly relevant to the disease area. Before the 2021 SLR updates were conducted, it was confirmed that abstracts from these conferences are published in peer-reviewed journals indexed in Embase and MEDLINE. It was therefore not considered necessary to search the websites and abstract booklets of

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these conferences manually; instead, relevant conference abstracts were identified via the electronic database searches.

- European Society for Clinical Nutrition and Metabolism (ESPEN) Congress, published in Clinical Nutrition
- American Society for Parenteral and Enteral Nutrition (ASPEN) Clinical Nutrition Week (CNW), published in the Journal of Parenteral and Enteral Nutrition
- American Society for Gastrointestinal Endoscopy (ASGE) Digestive Disease Week (DDW), published in GIE: Gastrointestinal Endoscopy
- British Society of Gastroenterology (BSG) Annual Meeting, published in Gut: An International Journal of Gastroenterology and Hepatology
- The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) USA and Europe, published in Value in Health.

For conference abstracts that progressed to the full-text review stage, posters were sought and used to determine eligibility where these were available. Where posters were not available, final eligibility was determined based on the abstract alone.

Reference lists

Bibliographic reference lists of SLRs and (network) meta-analyses ([N]MAs) were used to cross-check for any relevant studies which were not identified by the electronic database searches. Systematic literature reviews and (N)MAs likely to yield relevant studies were included at the title/abstract review stage before being excluded at the full-text review stage; SLRs and (N)MAs were not included in their own right.

Search strategy

The database search strings for the 2021 HRQoL and HSUV SLR updates were adapted directly from the 2016 HRQoL and HSUV SLR search strings. The only modifications made for the present updates were the translation of the original Embase and MEDLINE syntax to Ovid syntax, the insertion of one line to limit the search results to English language publications, and the addition of date limits to avoid the inclusion of publications already identified by the previous SLRs. The search strings for the 2021 HRQoL and HSUV SLR updates are presented in Table 107–Table 111. The search strings from the previous SLR conducted in 2015 are presented in Table 112– Table 115.

Embase search strategy (January 2021 SLR update)

- Platform: Ovid
- Databases searched: Embase
- Date searched: January 22nd 2021
- Hits: 215

Table 107: Embase search string for January 2021 HRQoL and HSUV SLR update

#	Searches	Results
1	short bowel syndrome/	6335
2	((short bowel or short intestinal or short intestine or short gut) adj2 (disease$ or syndrome)).mp.	7437
3	(intestinal failure or (intestin$ adj2 fail$)).mp.	4266
4	1 or 2 or 3	10124

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#	Searches	Results
5	exp quality of life/ or qol.ab,ti. or (quality adj2 life).ab,ti. or exp value of life/ or (value adj2 (money or monetary)).ab,ti. or life quality.ab,ti. or life qualities.ab,ti. or utility.ab,ti. or utilities.ab,ti. or disutility.ab,ti. or disutilities.ab,ti. or well being.ab,ti. or wellbeing.ab,ti. or quality adjusted life year/ or quality adjusted life.ab,ti. or qaly$.ab,ti. or qald$.ab,ti. or qale$.ab,ti. or qtime$.ab,ti. or disability adjusted life year.ab,ti. or disability adjusted life years.ab,ti. or daly$.ab,ti. or exp questionnaires/ or exp health survey/ or exp health status/ or exp health status indicator/ or self report/ or sf36.ab,ti. or sf 36.ab,ti. or short form 36.ab,ti. or shortform 36.ab,ti. or sf thirtysix.ab,ti. or sf thirty six.ab,ti. or shorform thirtysix.ab,ti. or shortform thirty six.ab,ti. or short form thirtysix.ab,ti. or short form thirty six.ab,ti. or sf 6.ab,ti. or sf6.ab,ti. or short form 6.ab,ti. or shortform 6.ab,ti. or sf six.ab,ti. or sfsix.ab,ti. or shortform six.ab,ti. or short form six.ab,ti. or sf12.ab,ti. or sf 12.ab,ti. or short form 12.ab,ti. or shortform 12.ab,ti. or sf twelve.ab,ti. or sftwelve.ab,ti. or shortform twelve.ab,ti. or short form twelve.ab,ti. or sf16.ab,ti. or sf 16.ab,ti. or short form 16.ab,ti. or shortform 16.ab,ti. or sf sixteen.ab,ti. or sfsixteen.ab,ti. or shortfrom sixteen.ab,ti. or short form sixteen.ab,ti. or sf20.ab,ti. or sf 20.ab,ti. or short form 20.ab,ti. or shortform 20.ab,ti. or sf twenty.ab,ti. or sftwenty.ab,ti. or shortform twenty.ab,ti. or short form twenty.ab,ti. or euroqol.ab,ti. or euro qol.ab,ti. or euroqol 5d.ab,ti. or euroqol-5d.ab,ti. or euroqol 5-d.ab,ti. or eq5d.ab,ti. or eq 5d.ab,ti. or hql.ab,ti. or hrql.ab,ti. or hqol.ab,ti. or h qol.ab,ti. or hrqol.ab,ti. or hr qol.ab,ti. or health$ year$ equivalent$.ab,ti. or hye.ab,ti. or hyes.ab,ti. or health utilities index.ab,ti. or hui.ab,ti. or hui1.ab,ti. or hui2.ab,ti. or hui-2.ab,ti. or hui3.ab,ti. or hui-3.ab,ti. or rosser.ab,ti. or (quality adj2 (wellbeing or well being)).ab,ti. or qwb.ab,ti. or (willingness adj2 pay).ab,ti. or wtp.ab,ti. or (patient adj1 report$).ab,ti. or standard gamble$.ab,ti. or (standard adj gamble$).ab,ti. or time trade off.ab,ti. or time tradeoff.ab,ti. or tto.ab,ti. or fatigue impact scale.ab,ti. or visual analogue scale.ab,ti. or vas.ab,ti. or visual analogue scale 10.ab,ti. or vas10.ab,ti. or vas 10.ab,ti. or grade scale.ab,ti. or sickness impact profile.ab,ti. or sip.ab,ti. or grogono-woodgate health index.ab,ti. or grogono-woodgate index.ab,ti. or grogono woodgate.ab,ti. or gw index.ab,ti. or psychological general well being.ab,ti. or psychological well being.ab,ti. or psychological wellbeing.ab,ti. or functional capacity.ab,ti. or frailty.ab,ti. or activity scales.ab,ti. or presenteeism.ab,ti. or absenteeism.ab,ti.	2483008
6	4 and 5	1095
7	(Letter or editorial).pt.	1841592
8	(Review.pt. or exp review literature as topic/ or literature review.ti.) not (meta-analysis.pt. or *meta-analysis as topic/ or systematic review.ti. or systematic literature review.ti. or meta-analysis.ab,ti. or meta analysis.ab,ti.)	2790433
9	exp animal/ not (exp animal/ and exp human/)	4747387
10	(case report$ or case series).ab,ti.	618311
11	7 or 8 or 9 or 10	9683837
12	6 not 11	770
13	limit 12 to english language	701
14	(Nov* 2016 or Dec* 2016 or Jan* 2017 or Feb* 2017 or Mar* 2017 or Apr* 2017 or May* 2017 or Jun* 2017 or Jul* 2017 or Aug* 2017 or Sep* 2017 or Oct* 2017 or Nov* 2017 or Dec* 2017 or Jan* 2018 or Feb* 2018 or Mar* 2018 or Apr* 2018 or May* 2018 or Jun* 2018 or Jul* 2018 or Aug* 2018 or Sep* 2018 or Oct* 2018 or Nov* 2018 or Dec* 2018 or Jan* 2019 or Feb* 2019 or Mar* 2019 or Apr* 2019 or May* 2019 or Jun* 2019 or Jul* 2019 or Aug* 2019 or Sep* 2019 or Oct* 2019 or Nov* 2019 or Dec* 2019 or Jan* 2020 or Feb* 2020 or Mar* 2020 or Apr* 2020 or May* 2020 or Jun* 2020 or Jul* 2020 or Aug* 2020 or Sep* 2020 or Oct* 2020 or Nov* 2020 or Dec* 2020 or Jan* 2021).dp.	2547399

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#	Searches	Results
15	13 and 14	171
16	limit 13 to dd=20161110-20210122	129
17	15 or 16	215

Embase search strategy (May 2021 SLR update)

- Platform: Ovid
- Databases searched: Embase
- Date searched: May 12th 2021
- Hits: 33

Table 108: Embase search string for May 2021 HRQoL and HSUV SLR update

#	Searches	Results
1	short bowel syndrome/	6504
2	((short bowel or short intestinal or short intestine or short gut) adj2 (disease$ or syndrome)).mp.	7636
3	(intestinal failure or (intestin$ adj2 fail$)).mp.	4433
4	1 or 2 or 3	10432
5	exp quality of life/ or qol.ab,ti. or (quality adj2 life).ab,ti. or exp value of life/ or (value adj2 (money or monetary)).ab,ti. or life quality.ab,ti. or life qualities.ab,ti. or utility.ab,ti. or utilities.ab,ti. or disutility.ab,ti. or disutilities.ab,ti. or well being.ab,ti. or wellbeing.ab,ti. or quality adjusted life year/ or quality adjusted life.ab,ti. or qaly$.ab,ti. or qald$.ab,ti. or qale$.ab,ti. or qtime$.ab,ti. or disability adjusted life year.ab,ti. or disability adjusted life years.ab,ti. or daly$.ab,ti. or exp questionnaires/ or exp health survey/ or exp health status/ or exp health status indicator/ or self report/ or sf36.ab,ti. or sf 36.ab,ti. or short form 36.ab,ti. or shortform 36.ab,ti. or sf thirtysix.ab,ti. or sf thirty six.ab,ti. or shorform thirtysix.ab,ti. or shortform thirty six.ab,ti. or short form thirtysix.ab,ti. or short form thirty six.ab,ti. or sf 6.ab,ti. or sf6.ab,ti. or short form 6.ab,ti. or shortform 6.ab,ti. or sf six.ab,ti. or sfsix.ab,ti. or shortform six.ab,ti. or short form six.ab,ti. or sf12.ab,ti. or sf 12.ab,ti. or short form 12.ab,ti. or shortform 12.ab,ti. or sf twelve.ab,ti. or sftwelve.ab,ti. or shortform twelve.ab,ti. or short form twelve.ab,ti. or sf16.ab,ti. or sf 16.ab,ti. or short form 16.ab,ti. or shortform 16.ab,ti. or sf sixteen.ab,ti. or sfsixteen.ab,ti. or shortfrom sixteen.ab,ti. or short form sixteen.ab,ti. or sf20.ab,ti. or sf 20.ab,ti. or short form 20.ab,ti. or shortform 20.ab,ti. or sf twenty.ab,ti. or sftwenty.ab,ti. or shortform twenty.ab,ti. or short form twenty.ab,ti. or euroqol.ab,ti. or euro qol.ab,ti. or euroqol 5d.ab,ti. or euroqol-5d.ab,ti. or euroqol 5-d.ab,ti. or eq5d.ab,ti. or eq 5d.ab,ti. or hql.ab,ti. or hrql.ab,ti. or hqol.ab,ti. or h qol.ab,ti. or hrqol.ab,ti. or hr qol.ab,ti. or health$ year$ equivalent$.ab,ti. or hye.ab,ti. or hyes.ab,ti. or health utilities index.ab,ti. or hui.ab,ti. or hui1.ab,ti. or hui2.ab,ti. or hui-2.ab,ti. or hui3.ab,ti. or hui-3.ab,ti. or rosser.ab,ti. or (quality adj2 (wellbeing or well being)).ab,ti. or qwb.ab,ti. or (willingness adj2 pay).ab,ti. or wtp.ab,ti. or (patient adj1 report$).ab,ti. or standard gamble$.ab,ti. or (standard adj gamble$).ab,ti. or time trade off.ab,ti. or time tradeoff.ab,ti. or tto.ab,ti. or fatigue impact scale.ab,ti. or visual analogue scale.ab,ti. or vas.ab,ti. or visual analogue scale 10.ab,ti. or vas10.ab,ti. or vas 10.ab,ti. or grade scale.ab,ti. or sickness impact profile.ab,ti. or sip.ab,ti. or grogono-woodgate health index.ab,ti. or grogono-woodgate index.ab,ti. or grogono woodgate.ab,ti. or gw index.ab,ti. or psychological general well being.ab,ti. or psychological well being.ab,ti. or psychological wellbeing.ab,ti. or functional capacity.ab,ti. or frailty.ab,ti. or activity scales.ab,ti. or presenteeism.ab,ti. or absenteeism.ab,ti.	2573450
6	4 and 5	1147
7	(Letter or editorial).pt.	1905255

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#	Searches	Results
8	(Review.pt. or exp review literature as topic/ or literature review.ti.) not (meta-analysis.pt. or *meta-analysis as topic/ or systematic review.ti. or systematic literature review.ti. or meta-analysis.ab,ti. or meta analysis.ab,ti.)	2867687
9	exp animal/ not (exp animal/ and exp human/)	4836507
10	(case report$ or case series).ab,ti.	640305
11	7 or 8 or 9 or 10	9927657
12	6 not 11	806
13	limit 12 to english language	736
14	(Jan* 2021 or Feb* 2021 or Mar* 2021 or Apr* 2021 or May* 2021).dp.	214511
15	13 and 14	22
16	limit 13 to dd=20210122-20210512	21
17	15 or 16	33

MEDLINE search strategy (January 2021 SLR update)

- Platform: Ovid
- Databases searched: MEDLINE Daily, In-Process & Other Non-indexed citations, and e-pub ahead-of-print
- Date searched: January 22nd 2021
- Hits: 133

Table 109: MEDLINE search string for January 2021 HRQoL and HSUV SLR update

#	Searches	Results
1	short bowel syndrome/	2975
2	((short bowel or short intestinal or short intestine or short gut) adj2 (disease$ or syndrome)).mp.	4547
3	(intestinal failure or (intestin$ adj2 fail$)).mp.	2313
4	1 or 2 or 3	6030

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#	Searches	Results
5	Quality of life/ or qol.ab,ti. or (quality adj2 life).ab,ti. or value of life/ or (value adj2 (money or monetary)).ab,ti. or life quality.ab,ti. or life qualities.ab,ti. or utility.ab,ti. or utilities.ab,ti. or disutility.ab,ti. or disutilities.ab,ti. or well being.ab,ti. or wellbeing.ab,ti. or quality adjusted life year/ or quality adjusted life.ab,ti. or qaly$.ab,ti. or qald$.ab,ti. or qale$.ab,ti. or qtime$.ab,ti. or disability adjusted life year.ab,ti. or disability adjusted life years.ab,ti. or daly$.ab,ti. or exp questionnaires/ or exp health survey/ or exp health status/ or exp health status indicator/ or self report/ or sf36.ab,ti. or sf 36.ab,ti. or short form 36.ab,ti. or shortform 36.ab,ti. or sf thirtysix.ab,ti. or sf thirty six.ab,ti. or shorform thirtysix.ab,ti. or shortform thirty six.ab,ti. or short form thirtysix.ab,ti. or short form thirty six.ab,ti. or sf 6.ab,ti. or sf6.ab,ti. or short form 6.ab,ti. or shortform 6.ab,ti. or sf six.ab,ti. or sfsix.ab,ti. or shortform six.ab,ti. or short form six.ab,ti. or sf12.ab,ti. or sf 12.ab,ti. or short form 12.ab,ti. or shortform 12.ab,ti. or sf twelve.ab,ti. or sftwelve.ab,ti. or shortform twelve.ab,ti. or short form twelve.ab,ti. or sf16.ab,ti. or sf 16.ab,ti. or short form 16.ab,ti. or shortform 16.ab,ti. or sf sixteen.ab,ti. or sfsixteen.ab,ti. or shortfrom sixteen.ab,ti. or short form sixteen.ab,ti. or sf20.ab,ti. or sf 20.ab,ti. or short form 20.ab,ti. or shortform 20.ab,ti. or sf twenty.ab,ti. or sftwenty.ab,ti. or shortform twenty.ab,ti. or short form twenty.ab,ti. or euroqol.ab,ti. or euro qol.ab,ti. or euroqol 5d.ab,ti. or euroqol-5d.ab,ti. or euroqol 5-d.ab,ti. or eq5d.ab,ti. or eq 5d.ab,ti. or hql.ab,ti. or hrql.ab,ti. or hqol.ab,ti. or h qol.ab,ti. or hrqol.ab,ti. or hr qol.ab,ti. or health$ year$ equivalent$.ab,ti. or hye.ab,ti. or hyes.ab,ti. or health utilities index.ab,ti. or hui.ab,ti. or hui1.ab,ti. or hui2.ab,ti. or hui-2.ab,ti. or hui3.ab,ti. or hui-3.ab,ti. or rosser.ab,ti. or (quality adj2 (wellbeing or well being)).ab,ti. or qwb.ab,ti. or (willingness adj2 pay).ab,ti. or wtp.ab,ti. or (patient adj1 report$).ab,ti. or standard gamble$.ab,ti. or (standard adj gamble$).ab,ti. or time trade off.ab,ti. or time tradeoff.ab,ti. or tto.ab,ti. or fatigue impact scale.ab,ti. or visual analogue scale.ab,ti. or vas.ab,ti. or visual analogue scale 10.ab,ti. or vas10.ab,ti. or vas 10.ab,ti. or grade scale.ab,ti. or sickness impact profile.ab,ti. or sip.ab,ti. or grogono-woodgate health index.ab,ti. or grogono-woodgate index.ab,ti. or grogono woodgate.ab,ti. or gw index.ab,ti. or psychological general well being.ab,ti. or psychological well being.ab,ti. or psychological wellbeing.ab,ti. or functional capacity.ab,ti. or frailty.ab,ti. or activity scales.ab,ti. or presenteeism.ab,ti. or absenteeism.ab,ti.	1803229
6	4 and 5	748
7	(Letter or editorial).pt.	1674614
8	(Review.pt. or exp review literature as topic/ or literature review.ti.) not (meta-analysis.pt. or *meta-analysis as topic/ or systematic review.ti. or systematic literature review.ti. or meta-analysis.ab,ti. or meta analysis.ab,ti.)	2649822
9	exp animals/ not (exp animals/ and humans/)	4779072
10	(Review.pt. or exp review literature as topic/ or literature review.ti.) not (meta-analysis.pt. or *meta-analysis as topic/ or systematic review.ti. or systematic literature review.ti. or meta-analysis.ab,ti. or meta analysis.ab,ti.)	458460
11	exp animals/ not (exp animals/ and humans/)	9252103
12	(case report$ or case series).ab,ti.	475
13	7 or 8 or 9 or 10	420

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#	Searches	Results
14	(2016 Nov* or 2016 Dec* or 2017 Jan* or 2017 Feb* or 2017 Mar* or 2017 Apr* or 2017 May* or 2017 Jun* or 2017 Jul* or 2017 Aug* or 2017 Sep* or 2017 Oct* or 2017 Nov* or 2017 Dec* or 2018 Jan* or 2018 Feb* or 2018 Mar* or 2018 Apr* or 2018 May* or 2018 Jun* or 2018 Jul* or 2018 Aug* or 2018 Sep* or 2018 Oct* or 2018 Nov* or 2018 Dec* or 2019 Jan* or 2019 Feb* or 2019 Mar* or 2019 Apr* or 2019 May* or 2019 Jun* or 2019 Jul* or 2019 Aug* or 2019 Sep* or 2019 Oct* or 2019 Nov* or 2019 Dec* or 2020 Jan* or 2020 Feb* or 2020 Mar* or 2020 Apr* or 2020 May* or 2020 Jun* or 2020 Jul* or 2020 Aug* or 2020 Sep* or 2020 Oct* or 2020 Nov* or 2020 Dec* or 2021 Jan*).dp.	2988237
15	13 and 14	66
16	limit 13 to dt=20161110-20210122	132
17	15 or 16	133

MEDLINE search strategy (May 2021 SLR update)

- Platform: Ovid
- Databases searched: MEDLINE Daily, In-Process & Other Non-indexed citations, and e-pub ahead-of-print
- Date searched: May 12th 2021
- Hits: 17

Table 110: MEDLINE search string for May 2021 HRQoL and HSUV SLR update

#	Searches	Results
1	short bowel syndrome/	3026
2	((short bowel or short intestinal or short intestine or short gut) adj2 (disease$ or syndrome)).mp.	4593
3	(intestinal failure or (intestin$ adj2 fail$)).mp.	2361
4	1 or 2 or 3	6103
5	Quality of life/ or qol.ab,ti. or (quality adj2 life).ab,ti. or value of life/ or (value adj2 (money or monetary)).ab,ti. or life quality.ab,ti. or life qualities.ab,ti. or utility.ab,ti. or utilities.ab,ti. or disutility.ab,ti. or disutilities.ab,ti. or well being.ab,ti. or wellbeing.ab,ti. or quality adjusted life year/ or quality adjusted life.ab,ti. or qaly$.ab,ti. or qald$.ab,ti. or qale$.ab,ti. or qtime$.ab,ti. or disability adjusted life year.ab,ti. or disability adjusted life years.ab,ti. or daly$.ab,ti. or exp questionnaires/ or exp health survey/ or exp health status/ or exp health status indicator/ or self report/ or sf36.ab,ti. or sf 36.ab,ti. or short form 36.ab,ti. or shortform 36.ab,ti. or sf thirtysix.ab,ti. or sf thirty six.ab,ti. or shorform thirtysix.ab,ti. or shortform thirty six.ab,ti. or short form thirtysix.ab,ti. or short form thirty six.ab,ti. or sf 6.ab,ti. or sf6.ab,ti. or short form 6.ab,ti. or shortform 6.ab,ti. or sf six.ab,ti. or sfsix.ab,ti. or shortform six.ab,ti. or short form six.ab,ti. or sf12.ab,ti. or sf 12.ab,ti. or short form 12.ab,ti. or shortform 12.ab,ti. or sf twelve.ab,ti. or sftwelve.ab,ti. or shortform twelve.ab,ti. or short form twelve.ab,ti. or sf16.ab,ti. or sf 16.ab,ti. or short form 16.ab,ti. or shortform 16.ab,ti. or sf sixteen.ab,ti. or sfsixteen.ab,ti. or shortfrom sixteen.ab,ti. or short form sixteen.ab,ti. or sf20.ab,ti. or sf 20.ab,ti. or short form 20.ab,ti. or shortform 20.ab,ti. or sf twenty.ab,ti. or sftwenty.ab,ti. or shortform twenty.ab,ti. or short form twenty.ab,ti. or euroqol.ab,ti. or euro qol.ab,ti. or euroqol 5d.ab,ti. or euroqol-5d.ab,ti. or euroqol 5-d.ab,ti. or eq5d.ab,ti. or eq 5d.ab,ti. or hql.ab,ti. or hrql.ab,ti. or hqol.ab,ti. or h qol.ab,ti. or hrqol.ab,ti. or hr qol.ab,ti. or health$ year$ equivalent$.ab,ti. or hye.ab,ti. or hyes.ab,ti. or health utilities index.ab,ti. or hui.ab,ti. or hui1.ab,ti. or hui2.ab,ti. or hui-2.ab,ti. or hui3.ab,ti. or hui-3.ab,ti. or rosser.ab,ti. or (quality adj2 (wellbeing or well being)).ab,ti. or qwb.ab,ti. or (willingness adj2 pay).ab,ti. or wtp.ab,ti. or (patient adj1 report$).ab,ti. or standard gamble$.ab,ti. or (standard adj gamble$).ab,ti. or time trade off.ab,ti. or time tradeoff.ab,ti. or tto.ab,ti. or fatigue	1844160

#	Searches	Results
	impact scale.ab,ti. or visual analogue scale.ab,ti. or vas.ab,ti. or visual analogue scale 10.ab,ti. or vas10.ab,ti. or vas 10.ab,ti. or grade scale.ab,ti. or sickness impact profile.ab,ti. or sip.ab,ti. or grogono-woodgate health index.ab,ti. or grogono-woodgate index.ab,ti. or grogono woodgate.ab,ti. or gw index.ab,ti. or psychological general well being.ab,ti. or psychological well being.ab,ti. or psychological wellbeing.ab,ti. or functional capacity.ab,ti. or frailty.ab,ti. or activity scales.ab,ti. or presenteeism.ab,ti. or absenteeism.ab,ti.	
6	4 and 5	763
7	(Letter or editorial).pt.	1701814
8	(Review.pt. or exp review literature as topic/ or literature review.ti.) not (meta-analysis.pt. or *meta-analysis as topic/ or systematic review.ti. or systematic literature review.ti. or meta-analysis.ab,ti. or meta analysis.ab,ti.)	2692174
9	exp animals/ not (exp animals/ and humans/)	4823995
10	(case report$ or case series).ab,ti.	468991
11	7 or 8 or 9 or 10	9373115
12	6 not 11	490
13	limit 12 to english language	435
14	(2021 Jan* or 2021 Feb* or 2021 Mar* or 2021 Apr* or 2021 May*).dp.	541205
15	13 and 14	15
16	limit 13 to dt=20210122-20210512	12
17	15 or 16	17

Centre for Reviews and Dissemination (CRD) databases search strategy (January 2021 SLR update)

- Platform: Ovid
- Databases searched: Centre for Reviews and Dissemination (CRD) Health Technology Assessment Database (HTAD) and CRD NHS Economic Evaluation Database (EED)
- Date searched: January 22nd 2021
- Hits: 9

Table 111: Centre for Reviews and Dissemination (CRD) databases search string for January 2021 HRQoL and HSUV SLR update

#	Searches		Results
1	short bowel syndrome/		7
2	((short bowel or short intestinal or short intestine or short gut) adj2 (disease$ or syndrome)).mp.		13
3	(intestinal failure or (intestin$ adj2 fail$)).mp.		10
4	1 or 2 or 3		22
5	limit 4 to english language		19
6	limit 5 to yr="2016 -Current"		9
		HTAD	9
		EED	0

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Table 112 MEDLINE and Embase: Embase.com 30 July, 2015

S. No.	Terms	Hits
1	'short bowel' NEXT/1 (disease* OR syndrome)	5052
2	'short intestinal' NEXT/1 (disease* OR syndrome)	2
3	'short intestine' NEXT/1 (disease* OR syndrome)	34
4	'short gut' NEXT/1 (disease* OR syndrome)	404
5	'intestinal failure' OR intestin* NEAR/2 fail*	2469
6	1 OR 2 OR 3 OR 4 OR 5	6868
7	'quality of life'	336875
8	'quality of life':ab,ti	237127
9	'life qualities':ab,ti	63
10	'life quality':ab,ti	7313
11	'hrql':ab,ti	3713
12	'qol':ab,ti	38792
13	'hrqol':ab,ti	13073
14	'utilities':ab,ti	6757
15	'utility':ab,ti	166881
16	'disutilities':ab,ti	127
17	'disutility':ab,ti	355
18	'well being':ab,ti	55037
19	'wellbeing':ab,ti	10767
20	'quality adjusted life year':ab,ti	3964
21	'quality adjusted life years':ab,ti	6087
22	'qaly':ab,ti	8409
23	'qalys':ab,ti	6039
24	'standard gamble':ab,ti	829
25	'sg':ab,ti	8561
26	'time-trade-off':ab,ti	1095
27	'time trade off':ab,ti	1095
28	'time tradeoff':ab,ti	228
29	'time trade-off':ab,ti	1095
30	'tto':ab,ti	1015
31	'eq-5d':ab,ti	6342
32	'eq5d':ab,ti	693
33	'euroqol':ab,ti	3749
34	'euroqol 5d':ab,ti	968
35	'euroqol-5d':ab,ti	968
36	'euroqol 5-d':ab,ti	39
37	'sf-36':ab,ti	21308
38	'sf36':ab,ti	1978
39	'sf 36':ab,ti	21308
40	'short form 36':ab,ti	8757
41	'short-form 36':ab,ti	8757
42	'shortform 36':ab,ti	24
43	'sf-12':ab,ti	3963

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S. No.	Terms	Hits
44	'sf12':ab,ti	479
45	'sf 12':ab,ti	3963
46	'short form 12':ab,ti	1412
47	'short-form 12':ab,ti	1412
48	'shortform 12':ab,ti	5
49	'sf-6d':ab,ti	781
50	'sf6d':ab,ti	57
51	'short form 6d':ab,ti	124
52	'shortform 6d':ab,ti	1
53	'short-form 6d':ab,ti	124
54	‘sf-20’:ab,ti	240
55	‘sf20’:ab,ti	30
56	‘sf 20’:ab,ti	240
57	‘short-form’ 20’:ab,ti	80
58	‘short form 20’:ab,ti	80
59	‘shortform 20’:ab,ti	0
60	‘sf-16’:ab,ti	32
61	‘sf16’:ab,ti	3
62	‘sf 16’:ab,ti	32
63	‘shortform 16’:ab,ti	0
64	‘short-form 16’:ab,ti	6
65	‘short form 16’:ab,ti	6
66	'health utilities index':ab,ti	686
67	'hui':ab,ti	1996
68	'hui2':ab,ti	152
69	'hui-2':ab,ti	47
70	'hui3':ab,ti	326
71	'hui-3':ab,ti	92
72	(patient NEAR/1 report*):ab,ti	26205
73	'health survey':ab,ti	20854
74	'health status':ab,ti	48020
75	'hospital anxiety and depression scale':ab,ti	7201
76	'had scale':ab,ti	434
77	'fatigue impact scale':ab,ti	558
78	'fis':ab,ti	1465
79	'gastrointestinal symptom rating scale':ab,ti	369
80	'gsrs':ab,ti	516
81	'short bowel syndrome-quality of life':ab,ti	2
82	'sbs-qol':ab,ti	5
83	'sbsqol':ab,ti	1
84	'sbs qol':ab,ti	5
85	'visual analogue scale':ab,ti	20659
86	'vas':ab,ti	44630
87	'visual analogue scale 10':ab,ti	15

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S. No.	Terms	Hits
88	'vas10':ab,ti	2
89	'vas 10':ab,ti	106
90	'grade scale':ab,ti	618
91	'sickness impact profile':ab,ti	1103
92	'sip':ab,ti	2569
93	'grogono-woodgate health index':ab,ti	0
94	'grogono-woodgate index':ab,ti	3
95	'grogono woodgate':ab,ti	3
96	'gw index':ab,ti	0
97	'psychological general well being':ab,ti	413
98	'psychological well being':ab,ti	6722
99	'psychological wellbeing':ab,ti	1011
100	'gastrointestinal quality of life index':ab,ti	368
101	'gastrointestinal quality of life':ab,ti	412
102	'giqli':ab,ti	376
103	'gqli':ab,ti	21
104	'gi quality of life':ab,ti	16
105	'inflammatory bowel disease questionnaire':ab,ti	564
106	'ibdq':ab,ti	506
107	'ibd questionnaire':ab,ti	70
108	'functional capacity':ab,ti	13199
109	'frailty':ab,ti	6756
110	'activity scales':ab,ti	126
111	'presenteeism':ab,ti	881
112	'absenteeism':ab,ti	5466
113	7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46 OR 47 OR 48 OR 49 OR 50 OR 51 OR 52 OR 53 OR 54 OR 55 OR 56 OR 57 OR 58 OR 59 OR 60 OR 61 OR 62 OR 63 OR 64 OR 65 OR 66 OR 67 OR 68 OR 69 OR 70 OR 71 OR 72 OR 73 OR 74 OR 75 OR 76 OR 77 OR 78 OR 79 OR 80 OR 81 OR 82 OR 83 OR 84 OR 85 OR 86 OR 87 OR 88 OR 89 OR 90 OR 91 OR 92 OR 93 OR 94 OR 95 OR 96 OR 97 OR 98 OR 99 OR 100 OR 101 OR 102 OR 103 OR 104 OR 105 OR 106 OR 107 OR 108 OR 109 OR 110 OR 111 OR 112	726901
114	6 AND 113	556

Publications ahead of print:

PubMed: http://www.ncbi.nlm.nih.gov/pubmed. 30 July 2015

Table 113 PubMed: 30 July 2015

S. No.	Terms	Hits
1	('short bowel') AND (disease* or syndrome)	7
2	('short intestinal') AND (disease* OR syndrome)	6
3	('short intestine') AND (disease* OR syndrome)	3

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4	('short gut') AND (disease* OR syndrome)	21
5	('intestinal failure') OR (intestin* AND fail*)	17031
6	1 OR 2 OR 3 OR 4 OR 5	17067
7	((publisher[sb] NOT pubstatusnihms NOT pubstatuspmcsd NOT pmcbook) OR (pubstatusaheadofprint))	413726
8	6 AND 7	162

Cochrane Library:

Cochrane Library: Wiley Interscience. 30 July 2015.

Health Technology Assessment Database (HTA): Wiley Interscience.

NHS Economic Evaluation Database (NHS EED): Wiley Interscience

Table 114 Cochrane Library 30 July 2015

S. No.	Search Terms	Hits
#1	MeSH descriptor: [Short Bowel Syndrome] explode all trees	57
#2	'short bowel' next/1 (disease* or syndrome)	580
#3	'short intestinal' next/1 (disease* or syndrome)	38
#4	'short intestine' next/1 (disease* or syndrome)	9
#5	'short gut' next/1 (disease* or syndrome)	9
#6	'intestinal failure' or intestin* near/2 fail*	900
#7	#1 or #2 or #3 or #4 or #5 or #6	1406
#8	#7 and HTA database	11
#9	#7 and NHS EED	43

Econlit:

EBSCO Discovery Service Search Screen. 30 July 2015.

Table 115 EBSCO Discovery Service Search Screen. 30 July 2015

Search ID#	Search Terms	Hits
S1	'short bowel' NEXT1 (disease* or syndrome)	3478
S2	'short intestinal' NEXT/1 (disease* or syndrome)	2706
S3	'short intestine' NEXT/1 (disease* or syndrome)	2706
S4	'short gut' NEXT/1 (disease* or syndrome)	5762
S5	'intestinal failure' OR intestine* NEAR/2 fail*	491423
S6	S1 OR S2 OR S3 OR S4 OR S5	499236
S7	S1 OR S2 OR S3 OR S4 OR S5 Source - EconLit	0

Inclusion and exclusion criteria

The population, intervention, comparator(s), outcomes and study design (PICOS) elements used to assess study eligibility in the 2021 HRQoL and HSUV SLR updates are presented in Table 116. The PICOS elements used to assess study eligibility in the previous SLR conducted in 2015 are presented in Table 117.

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Table 116 Eligibility criteria (PICOS) for the January 2021 and May 2021 HRQoL and HSUV SLR updates

Characteristic	Inclusion criteria	Exclusion criteria
Population	Adult or paediatric patients with SBS, also known as short gut syndrome or simply short gut, with IF Type III (Patients labelled as having SBS-IF were assumed to have IF Type III unless otherwise stated)	Healthy volunteers
Interventions/comparators	No restrictions	No restrictions
Outcomes	HRQoL data Utility data	HRQoL or utility outcomes not presented as absolute values (e.g. time to deterioration, hazard ratios or p-values only) Measures of performance status (e.g. KPS, ECOG-PS) Any other outcomes
Study design/publication type	Any study type collecting HRQoL data Any study type collecting utility data (e.g. by standard gamble or time trade-off techniques) Economic evaluations reporting original/novel utility data Mapping studies in which utility values are derived SLRs/(N)MAs[a]	Comments Letters Case studies/case reports/case series Editorials Clinical guidelines Non-systematic (i.e. narrative) literature reviews Animal studies/preclinical studies/*in vitro* studies
Date limits (January 2021 SLR update)	Adult studies • Full texts published December 13th 2016 to January 22nd 2021 • Conference abstracts published 2019 to January 22nd 2021 Paediatric studies • Full texts published November 10th 2016 to January 22nd 2021 • Conference abstracts published 2019 to January 22nd 2021	Adult studies • Full texts published before December 13th 2016 • Conference abstracts published before 2019 Paediatric studies • Full texts published before November 10th 2016 • Conference abstracts published before 2019
Date limits (May 2021 SLR update)	Adult or paediatric studies: full texts or congress abstracts published January 22nd 2021 to present (May 12th 2021)	Adult or paediatric studies: full texts or congress abstracts published before January 22nd 2021
Countries	No restrictions	No restrictions
Languages	English language publications (English language abstracts of foreign language publications can be considered for inclusion)	Non-English language publications

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Table 117 Eligibility criteria (PICOS) for the July 2015 HRQoL and HSUV SLR

Inclusion criteria	Exclusion criteria
*Population**	*Population**
• Studies which include patients with SBS-IF. The disease is also known as short gut syndrome or simply short gut	• Healthy volunteers • Diseases other than SBS-IF • Studies with children only
Interventions and comparator	*Interventions and comparator*
• No exclusion on intervention and comparator	• No exclusion on intervention and comparator
Outcomes	*Outcomes*
• Utility values	• Disease-specific and non-preference-based measures not converted to utilities
Study design	*Study design*
• HRQL studies • Economic evaluations reporting patient utility values • Observational studies reporting HRQL/utility data	• Reviews, letters and comment articles • Systematic review will be flagged
Other criteria	*Other criteria*
• Studies must present sufficient detail regarding the methodology used • Studies must provide extractable results	• Studies that fail to present sufficient methodological detail • Studies that fail to present extractable results
Key: HRQL, health-related quality of life; SBS-IF, short bowel syndrome with intestinal failure. **Note:** *For the adult search, paediatric populations were excluded, and *vice versa*.	

The following steps were performed to select relevant literature:

Two independent reviewers screened citations by title/abstract, with any conflicts regarding eligibility resolved by discussion between the two reviewers. Where necessary, arbitration was provided by a third, more senior reviewer Full-text publications were also evaluated by two independent reviewers, with any disputes regarding eligibility resolved by dialogue between the two reviewers. Again, arbitration was provided by a third, more senior reviewer if required. A record was kept of all publications excluded at this stage along with a clear justification for their exclusion. Identification of relevant publications is presented in PRISMA flow diagrams in
Figure 47 for the January update. No PRISMA diagram is presented for the May update as all studies were excluded. Further, identification of relevant publications from the original SLR is presented in PRISMA flow diagram in Figure 48.

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Figure 47 PRISMA flow diagram for January 2021 HRQoL and HSUV SLR updates

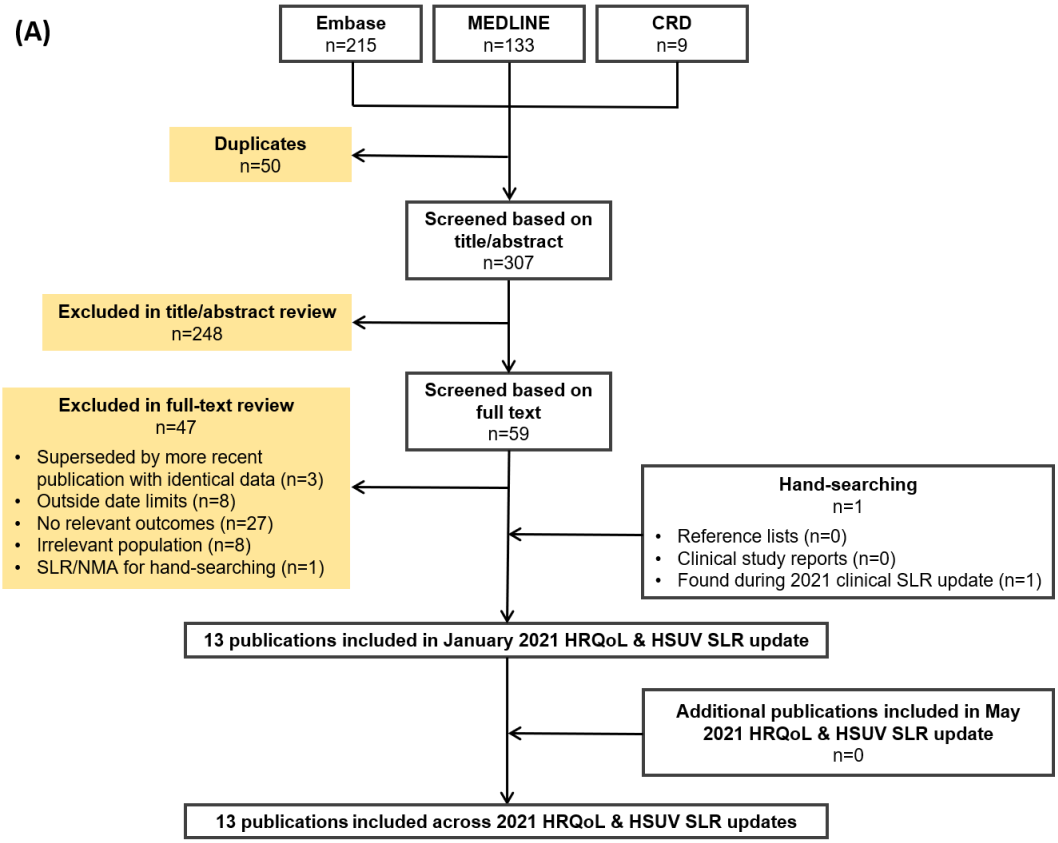
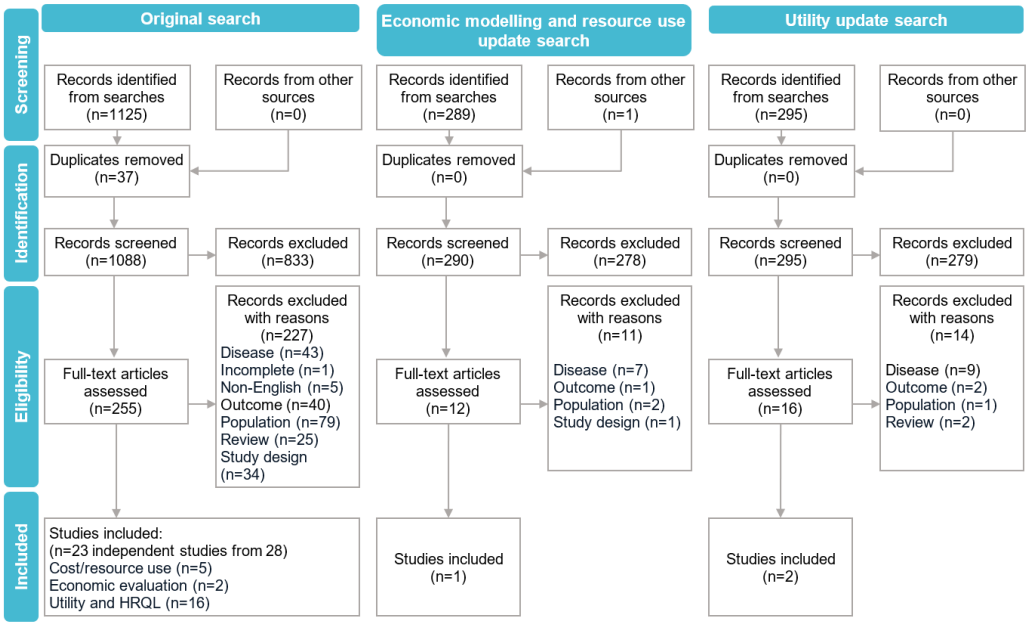


Figure 48 PRISMA flow diagram for 2015 and 2016 updated Economic, HRQoL and HSUV SLR



Description of identified studies in the updated SLR from 2021

In the January 2021 HRQoL and HSUV SLR update, 357 publications were identified through the electronic database searches. After the removal of 50 duplicates, 307 publications were reviewed based on their titles and abstracts. A total of 248 publications were excluded at the title/abstract review stage, leaving 59 potentially relevant publications that were procured for full-text review. By reviewing the full-text publications, a further 47 publications were excluded. Hand-searching yielded one additional relevant publication, which was identified during the 2021 clinical SLR update, resulting in a total of 13 publications for final inclusion in the review. All 13 of the included publications were full manuscripts rather than conference abstracts/posters.
In the May 2021 HRQoL and HSUV SLR update, 50 publications were identified through the electronic database searches. After the removal of 10 duplicates, 40 publications were reviewed based on their titles and abstracts. A total of 22 publications were excluded at the title/abstract review stage, leaving 18 potentially relevant publications that were procured for full-text review. By reviewing the full-text publications, all 18 publications were excluded. Hand-searching yielded no additional relevant publications.
The flow of publications through the 2021 HRQoL and HSUV SLR updates is reported in the PRISMA flow diagram in Figure 47. A list of publications excluded at the full-text review stage, along with a rationale for their exclusion, is provided in Table 119 for the January 2021 update, and Table 120 for the May 2021 update.

List of included studies in the updated SLR from 2021

A list of publications included in the January 2021 HRQoL and HSUV SLR update is provided in Table 118. No additional relevant publications were identified during the May 2021 HRQoL and HSUV SLR update.

Table 118: Full references of publications reporting HSUV and HRQoL data included in the January 2021 HRQoL and HSUV SLR update (n=13)

Publication	Intervention(s)	Full reference
Health-state utility value (HSUV) publications (n=4)		
Ballinger 2018[79]	PS	Ballinger R, Macey J, Lloyd A, Brazier J, Ablett J, Burden S, et al. Measurement of Utilities Associated with Parenteral Support Requirement in Patients with Short Bowel Syndrome and Intestinal Failure. Clinical Therapeutics. 2018;40(11):1878.
Carey 2019[80]	HPN, TED, intestinal transplant	Carey S, Tu W, Hyde-Jones L, Koh C. Assessing Patient Preferences for Intestinal Failure Management Using the Time Trade-Off Methodology. JPEN Journal of parenteral and enteral nutrition. 2019;43(7):912-7.
Raghu 2020a[81]	PN, TED	Raghu VK, Binion DG, Smith KJ. Cost-effectiveness of teduglutide in adult patients with short bowel syndrome: Markov modeling using traditional cost-effectiveness criteria. The American journal of clinical nutrition. 2020;111(1):141-8.
Raghu 2020b[82]	PN, TED, intestinal transplant	Raghu VK, Rudolph JA, Smith KJ. Cost-effectiveness of teduglutide in pediatric patients with short bowel syndrome: Markov modeling using traditional cost-effectiveness criteria. The American journal of clinical nutrition. 2020;113(1):172–8.
Health-related quality-of-life (HRQoL) publications (n=9)		
Beurskens-Meijerink 2020[99]	HPN	Beurskens-Meijerink J, Huisman-de Waal G, Wanten G. Evaluation of quality of life and caregiver burden in home parenteral nutrition patients: A cross sectional study. Clinical Nutrition ESPEN. 2020;37:50-7.
Burden 2019[100]	HPN	Burden ST, Jones DJ, Gittins M, Ablett J, Taylor M, Mountford C, et al. Needs-based quality of life in adults dependent on home parenteral nutrition. Clinical Nutrition. 2019;38(3):1433-8.

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Publication	Intervention(s)	Full reference
Chen 2018[101]	TED, PBO	Chen KS, Xie J, Tang W, Zhao J, Jeppesen PB, Signorovitch JE. Identifying a subpopulation with higher likelihoods of early response to treatment in a heterogeneous rare disease: a post hoc study of response to teduglutide for short bowel syndrome. Ther Clin Risk Manag. 2018;14:1267-77.
Chen 2020[6]	TED, PBO	Chen K, Mu F, Xie J, Kelkar SS, Olivier C, Signorovitch J, et al. Impact of Teduglutide on Quality of Life Among Patients With Short Bowel Syndrome and Intestinal Failure. JPEN Journal of parenteral and enteral nutrition. 2020;44(1):119-28.
Hurt 2017[102]	HPN, ORS	Hurt RT, Vallumsetla N, Edakkanambeth Varayil J, Bonnes SL, Nanda S, Nadeau J, et al. Pilot Study Comparing 2 Oral Rehydration Solutions in Patients With Short Bowel Syndrome Receiving Home Parenteral Nutrition: A Prospective Double-Blind Randomized Controlled Trial. Nutrition in clinical practice : official publication of the American Society for Parenteral and Enteral Nutrition. 2017;32(6):814-9.
Kurin 2020[103]	HPN, TED	Kurin M, Anderson A, Ramos Rivers C, Koutroumpakis F, Centa P, Bender-Heine J, et al. Clinical Characteristics of Inflammatory Bowel Disease Patients Requiring Long-Term Parenteral Support in the Present Era of Highly Effective Biologic Therapy. Journal of Parenteral and Enteral Nutrition. 2020;Online ahead of print.
Nordsten 2020[104]	HPS	Nordsten CB, Molsted S, Bangsgaard L, Fuglsang KA, Brandt CF, Niemann MJ, et al. High Parenteral Support Volume Is Associated With Reduced Quality of Life Determined by the Short-Bowel Syndrome Quality of Life ScaleTM in Nonmalignant Intestinal Failure Patients. Journal of Parenteral and Enteral Nutrition. 2020;Online ahead of print.
Pederiva 2019[105]	PN, AGIRS	Pederiva F, Khalil B, Morabito A, Wood SJ. Impact of Short Bowel Syndrome on Quality of Life and Family: The Patient's Perspective. European journal of pediatric surgery: official journal of Austrian Association of Pediatric Surgery. 2019;29(2):196-202.
Wilburn 2018[106]	HPN	Wilburn J, McKenna SP, Heaney A, Rouse M, Taylor M, Culkin A, et al. Development and validation of the Parenteral Nutrition Impact Questionnaire (PNIQ), a patient-centric outcome measure for Home Parenteral Nutrition. Clinical Nutrition. 2018;37(3):978-83.

Abbreviations: AGIRS, autologous gastrointestinal reconstruction surgery; HPN, home parenteral nutrition; HPS, home parenteral support; HRQoL, health-related quality-of-life; HSUV, health-state utility value; ORS, oral rehydration solution; PBO, placebo; PN, parenteral nutrition; PS, parenteral support; TED, teduglutide.

List of excluded studies on full-text review in the updated SLR from 2021

A list of publications excluded during the full-text review of the January 2021 HRQoL and HSUV SLR update is provided in Table 119. A list of publications excluded during the full-text review of the May 2021 HRQoL and HSUV SLR update is provided in Table 120.

Table 119: List of studies excluded on full-text review in the January 2021 HRQoL and HSUV SLR update (n=47)

Authors	Year	Title	Exclusion reason
Ablett J.; Vasant D.H.; Taylor M.; Cawley C.; Lal S.	2019	Poor Social Support and Unemployment Are Associated With Negative Affect in Home Parenteral Nutrition-Dependent Patients With Chronic Intestinal Failure	No relevant outcomes
Ambrose T.; Holdaway L.; Smith A.; Howe H.; Vokes L.; Vrakas G.; Reddy S.; Giele H.; Travis S.P.L.; Friend P.J.; Allan P.J.	2020	The impact of intestinal transplantation on quality of life	No relevant outcomes
Arhip, L; Serrano-Moreno, C; Romero, I; Camblor, M; Cuerda, C	2020	The economic costs of home parenteral nutrition: Systematic review of partial and full economic evaluations.	SLR/NMA for hand-searching
Baxter J.P.; Fayers P.M.; Bozzetti F.; Kelly D.; Joly F.; Wanten G.; Jonkers C.; Cuerda C.; van Gossum A.; Klek S.; Boudreault M.-F.; Gilbert A.; Jobin M.; Staun M.; Gillanders L.; Forbes A.; O'Callaghan M.; Faedo C.M.; Brunelli C.; Mariani L.; Pironi L.	2019	An international study of the quality of life of adult patients treated with home parenteral nutrition	No relevant outcomes
Bednarsch J.; Bluthner E.; Karber M.; Gerlach U.A.; Pascher A.; Maasberg S.; Pevny S.; Pratschke J.; Pape U.-F.; Stockmann M.	2020	Oral intake and plasma citrulline predict quality of life in patients with intestinal failure	Irrelevant population
Bluthner E.; Pape U.-F.; Stockmann M.; Karber M.; Maasberg S.; Pevny S.; Gerlach-Runge U.; Pascher A.; Pratschke J.; Tacke F.; Bednarsch J.	2020	Assessing non-invasive liver function in patients with intestinal failure receiving total parenteral nutrition-results from the prospective PNliver trial	Irrelevant population
Bluthner, Elisabeth; Bednarsch, Jan; Stockmann, Martin; Karber, Mirjam; Pevny, Sophie; Maasberg, Sebastian; Gerlach, Undine A; Pascher, Andreas; Wiedenmann, Bertram; Pratschke, Johann; Pape, Ulrich-Frank	2020	Determinants of Quality of Life in Patients With Intestinal Failure Receiving Long-Term Parenteral Nutrition Using the SF-36 Questionnaire: A German Single-Center Prospective Observational Study.	Irrelevant population
Boctor D.L.; Fenton T.; Hassan W.; Shourounis J.; Galante G.; Goulet O.; Lambe C.	2020	Eating behaviours in children with intestinal failure	No relevant outcomes
Carter B.; Cohran V.; Hill S.; Horslen S.; Kaufman S.; Kocoshis S.; Mercer D.; Merritt R.; Pakarinen M.; Protheroe S.; Smith S.; Thompson J.; Vanderpool C.; Venick R.; Wales P.; Yoon M.J.; Grimm A.	2019	Safety findings in children treated with teduglutide for short bowel syndrome-associated intestinal failure: Pooled analysis of 4 clinical studies	No relevant outcomes
ECRI	2016	Intestine and intestine-liver transplantation : update (Structured abstract)	Outside date limits
Esme M.; Balci C.; Oz G.; Kelleci B.; Tamer F.; Akcay K.; Doganci N.; Atac S.; Topeli Iskit A.; Akinci S.B.; Abbasoglu O.; Halil M.G.	2019	The relationship between parenteral nutrition at home and quality of life and catheter infections	No relevant outcomes

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Authors	Year	Title	Exclusion reason
Gao X.; Zhang L.; Zhang Y.; Liu H.; Liu S.; Zhou D.; Wang X.	2019	Effect of home enteral nutrition in malnourished patients with intestinal failure/intestinal insufficiency	Irrelevant population
Garcia Aroz S.; Tzvetanov I.; Hetterman E.A.; Jeon H.; Oberholzer J.; Testa G.; John E.; Benedetti E.	2017	Long-term outcomes of living-related small intestinal transplantation in children: A single-center experience	No relevant outcomes
Harrison L.; Hughes S.J.; Green M.	2020	A review investigating the role of a support group among intestinal failure adult patients within the regional intestinal failure service Northern Ireland	Irrelevant population
Hassan K.; Sher G.; Hamid E.; Hazima K.A.; Abdelrahman H.; Al Mudahka F.; Al-Masri W.; Sankar J.; Daryaee M.; Shawish R.; Khan M.A.; Nawaz Z.	2020	Outcome associated with EPCAM founder mutation c.499dup in Qatar	No relevant outcomes
HAYES; Inc	2016	Living related donor small bowel transplantation for intestinal failure (Structured abstract)	Outside date limits
HAYES; Inc	2016	Serial Transverse Enteroplasty (STEP) for short bowel syndrome (Structured abstract)	Outside date limits
Heaney A.; McKenna S.P.; Wilburn J.; Rouse M.; Taylor M.; Burden S.; Lal S.	2018	The impact of Home Parenteral Nutrition on the lives of adults with Type 3 Intestinal Failure	No relevant outcomes
Jennings V.; Jukes A.; Hewett R.	2020	Patient eligibility for visceral transplant at a tertiary home parental nutrition centre	No relevant outcomes
Li Y.; Zheng L.; Wang J.; Yao D.; Mao Q.	2020	The clinical and nutritional effects of the serial transverse enteroplasty procedure in adult short bowel syndrome: A single-center 6-year experience	No relevant outcomes
Martinuzzi A.L.N.; Cascaron F.; Nunez A.; Bogado M.; Betancurt C.; Roel P.; Tonnelier M.; Ocampo L.R.; Carcamo C.; Traverso M.; Maldonado N.	2019	Home parenteral nutrition in patients with type iii intestinal failure. patagonian experience	No relevant outcomes
Medical Advisory Secretariat; Ontario Ministry of Health and Long-Term Care (MAS)	2016	Small bowel transplant: an evidence-based analysis (Structured abstract)	Outside date limits
Murphy, G; Perras, C; Desjardins, B; Chen, S; Moulton, K; Jonker, D; Perlman, K; Pasieka, J; Ezzat, S; Cripps, C; Mensinkai, S; Skidmore, B	2016	Octreotide for endocrine, oncologic, and gastrointestinal disorders: systematic review and budget impact analysis (Structured abstract)	Outside date limits
Namjoshi S.S.; Muradian S.; Bechtold H.; Reyen L.; Venick R.S.; Marcus E.A.; Vargas J.H.; Wozniak L.J.	2018	Nutrition Deficiencies in Children With Intestinal Failure Receiving Chronic Parenteral Nutrition	No relevant outcomes
National Horizon Scanning Centre	2016	Teduglutide for short bowel syndrome (Structured abstract)	Outside date limits
Neam V.C.; Oron A.P.; Nair D.; Edwards T.; Horslen S.P.; Javid P.J.	2020	Factors Associated with Health-Related Quality of Life in Children with Intestinal Failure	No relevant outcomes
NIHR, HSRIC	2016	Teduglutide (Revestive) - short bowel syndrome: in paediatric patients aged 1-17	Outside date limits

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Authors	Year	Title	Exclusion reason
		years who are dependent on parenteral nutrition (Project record)	
Petrov D.; Aver'ianova I.; Makarov S.; Zhelezoglo E.; Ermolaeva A.	2019	Preventive treatment of various complications in the management of short bowel syndrome and gastrointestinal neuromuscular diseases	No relevant outcomes
Proli F.; Rossi M.; D'Arcangelo G.; Talbotec C.; Lambe C.; Goulet O.; Lacaille F.	2019	Quality of life in children after intestinal transplantation: Comparison with liver transplantation and home parenteral nutrition	Irrelevant population
Raghu V.; Binion D.G.; Smith K.J.	2019	Cost-effectiveness of teduglutide in adult patients with intestinal failure: Markov modeling using traditional costeffectiveness criteria	Superseded by more recent publication with identical data
Raghu V.; Rudolph J.; Smith K.	2019	Cost-effectiveness of teduglutide in pediatric patients with intestinal failure using markov modeling	Superseded by more recent publication with identical data
Reber E.; Muhlebach S.; Stanga Z.	2020	Management of home parenteral nutrition: quality of life, complications and survival swisshpn ii study	No relevant outcomes
Regano N.; Mazzuoli S.; Lamacchia S.; Guglielmi F.W.	2019	Efficacy of teduglutide in patients with short bowel syndrome on home parenteral nutrition: a real life study	No relevant outcomes
Richards, DM; Deeks, JJ; Sheldon, TA; Shaffer, JL	2016	Home parenteral nutrition: a systematic review (Structured abstract)	Outside date limits
Schubert L.; Billiauws L.; Boehm V.; Joly F.	2019	Chronic intestinal failure: When children become adults	No relevant outcomes
Schubert L.; Billiauws L.; Boehm V.; Joly F.	2019	Chronic intestinal failure: When children become adults	Superseded by more recent publication with identical data
Shores, Darla R; Mogul, Douglas; Allen, Julia; Delarmente, Benjo A; Padula, William	2020	Cost-effectiveness Analysis of Feeding Guidelines for Infants Following Intestinal Surgery.	No relevant outcomes
Singh A.; Nan L.; Shen B.; Kirby D.F.; Regueiro M.	2019	Effect of short bowel syndrome on disease activity in patients with Crohn's disease	No relevant outcomes
So S.; Patterson C.; Betts Z.; Belza C.; Avitzur Y.; Wales P.W.	2019	Physical activity, strength and fatigue in children with intestinal failure on parenteral nutrition	Irrelevant population
Sobocki J.; Zaczek Z.; Jurczak P.; Lachowicz K.; Kunecki M.; Groszek P.; Majewska K.; Panczyk M.; Forbes A.	2020	Restricted vs unrestricted oral intake in high output end-jejunostomy patients referred to reconstructive surgery	No relevant outcomes

Authors	Year	Title	Exclusion reason
Solar H.; Doeyo M.; Ortega M.; De Barrio S.; Olano E.; Moreira E.; Buncuga M.; Manzur A.; Crivelli A.; Gondolesi G.	2020	Postsurgical Intestinal Rehabilitation Using Semisynthetic Glucagon-Like Peptide-2 Analogue (sGLP-2) at a Referral Center: Can Patients Achieve Parenteral Nutrition and sGLP-2 Independency?	No relevant outcomes
Sowerbutts, A M; Panter, C; Dickie, G; Bennett, B; Ablett, J; Burden, S; Lal, S	2020	Short bowel syndrome and the impact on patients and their families: a qualitative study.	No relevant outcomes
Theilla M.; Chernov K.; Cohen J.; Kagan I.; Singer P.	2018	Self-Evaluation of Quality of Life Among Patients Receiving Home Parenteral Nutrition: A Validation Study	Irrelevant population
Tran L.C.; Lazonby G.; Morello R.; Pham D.; Ellis D.; Goldthorpe J.; Iglesias N.; Steele J.; Zamvar V.; Puntis J.W.L.; Vora R.	2019	How good is quality-of-life for children receiving home parenteral nutrition? - A pilot study	No relevant outcomes
Winkler M.F.; Machan J.T.; Xue Z.; Compher C.	2020	Home Parenteral Nutrition Patient-Reported Outcome Questionnaire: Sensitive to Quality of Life Differences Among Chronic and Prolonged Acute Intestinal Failure Patients	No relevant outcomes
Wong, Christina; Lucas, Beverley; Wood, Diana	2018	Patients' experiences with home parenteral nutrition: A grounded theory study.	No relevant outcomes
Wright S.; Thompson N.; Yadrich D.; Bruce A.; Bonar J.R.M.; Spaulding R.; Smith C.E.	2020	Using telehealth to assess depression and suicide ideation and provide mental health interventions to groups of chronically ill adolescents and young adults	No relevant outcomes

Abbreviations: HRQoL, health-related quality-of-life; HSUV, health-state utility value; NMA, network meta-analysis; SLR, systematic literature review.

Table 120: List of studies excluded on full-text review in the May 2021 HRQoL and HSUV SLR update (n=18)

Authors	Year	Title	Exclusion reason
Bell, Mercedes; Cole, Conrad R.; Hansen, Nellie I.; Duncan, Andrea F.; Hintz, Susan R.; Adams-Chapman, Ira	2021	Neurodevelopmental and Growth Outcomes of Extremely Preterm Infants with Short Bowel Syndrome	No relevant outcomes
Beurskens-Meijerink, Judith; Wanten, Geert; Waal, Getty Huisman-de	2021	Identifying patients with benign chronic intestinal failure on home parenteral nutrition in whom a psychological support intervention may improve quality of life	Irrelevant population
Eliasson, Johanna; Hvistendahl, Mark Krogh; Bolognani, Federico; Meyer, Christian; Jeppesen, Palle Bekker	2021	Apraglutide, a once weekly glucagon-like peptide-2 analogue, improves intestinal absorption in patients with short bowel syndrome intestinal failure: A placebo-controlled, randomized phase 2 trial	No relevant outcomes
Gilmore, R.; Ma, R.; Chapman, B.; Hamilton, K.; Wong, D.; Testro, A.; De Cruz, P.	2020	Health care costs associated with Australian home parenteral nutrition use	No relevant outcomes
McCaig, Jessica K.; Henry, Owen S.; Stamm, Danielle A.; Dorval, Gaby; Hurley, Alexis; Han, Sam M.; Hong, Charles R.; Staffa, Steven J.; Modi, Biren P.	2021	Generic and Disease-Specific Health-Related Quality of Life in Pediatric Intestinal Failure	Irrelevant population

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Authors	Year	Title	Exclusion reason
Metou-Lopes, Adamadia; Ayachi, Amel; Rossi, Matilde; D'Arcangelo, Giulia; Lambe, Cecile; Talbotec, Cecile; Goulet, Olivier; Lacaille, Florence; Proli, Francesco; Faragalli, Andrea; Chardot, Christophe	2021	Quality of life in long term survivors of pediatric intestinal transplantation compared with liver transplantation and home parenteral nutrition: A prospective single-center pilot study	No relevant outcomes
Pevny, S.; Buttner, J.; Bluthner, E.; Tacke, F.; Wehkamp, J.; Fusco, S.; Zopf, Y.; Herrmann, H.J.; Lamprecht, G.; Jacob, T.; Schiefke, I.; von Websky, M.W.; Pape, U.-F.; Maasberg, S.	2020	Teduglutide treatment for chronic intestinal failure patients in germany - insights from a patient home care service program	No relevant outcomes
Raghu, Vikram Kalathur; Rudolph, Jeffrey A.; Mezoff, Ethan A.; Cole, Conrad R.; Smith, Kenneth J.	2021	Cost-effectiveness of ethanol lock prophylaxis to prevent central line-associated bloodstream infections in children with intestinal failure in the United States	Irrelevant population
Raghu, Vikram Kalathur; Rudolph, Jeffrey A.; Smith, Kenneth J.	2021	Cost-effectiveness of teduglutide in pediatric patients with short bowel syndrome: Markov modeling using traditional cost-effectiveness criteria	Included in Jan 2021 HRQoL and HSUV SLR
Raghu, Vikram; Rudolph, Jeffrey; Mezoff, Ethan; Cole, Conrad; Smith, Kenneth	2021	Cost-effectiveness analysis of ethanol lock prophylaxis in the prevention of central line-associated bloodstream infections in children with intestinal failure in the United States	Irrelevant population
Reber, Emilie; Schonenberger, Katja A.; Stanga, Anastasia; Stanga, Zeno; Staub, Kaspar; Leuenberger, Michele; Pichard, Claude; Schuetz, Philipp; Muhlebach, Stefan	2021	Management of Home Parenteral Nutrition: Complications and Survival	No relevant outcomes
Ritchey, Christina; Ortiz, Amanda; Henderson-Davis, La Hily	2021	Clinical and quality of life effects of home parenteral nutrition patients during covid-19	No relevant outcomes
So, Stephanie; Patterson, Catherine; Betts, Zachary; Belza, Christina; Avitzur, Yaron; Wales, Paul W.	2021	Physical Activity and Fatigue in Children with Intestinal Failure on Parenteral Nutrition	Irrelevant population
Sobocki, Jacek; Zaczek, Zuzanna; Jurczak, Paulina; Lachowicz, Karolina; Kunecki, Marek; Groszek, Patrycja; Majewska, Krystyna; Panczyk, Mariusz; Forbes, Alastair	2021	Restricted v. unrestricted oral intake in high output end-jejunostomy patients referred to reconstructive surgery.	No relevant outcomes
Sowerbutts, Anne Marie; Jones, Debra; Lal, Simon; Burden, Sorrel	2021	Quality of life in patients and in family members of those receiving home parenteral support with intestinal failure: A systematic review.	SLR/NMA for hand-searching
Swinn, J.; Steinbrecher, C.; Pepperrell, S.; Clarke, E.J.; Hollingworth, T.W.; King, A.T.; Richardson, C.; Smith, T.R.; Rutter, C.S.	2021	Dedicated physiotherapy in intestinal failure improves patient outcomes and quality of life	Irrelevant population
Wall, Elizabeth; Lakananurak, Narisorn; Pevny, Sophie; Catron, Hilary; Mercer, David; Berner-Hansen, Mark; Herlitz, Jean; Lozano, Scott; Delgado, Adela; Moccia, Lisa; Gramlich, Leah	2021	Gaps and opportunities in themanagement of short bowel syndrome: An international inquiry	Irrelevant study design
Wang, Peng; Yang, Jianbo; Zhang, Yupeng; Zhang, Li; Gao, Xuejin; Wang, Xinying	2020	Risk Factors for Renal Impairment in Adult Patients With Short Bowel Syndrome.	No relevant outcomes

Abbreviations: HRQoL, health-related quality-of-life; HSUV, health-state utility value; NMA, network meta-analysis; SLR, systematic literature review.

List of included studies in the original SLR from 2015 including the 2016 update

Eighteen potentially relevant utility studies were identified and are described in Table 121.

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Table 121 List of included studies in the 2015 and 2016 updated SLR

Reference	Population	Intervention & comparators	Study type	Method	Outcomes (EQ-5D)
Lloyd *et al.*	General UK population	Not specified	Mapping study	SBS-QoL	No utilities reported based on EQ-5D-3L
Jeppesen *et al.*	SBS-IF patients	Teduglutide vs placebo	HRQL	SBS-QoL	No utilities reported based on EQ-5D-3L
Pironi *et al.*	Patients on HPN and patients after ITx	HPN vs ITx	HRQL	HPN-QoL and HPN-QoL adapted to ITx recipients	No utilities reported based on EQ-5D-3L
Carvalho *et al.*	SBS patients	Not specified	HRQL	QoL	No utilities reported based on EQ-5D-3L
Winkler *et al.*	Patients on PN	HPN	HRQL	Not Reported	No utilities reported based on EQ-5D-3L
Madsen *et al.*	SBS patients	GLP-1, GLP-2, and GLP-1+2 vs placebo	HRQL study reporting VAS scores	VAS from 0 to 10 cm	No utilities reported based on EQ-5D-3L
Culkin *et al.*	CIF patients	HPN (33 patients out of 48 CIF patients)	HRQL	QoL was calculated using EQ-5D-3L VAS, EQ-5D index & SF-36	1. Quality of Life EQ-5D Index; all patients (n=48): 0.75 ± 0.19, HPN patients (n=33): 0.77 ± 0.16 2. Changes in quality of life indices for patients dependent & independent on HPN EQ-5D Index (median, IQR); No HPN patients (n=15): 0.00, -0.11 - 0.04, HPN patients (n=32): 0.07, 0.00 - 0.13.
Pagoldh *et al.*	Intestinal resected patients	Non-processed cereals (NPCs) vs specially processed cereals (SmPCs)	HRQL	Accumulated self-estimated abdominal pain/ discomfort score; and SF-36	No utilities reported based on EQ-5D-3L
Kalaitzakis *et al.*	SBS patients	HPN	HRQL	SF36, HADS, FIS	No utilities reported based on EQ-5D-3L
Pironi *et al.*	Patients on HPN and patients who underwent ITx	HPN	HRQL	SF-36 (Italian version)	No utilities reported based on EQ-5D
Chambers *et al.*		Telemedicine support vs standard treatment	HRQL	SF-36, EQ-5D, HADS	No utilities reported based on EQ-5D-3L only SF-36
Pironi *et al.*	IF-patients	HPN	HRQL	SF-36	No utilities reported based on EQ-5D-3L
Carlsson *et al.*	SBS patients	HPN	HRQL	VAS from 0 to 100 mm, SF-36, RFIPC	No utilities reported based on EQ-5D
Pironi *et al.*	CIF patients	HPN	HRQL	SF-36	No utilities reported based on EQ-5D
Rovera *et al.*	ITx patients and patients on HPN	HPN	HRQL	Self-administered QOLI of 125 questions organised into 25 domains	No utilities reported based on EQ-5D

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Mughal *et al.*	Patients on HPN	HPN	HRQL	Not Specified	No utilities reported based on EQ-5D
Lachaine *et al.*	SBS patients and the Canadian general population	Days and/or hours per day on PS	HRQL	General population TTO survey to elicit health state utility values	• PS0 = 0.74 • PS1 = 0.70 • PS2 = 0.65 • PS3 = 0.61 • PS4 = 0.57 • PS5 = 0.52 • PS6 = 0.48 • PS7 Low = 0.44 • PS7 High = 0.39 Increased use of PS was associated with a decrement to utility (R^2= 0.94)
Ballinger *et al.*	SBS patients, HCPs, scientific advisors, UK general population. HRQL utility values only available for SBS patients.	Days per week dependent on PS	HRQL	Participants valued each state using the TTO method. Regression modelling of the resultant data was then undertaken to correlate number of days on PS and the increased health state.	HRQL utility values: PS0 = 0.82 (SD=0.16) PS7 = 0.36 (SD=0.18) Regression analysis: VAS β=-5.96 (SE=0.27) TTO β=-0.07 (SE=0.004)

Key: CIF, chronic intestinal failure; EQ-5D, EuroQoL 5 dimensions; FIS, Fatigue Impact Scale; GLP, glucagon-like peptide; HADS, Hospital Anxiety and Depression Scale; HCP, health care professional; HPN, home parenteral nutrition; HRQL, health-related quality of life; IF, intestinal failure; ITx, intestinal transplantation; PN, parenteral nutrition; QoL, quality of life; QOLI, Quality of Life Inventory; RFIPC, Rating Form of Inflammatory Bowel Disease Patient Concerns; SBS, short bowel syndrome; SF-36, 36-item short form survey; TTO, time trade-off; VAS, visual analogue scale.

Quality assessment and generalizability of estimates

Key characteristics of each of these studies are presented in Table 121, with full results and quality assessments in Appendix 18 and 19, respectively. Of these, 13 were HRQL studies that did not report utilities. This included STEPS. These are therefore not consistent with the reference case.
From the original systematic literature review, three studies were identified as potentially suitable for utilization in the cost-effectiveness model: one study was designed to develop an algorithm to estimate utility scores for a patient-reported SBS-specific quality of life scale, and two studies used the EQ-5D.

Lloyd et al. mapped utilities based on SBS-QoL outcomes to equivalent EQ-5D utilities. Six-dimension health states were developed using eight SBS-QoL items. SBS health states were then valued by a UK general population using the lead-time TTO method. This method was used to map SBS-QoL data from the STEPS trials to utilities. As SBS-QoL was a secondary endpoint of STEPS the study was not powered to show a statistical difference between the study arms; therefore, the Lloyd et al. publication was not used for the base-case utility values in the economic model. However, it has been used in a scenario analysis as this is still a potentially relevant source of data.

For the two studies with EQ-5Q measured, one study reported VAS scores, which are not considered utilities and should therefore not be used in economic models, and the EQ-5D index, which could be used in an economic model. However, because the approach of the cost-effectiveness model is based on the reduction in the number of days a patient requires PS, and this study is not based on the number of days of PS use (and no patient-level data are

available to re-calculate the utility values), it is not deemed appropriate for use in this economic model. The second study only reported values based on SF-36 and only showed the number of patients having a worse, improved or unchanged EQ-5D score and the utility scores for anxiety and depression after 2 days and 6 months for both groups studied. The EQ-5D was only used to supplement the SF-36. Therefore, no utility values could be extracted from this study, and this study is not considered relevant to inform utility values in this submission.

Two additional studies were identified in the update of the utilities systematic search, and were both general population survey studies. The study by Lachaine et al. was a web-based survey conducted on the Canadian general population to elicit health state utility values for days per week dependent on PS. Health state utility values from this study were not used, as the patient population was not from the UK, and the EQ-5D was not used to elicit utility values. The second study identified in the systematic review update was by Ballinger et al This study also used a general population sample, this time from the UK, to elicit health state utility values for zero days per week dependent on PS (while still being affected by SBS-IF), as compared to 7 days per week dependent on PS. However, Ballinger et al. also incorporated EQ-5D measurements into their analysis.

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Appendix I

Mapping of HRQoL data

The mapping algorithm used to map SBS-QoL from steps to utility values (UK preference weights) was developed by Lloyd et al. in the publication described in Table 122.

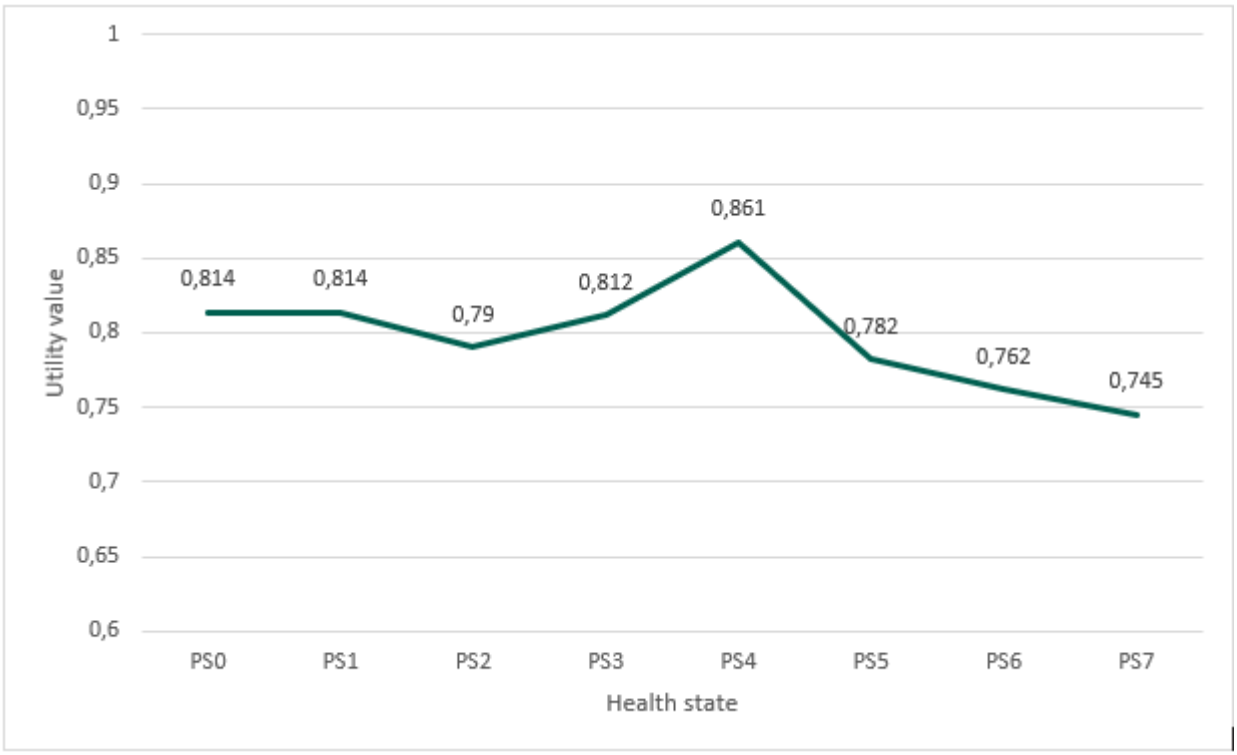
Table 122 Mapping study used to map the non-preference based instrument SBS-QoL to utility values with UK preference weights

Author and year of publication	Lloyd (2014)[86]
Study name	Economic evaluation in short bowel syndrome (SBS): an algorithm to estimate utility scored for a patient-reported SBS-specific quality of life scale (SBS-QoL)
Brief study description	Observational economic evaluation study designed to develop an algorithm to estimate utility scores for a patient-reported SBS-QoL. Random and fixed effects models were also estimated using maximum likelihood estimation (MLE) in order to take into account the structure of the data. A mean model was also estimated using ordinary least squares where the data consist of one mean value per state. The final choice of model was based on a combination of consistency and predictive performance. A subset of 8 core SBS-QoL items were selected from the full 17-item scale. Six-dimension health states were developed using 8 SBS-QoL items (2 dimensions combined with 2 SBS-QoL items). SBS health states were valued by a UK general population sample (N=250) using the lead time–time trade-off method (LT-TTO). Preference weights or 'utility decrements' for each severity level of each dimension were estimated by regression models and used to develop the scoring algorithm.
Population in which health effects were measured	SBS patients UK general population
Information on recruitment	Inclusion criteria: Patients aged ≥18 having SBS, having a wide range of diversity in ethnicity, employment status and educational level
Intervention and comparators	Not specified
Sample size	N=250 (UK general population)
Response rates (final number of study participants)	N=250
Description of health states and source of definitions	Not reported
Adverse events	Not reported
Appropriateness of health states, given condition and treatment pathway	Not reported
Method of elicitation and valuation	The complexity of the scale was reduced by simplifying to a smaller number of questions. These questions and their possible response options were then combined with other questions to create health state descriptions. Regression modelling of the resultant data was then undertaken to estimate differences in utility related to different responses to questions on the SBS-QoL. Participants valued each state using the LT-TTO method.
Mapping and uncertainty around mapped values	Yes, QoL values were mapped to utility values (EQ-5D was used). No uncertainty was reported by the author.

Point when measurements were made	Not reported
Baseline/population values with confidence intervals	The proportion of participants in the sample reporting some or extreme problems on the EQ-5D was lower than in the UK general population.
Values by health state with confidence intervals	Mean utilities for the SBS health states ranged from -0.46 (worst health state, very much affected on all dimensions) to 0.92 (best health state, not at all affected on all dimensions). LT-TTO; observed LT-TTO utilities for the best SBS health state were 0.86 and 0.92 in set 1 and set 2, respectively, and for the worst health state were -0.45 and -0.46, respectively. For the random effects MLE model, the range of predicted values was 0.934 (best state, 000000) to -0.362 (worst state, 111111).
Consistency with NICE reference case	Yes, the study was performed in a UK population.
Appropriateness for current cost-effectiveness analysis	Might be appropriate for mapping

The mapped utility values for each health state are presented below in Figure 49, indicating that patients in the trial prefer receiving parenteral support 4 days per week over any other health state, including parenteral autonomy. This is clearly not aligned with any other utility study or any statement we have received from patients and clinical experts, who claim that fewer parenteral support days is associated with higher quality of life. These results, while included as a scenario, should consequently be disregarded.

Figure 49 Utilities mapped from the SBS-QoL data in STEPS (using the Lloyd algorithm) by number of days per week of PS



Source: Lloyd (2013), STEPS data

Key: SBS-QoL: Short Bowel Syndrome Quality of Life, PS; Parenteral Support

Appendix J

Probabilistic sensitivity analyses

If no distribution information is known for a parameter, SE is estimated to be 20%. This assumption can be manipulated in the 'PSA' sheet of the Excel model.

Controls

Parameter	Base Value	SE	Lower Bound	Upper Bound	Distribution	Alpha	Beta
Cycle Length (Months)	28,0000	Not included in SA					
Model Time Horizon (Days)	14610,0000	Not included in SA					
Annual Costs Discount Rate (fixed)	0,0350	Not included in SA					
Annual Effects Discount Rate (fixed)	0,0350	Not included in SA					
Annual Cost & Effects Discount Rate 0-35 years	0,0350	Not included in SA					
Annual Cost & Effects Discount Rate 36-70 years	0,0250	Not included in SA					
Annual Cost & Effects Discount Rate >70 years	0,0150	Not included in SA					
Starting age	50,0000	Not included in SA					
Percentage female	0,5349	Not included in SA					
Proportion discontinuing teduglutide - PS0	0,0000	0,0000	0,0000	0,0000	Beta	0,0000	0,0000
Proportion discontinuing teduglutide - PS1	0,0000	0,0000	0,0000	0,0000	Beta	0,0000	0,0000
Proportion discontinuing teduglutide - PS2	0,0000	0,0000	0,0000	0,0000	Beta	0,0000	0,0000
Proportion discontinuing teduglutide - PS3	0,6667	0,1333	0,3957	0,8873	Beta	8,3333	4,1667
Proportion discontinuing teduglutide - PS4	0,3333	0,0667	0,2109	0,4683	Beta	16,6667	33,3333
Proportion discontinuing teduglutide - PS5	0,3333	0,0667	0,2109	0,4683	Beta	16,6667	33,3333
Proportion discontinuing teduglutide - PS6	0,1667	0,0333	0,1069	0,2365	Beta	20,8333	104,1667
Proportion discontinuing teduglutide - PS7	1,0000	0,2000	0,0000	0,0000	Beta	0,0000	0,0000

Transition probabilities – Dirichlet probabilities

Explained in **8.7.2** and included in the 'Lists' sheet of the Excel model. See base case transition probabilities in **Appendix L**.

Survival – adults, Salazar 2021

Gompertz

	Deterministic
Rate	-3,00817915
Shape	-0,01501417

Covariance matrix

	Constant	gamma
Rate	0,0592574	
Shape	-0,01145	3,76E-03

Weibull

	Deterministic
Shape	0,05573592
Scale	2,98000828

Covariance matrix

	Constant	ln(p)
Shape	0,0167325	
Scale	-0,021586	0,0496646

Log-logistic

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	Deterministic
Shape	0,1460642
Scale	2,7251536

Covariance matrix

	Shape	Scale
Shape	0,0167302	
Scale	-0,020254	0,0484833

Log normal

	Deterministic
meanlog	2,9059488
sdlog	0,5129368

Covariance matrix

	Constant	ln(sigma)
meanlog	0,0689921	
sdlog	0,0244702	0,0142592

Generalised gamma

	Deterministic
Constant	2,9257593
Ln(sigma)	0,4544514
Kappa	0,1275637

Covariance matrix

	Constant	ln(sigma)	Kappa
Constant	0,0746237		
ln(sigma)	-0,002364	0,1060253	
Kappa	0,056026	-0,192081	0,40348

Survival pediatrics, Pironi 2011

Gompertz

	Deterministic
Rate	-4,17560668
Shape	0,08547691

Covariance matrix

	Shape	Rate
Rate	0,5422269	
Shape	-0,158649	6,03E-02

Weibull

	Deterministic
Shape	0,2411106
Scale	3,4498372

Covariance matrix

	Shape	Scale
Shape	0,1212868	
Scale	-0,225931	0,4980369

Log-logistic

	Deterministic
Shape	0,2649912
Scale	3,3673961

Covariance matrix

	Shape	Scale
Shape	0,118137	
Scale	-0,212787	0,4640279

Log normal

	Deterministic
meanlog	3,824653
sdlog	0,5120545

Covariance matrix

	Constant	ln(sigma)
meanlog	0,6635508	
sdlog	0,2342958	0,0962321

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Generalised gamma

	Deterministic
Constant	0,05556836
Ln(sigma)	-1,15899725
Kappa	-52,16687823

Covariance matrix

	Constant	ln(sigma)	Kappa
Constant	0,0073605		
ln(sigma)	0,1180138	2,2502259	
Kappa	5,9716752	110,74708	5768,36

Adverse events

Parameter	Base Value	SE	Lower Bound	Upper Bound	Distribution	Alpha	Beta
Abdominal distension probability, teduglutide months 0-6	0,0543	0,0109	0,0350	0,0774	Beta	23,6434	412,0709
Abdominal pain probability, teduglutide months 0-6	0,0543	0,0109	0,0350	0,0774	Beta	23,6434	412,0709
Arthralgia probability, teduglutide months 0-6	0,0116	0,0023	0,0075	0,0166	Beta	24,7093	2100,2907
Bacteraemia probability, teduglutide months 0-6	0,0000	0,0000	0,0000	0,0000	Beta	0,0000	0,0000
Catheter related infection probability, teduglutide months 0-6	0,0233	0,0047	0,0150	0,0332	Beta	24,4186	1025,5814
Central line infection probability, teduglutide months 0-6	0,0116	0,0023	0,0075	0,0166	Beta	24,7093	2100,2907
Constipation probability, teduglutide months 0-6	0,0039	0,0008	0,0025	0,0055	Beta	24,9031	6400,0969
Decreased appetite probability, teduglutide months 0-6	0,0116	0,0023	0,0075	0,0166	Beta	24,7093	2100,2907
Dehydration probability, teduglutide months 0-6	0,0078	0,0016	0,0050	0,0111	Beta	24,8062	3175,1938
Diarrhoea probability, teduglutide months 0-6	0,0155	0,0031	0,0100	0,0221	Beta	24,6124	1562,8876
Dizziness probability, teduglutide months 0-6	0,0039	0,0008	0,0025	0,0055	Beta	24,9031	6400,0969
Dyspnoea probability, teduglutide months 0-6	0,0116	0,0023	0,0075	0,0166	Beta	24,7093	2100,2907
Fatigue probability, teduglutide months 0-6	0,0194	0,0039	0,0125	0,0277	Beta	24,5155	1240,4845
Flatulence probability, teduglutide months 0-6	0,0194	0,0039	0,0125	0,0277	Beta	24,5155	1240,4845
Gastrointestinal stoma complication probability, teduglutide months 0-6	0,0426	0,0085	0,0275	0,0608	Beta	23,9341	537,4295
Headache probability, teduglutide months 0-6	0,0078	0,0016	0,0050	0,0111	Beta	24,8062	3175,1938
Injection site haematoma probability, teduglutide months 0-6	0,0078	0,0016	0,0050	0,0111	Beta	24,8062	3175,1938
Injection site pain probability, teduglutide months 0-6	0,0155	0,0031	0,0100	0,0221	Beta	24,6124	1562,8876
Muscle spasms probability, teduglutide months 0-6	0,0078	0,0016	0,0050	0,0111	Beta	24,8062	3175,1938
Nausea probability, teduglutide months 0-6	0,0736	0,0147	0,0475	0,1049	Beta	23,1589	291,3148
Peripheral oedema probability, teduglutide months 0-6	0,0310	0,0062	0,0200	0,0442	Beta	24,2248	757,0252
Bacterial overgrowth probability, teduglutide months 0-6	0,0155	0,0031	0,0100	0,0221	Beta	24,6124	1562,8876
Pain probability, teduglutide months 0-6	0,0000	0,0000	0,0000	0,0000	Beta	0,0000	0,0000
Procedural site reactions probability, teduglutide months 0-6	0,0116	0,0023	0,0075	0,0166	Beta	24,7093	2100,2907
Pyrexia probability, teduglutide months 0-6	0,0194	0,0039	0,0125	0,0277	Beta	24,5155	1240,4845
Renal colic probability, teduglutide months 0-6	0,0388	0,0078	0,0250	0,0553	Beta	24,0310	595,9690
Small intestinal stenosis probability, teduglutide months 0-6	0,0116	0,0023	0,0075	0,0166	Beta	24,7093	2100,2907
Upper respiratory tract infection probability, teduglutide months 0-6	0,0078	0,0016	0,0050	0,0111	Beta	24,8062	3175,1938
Urinary tract infection probability, teduglutide months 0-6	0,0233	0,0047	0,0150	0,0332	Beta	24,4186	1025,5814
Vomiting probability, teduglutide months 0-6	0,0194	0,0039	0,0125	0,0277	Beta	24,5155	1240,4845
Decreased weight probability, teduglutide months 0-6	0,0039	0,0008	0,0025	0,0055	Beta	24,9031	6400,0969

Increased weight probability, teduglutide months 0-6	0,0116	0,0023	0,0075	0,0166	Beta	24,7093	2100,2907
Abdominal distension probability, teduglutide after month 6	0,0101	0,0020	0,0066	0,0145	Beta	24,7466	2416,9200
Abdominal pain probability, teduglutide after month 6	0,0146	0,0029	0,0095	0,0209	Beta	24,6340	1658,0583
Arthralgia probability, teduglutide after month 6	0,0034	0,0007	0,0022	0,0048	Beta	24,9155	7350,0845
Bacteraemia probability, teduglutide after month 6	0,0011	0,0002	0,0007	0,0016	Beta	24,9718	22150,0282
Catheter related infection probability, teduglutide after month 6	0,0045	0,0009	0,0029	0,0064	Beta	24,8874	5500,1126
Central line infection probability, teduglutide after month 6	0,0079	0,0016	0,0051	0,0113	Beta	24,8029	3121,6256
Constipation probability, teduglutide after month 6	0,0011	0,0002	0,0007	0,0016	Beta	24,9718	22150,0282
Decreased appetite probability, teduglutide after month 6	0,0000	0,0000	0,0000	0,0000	Beta	0,0000	0,0000
Dehydration probability, teduglutide after month 6	0,0068	0,0014	0,0044	0,0096	Beta	24,8311	3650,1689
Diarrhoea probability, teduglutide after month 6	0,0124	0,0025	0,0080	0,0177	Beta	24,6903	1968,4915
Dizziness probability, teduglutide after month 6	0,0023	0,0005	0,0015	0,0032	Beta	24,9437	11050,0563
Dyspnoea probability, teduglutide after month 6	0,0011	0,0002	0,0007	0,0016	Beta	24,9718	22150,0282
Fatigue probability, teduglutide after month 6	0,0011	0,0002	0,0007	0,0016	Beta	24,9718	22150,0282
Flatulence probability, teduglutide after month 6	0,0079	0,0016	0,0051	0,0113	Beta	24,8029	3121,6256
Gastrointestinal stoma complication probability, teduglutide after month 6	0,0113	0,0023	0,0073	0,0161	Beta	24,7185	2170,2815
Headache probability, teduglutide after month 6	0,0056	0,0011	0,0036	0,0080	Beta	24,8592	4390,1408
Injection site haematoma probability, teduglutide after month 6	0,0011	0,0002	0,0007	0,0016	Beta	24,9718	22150,0282
Injection site pain probability, teduglutide after month 6	0,0000	0,0000	0,0000	0,0000	Beta	0,0000	0,0000
Muscle spasms probability, teduglutide after month 6	0,0068	0,0014	0,0044	0,0096	Beta	24,8311	3650,1689
Nausea probability, teduglutide after month 6	0,0090	0,0018	0,0058	0,0129	Beta	24,7748	2725,2252
Peripheral oedema probability, teduglutide after month 6	0,0113	0,0023	0,0073	0,0161	Beta	24,7185	2170,2815
Bacterial overgrowth probability, teduglutide after month 6	0,0000	0,0000	0,0000	0,0000	Beta	0,0000	0,0000
Pain probability, teduglutide after month 6	0,0011	0,0002	0,0007	0,0016	Beta	24,9718	22150,0282
Procedural site reactions probability, teduglutide after month 6	0,0056	0,0011	0,0036	0,0080	Beta	24,8592	4390,1408
Pyrexia probability, teduglutide after month 6	0,0079	0,0016	0,0051	0,0113	Beta	24,8029	3121,6256
Renal colic probability, teduglutide after month 6	0,0113	0,0023	0,0073	0,0161	Beta	24,7185	2170,2815
Small intestinal stenosis probability, teduglutide after month 6	0,0000	0,0000	0,0000	0,0000	Beta	0,0000	0,0000
Upper respiratory tract infection probability, teduglutide after month 6	0,0000	0,0000	0,0000	0,0000	Beta	0,0000	0,0000
Urinary tract infection probability, teduglutide after month 6	0,0146	0,0029	0,0095	0,0209	Beta	24,6340	1658,0583
Vomiting probability, teduglutide after month 6	0,0045	0,0009	0,0029	0,0064	Beta	24,8874	5500,1126
Decreased weight probability, teduglutide after month 6	0,0169	0,0034	0,0109	0,0241	Beta	24,5777	1430,4223
Increased weight probability, teduglutide after month 6	0,0011	0,0002	0,0007	0,0016	Beta	24,9718	22150,0282
Abdominal distension probability, standard care	0,0078	0,0016	0,0050	0,0111	Beta	24,8062	3175,1938
Abdominal pain probability, standard care	0,0543	0,0109	0,0350	0,0774	Beta	23,6434	412,0709
Arthralgia probability, standard care	0,0116	0,0023	0,0075	0,0166	Beta	24,7093	2100,2907
Bacteraemia probability, standard care	0,0116	0,0023	0,0075	0,0166	Beta	24,7093	2100,2907
Catheter related infection probability, standard care	0,0039	0,0008	0,0025	0,0055	Beta	24,9031	6400,0969
Central line infection probability, standard care	0,0155	0,0031	0,0100	0,0221	Beta	24,6124	1562,8876
Constipation probability, standard care	0,0116	0,0023	0,0075	0,0166	Beta	24,7093	2100,2907
Decreased appetite probability, standard care	0,0039	0,0008	0,0025	0,0055	Beta	24,9031	6400,0969

Dehydration probability, standard care	0,0116	0,0023	0,0075	0,0166	Beta	24,7093	2100,2907
Diarrhoea probability, standard care	0,0271	0,0054	0,0175	0,0387	Beta	24,3217	872,1069
Dizziness probability, standard care	0,0116	0,0023	0,0075	0,0166	Beta	24,7093	2100,2907
Dyspnoea probability, standard care	0,0000	0,0000	0,0000	0,0000	Beta	0,0000	0,0000
Fatigue probability, standard care	0,0116	0,0023	0,0075	0,0166	Beta	24,7093	2100,2907
Flatulence probability, standard care	0,0116	0,0023	0,0075	0,0166	Beta	24,7093	2100,2907
Gastrointestinal stoma complication probability, standard care	0,0116	0,0023	0,0075	0,0166	Beta	24,7093	2100,2907
Headache probability, standard care	0,0426	0,0085	0,0275	0,0608	Beta	23,9341	537,4295
Injection site haematoma probability, standard care	0,0116	0,0023	0,0075	0,0166	Beta	24,7093	2100,2907
Injection site pain probability, standard care	0,0000	0,0000	0,0000	0,0000	Beta	0,0000	0,0000
Muscle spasms probability, standard care	0,0155	0,0031	0,0100	0,0221	Beta	24,6124	1562,8876
Nausea probability, standard care	0,0465	0,0093	0,0300	0,0663	Beta	23,8372	488,6628
Peripheral oedema probability, standard care	0,0116	0,0023	0,0075	0,0166	Beta	24,7093	2100,2907
Bacterial overgrowth probability, standard care	0,0000	0,0000	0,0000	0,0000	Beta	0,0000	0,0000
Pain probability, standard care	0,0116	0,0023	0,0075	0,0166	Beta	24,7093	2100,2907
Procedural site reactions probability, standard care	0,0039	0,0008	0,0025	0,0055	Beta	24,9031	6400,0969
Pyrexia probability, standard care	0,0194	0,0039	0,0125	0,0277	Beta	24,5155	1240,4845
Renal colic probability, standard care	0,0000	0,0000	0,0000	0,0000	Beta	0,0000	0,0000
Small intestinal stenosis probability, standard care	0,0000	0,0000	0,0000	0,0000	Beta	0,0000	0,0000
Upper respiratory tract infection probability, standard care	0,0155	0,0031	0,0100	0,0221	Beta	24,6124	1562,8876
Urinary tract infection probability, standard care	0,0194	0,0039	0,0125	0,0277	Beta	24,5155	1240,4845
Vomiting probability, standard care	0,0388	0,0078	0,0250	0,0553	Beta	24,0310	595,9690
Decreased weight probability, standard care	0,0271	0,0054	0,0175	0,0387	Beta	24,3217	872,1069
Increased weight probability, standard care	0,0116	0,0023	0,0075	0,0166	Beta	24,7093	2100,2907

Utilities

Parameter	Base Value	SE	Lower Bound	Upper Bound	Distribution	Alpha	Beta
Utility PS0	0,8200	0,1640	0,4426	0,9947	Beta	4,5000	0,9878
Utility decrement PS1	-0,0400	0,0080	-0,0258	-0,0571	Beta	24,0000	576,0000
Utility decrement PS2	-0,1000	0,0200	-0,0644	-0,1423	Beta	22,5000	202,5000
Utility decrement PS3	-0,1700	0,0340	-0,1090	-0,2412	Beta	20,7500	101,3088
Utility decrement PS4	-0,2400	0,0480	-0,1531	-0,3393	Beta	19,0000	60,1667
Utility decrement PS5	-0,3100	0,0620	-0,1966	-0,4363	Beta	17,2500	38,3952
Utility decrement PS6	-0,4100	0,0820	-0,2572	-0,5722	Beta	14,7500	21,2256
Utility decrement PS7	-0,4600	0,0920	-0,2866	-0,6385	Beta	13,5000	15,8478
Carer utility PS0	0,0000	Not included in SA					
Carer utility decrement PS1	0,0000	Not included in SA					
Carer utility decrement PS2	0,0000	Not included in SA					
Carer utility decrement PS3	0,0000	Not included in SA					
Carer utility decrement PS4	0,0000	Not included in SA					
Carer utility decrement PS5	0,0000	Not included in SA					
Carer utility decrement PS6	0,0000	Not included in SA					

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Carer utility decrement PS7	0,0000	Not included in SA					
Utility liver disease	0,5957	0,1191	0,5310	0,6588	Beta	134,0404	90,9596
Abdominal distension utility decrement	-0,0512	0,0102	-0,0331	-0,0730	Beta	23,7200	439,5613
Abdominal pain utility decrement	-0,0512	0,0102	-0,0331	-0,0730	Beta	23,7200	439,5613
Arthralgia utility decrement	-0,0230	0,0046	-0,0149	-0,0328	Beta	24,4250	1037,5315
Bacteraemia utility decrement	-0,5200	0,1040	-0,3208	-0,7159	Beta	12,0000	11,0769
Catheter related infection utility decrement	-0,5200	0,1040	-0,3208	-0,7159	Beta	12,0000	11,0769
Central line infection utility decrement	-0,5200	0,1040	-0,3208	-0,7159	Beta	12,0000	11,0769
Constipation utility decrement	-0,0512	0,0102	-0,0331	-0,0730	Beta	23,7200	439,5613
Decreased appetite utility decrement	0,0000	0,0000	0,0000	0,0000	Beta	0,0000	0,0000
Dehydration utility decrement	0,0000	0,0000	0,0000	0,0000	Beta	0,0000	0,0000
Diarrhoea utility decrement	0,0000	0,0000	0,0000	0,0000	Beta	0,0000	0,0000
Dizziness utility decrement	0,0000	0,0000	0,0000	0,0000	Beta	0,0000	0,0000
Dyspnoea utility decrement	0,0000	0,0000	0,0000	0,0000	Beta	0,0000	0,0000
Fatigue utility decrement	0,0000	0,0000	0,0000	0,0000	Beta	0,0000	0,0000
Flatulence utility decrement	0,0000	0,0000	0,0000	0,0000	Beta	0,0000	0,0000
Gastrointestinal stoma complication utility decrement	0,0000	0,0000	0,0000	0,0000	Beta	0,0000	0,0000
Headache utility decrement	0,0000	0,0000	0,0000	0,0000	Beta	0,0000	0,0000
Injection site haematoma utility decrement	-0,0300	0,0060	-0,0194	-0,0428	Beta	24,2500	784,0833
Injection site pain utility decrement	-0,0300	0,0060	-0,0194	-0,0428	Beta	24,2500	784,0833
Muscle spasms utility decrement	0,0000	0,0000	0,0000	0,0000	Beta	0,0000	0,0000
Nausea utility decrement	0,0000	0,0000	0,0000	0,0000	Beta	0,0000	0,0000
Peripheral oedema utility decrement	-0,0508	0,0102	-0,0328	-0,0724	Beta	23,7300	443,3960
Bacterial overgrowth utility decrement	-0,5200	0,1040	-0,3208	-0,7159	Beta	12,0000	11,0769
Pain utility decrement	0,0000	0,0000	0,0000	0,0000	Beta	0,0000	0,0000
Procedural site reactions utility decrement	-0,0300	0,0060	-0,0194	-0,0428	Beta	24,2500	784,0833
Pyrexia utility decrement	0,0000	0,0000	0,0000	0,0000	Beta	0,0000	0,0000
Renal colic utility decrement	0,0000	0,0000	0,0000	0,0000	Beta	0,0000	0,0000
Small intestinal stenosis utility decrement	-0,0512	0,0102	-0,0331	-0,0730	Beta	23,7200	439,5613
Upper respiratory tract infection utility decrement	-0,0900	0,0180	-0,0580	-0,1281	Beta	22,7500	230,0278
Urinary tract infection utility decrement	-0,0900	0,0180	-0,0580	-0,1281	Beta	22,7500	230,0278
Vomiting utility decrement	-0,0512	0,0102	-0,0331	-0,0730	Beta	23,7200	439,5613
Decreased weight utility decrement	0,0000	0,0000	0,0000	0,0000	Beta	0,0000	0,0000
Increased weight utility decrement	0,0000	0,0000	0,0000	0,0000	Beta	0,0000	0,0000
IFALD	0,7700	0,1540	0,4336	0,9740	Beta	5,7500	1,7175
Extensive fibrosis	0,6600	0,1320	0,3927	0,8804	Beta	8,5000	4,3788
Cirrhosis	0,5700	0,1140	0,3480	0,7779	Beta	10,7500	8,1096
CKD V	0,7100	0,1420	0,4139	0,9291	Beta	7,2500	2,9613

Costs & Resource use

Parameter	Base Value	SE	Lower Bound	Upper Bound	Distribution	Alpha	Beta
Cost per nurse-administration	580,8068	116,1614	375,8676	829,6267	Gamma	25	23,2323

Cost per colonoscopy	5485,0000	1097,0000	3549,6028	7834,7954	Gamma	25	219,4000
Abdominal distension cost	22789,0000	4557,8000	14747,8392	32551,8966	Gamma	25	911,5600
Abdominal pain cost	22789,0000	4557,8000	14747,8392	32551,8966	Gamma	25	911,5600
Arthralgia cost	9602,0000	1920,4000	6213,9081	13715,5343	Gamma	25	384,0800
Bacteraemia cost	42770,0000	8554,0000	27678,4889	61092,8350	Gamma	25	1710,8000
Catheter related infection cost	19185,0000	3837,0000	12415,5205	27403,9289	Gamma	25	767,4000
Central line infection cost	19185,0000	3837,0000	12415,5205	27403,9289	Gamma	25	767,4000
Constipation cost	2673,0000	534,6000	1729,8247	3818,1236	Gamma	25	106,9200
Decreased appetite cost	0,0000	0,0000	0,0000	0,0000		0	0,0000
Dehydration cost	0,0000	0,0000	0,0000	0,0000		0	0,0000
Diarrhoea cost	5130,0000	1026,0000	3319,8655	7327,7120	Gamma	25	205,2000
Dizziness cost	285,0000	57,0000	184,4370	407,0951	Gamma	25	11,4000
Dyspnoea cost	285,0000	57,0000	184,4370	407,0951	Gamma	25	11,4000
Fatigue cost	0,0000	0,0000	0,0000	0,0000		0	0,0000
Flatulence cost	0,0000	0,0000	0,0000	0,0000		0	0,0000
Gastrointestinal stoma complication cost	5130,0000	1026,0000	3319,8655	7327,7120	Gamma	25	205,2000
Headache cost	0,0000	0,0000	0,0000	0,0000		0	0,0000
Injection site haematoma cost	285,0000	57,0000	184,4370	407,0951	Gamma	25	11,4000
Injection site pain cost	285,0000	57,0000	184,4370	407,0951	Gamma	25	11,4000
Muscle spasms cost	285,0000	57,0000	184,4370	407,0951	Gamma	25	11,4000
Nausea cost	2673,0000	534,6000	1729,8247	3818,1236	Gamma	25	106,9200
Peripheral oedema cost	1529,0000	305,8000	989,4882	2184,0296	Gamma	25	61,1600
Bacterial overgrowth cost	35768,0000	7153,6000	23147,1637	51091,1508	Gamma	25	1430,7200
Pain cost	1643,0000	328,6000	1063,2630	2346,8676	Gamma	25	65,7200
Procedural site reactions cost	285,0000	57,0000	184,4370	407,0951	Gamma	25	11,4000
Pyrexia cost	285,0000	57,0000	184,4370	407,0951	Gamma	25	11,4000
Renal colic cost	22789,0000	4557,8000	14747,8392	32551,8966	Gamma	25	911,5600
Small intestinal stenosis cost	22789,0000	4557,8000	14747,8392	32551,8966	Gamma	25	911,5600
Upper respiratory tract infection cost	15166,0000	3033,2000	9814,6356	21663,1736	Gamma	25	606,6400
Urinary tract infection cost	24431,0000	4886,2000	15810,4550	34897,3358	Gamma	25	977,2400
Vomiting cost	5130,0000	1026,0000	3319,8655	7327,7120	Gamma	25	205,2000
Decreased weight cost	0,0000	0,0000	0,0000	0,0000		0	0,0000
Increased weight cost	0,0000	0,0000	0,0000	0,0000		0	0,0000
PN-related LD costs	0,0000	0,0000	0,0000	0,0000		0	0,0000
fibrosis costs	2734,0000	546,8000	1769,3006	3905,2563	Gamma	25	109,3600
cirrhosis costs	30893,0000	6178,6000	19992,3207	44127,6818	Gamma	25	1235,7200
CKD V costs	34245,0000	6849,0000	22161,5584	48915,6917	Gamma	25	1369,8000

PS-related costs

Parameter	Base Value	SE	Lower Bound	Upper Bound	Distribution	Alpha	Beta
PN bag (≥8 ingredients) band A	1050,0000	210,0000	679,5046	1499,8241	Gamma	25	42,0000

Delivery	98,5600	19,7120	63,7828	140,7835	Gamma	25	3,9424
Nurse time (PS related, distinct from training costs)	550,0000	110,0000	355,9310	785,6221	Gamma	25	22,0000
Taurolock	0,0000	0,0000	0,0000	0,0000		0	0,0000
Proton pump inhibitors	0,1019	0,0204	0,0659	0,1456	Gamma	25	0,0041
Antimotility agents	10,4783	2,0957	6,7810	14,9673	Gamma	25	0,4191
Fragmin 5	17,4492	3,4898	11,2922	24,9245	Gamma	25	0,6980
Ondansetron	3,2000	0,6400	2,0709	4,5709	Gamma	25	0,1280
Specialist visits (adults)	646,8700	129,3740	418,6202	923,9916	Gamma	25	25,8748
Specialist visits (paediatrics)	646,8700	129,3740	418,6202	923,9916	Gamma	25	25,8748
Haematology tests (paediatrics only)	393,0000	78,6000	254,3289	561,3627	Gamma	25	15,7200
Inflammatory markers/Clinical biochemistry (paediatrics only)	24,0000	4,8000	15,5315	34,2817	Gamma	25	0,9600
Line sepsis	42770,0000	8554,0000	27678,4889	61092,8350	Gamma	25	1710,8000
Line fracture occlusion (adult)	2352,0000	470,4000	1522,0904	3359,6060	Gamma	25	94,0800
Line fracture occlusion (paediatric)	2352,0000	470,4000	1522,0904	3359,6060	Gamma	25	94,0800
PS administration time, patient	179,0000	35,8000	115,8394	255,6843	Gamma	25	7,1600
PS administration time, relative (paediatrics)	179,0000	35,8000	115,8394	255,6843	Gamma	25	7,1600
Support besides PS administration, doctor	811,4950	162,2990	525,1568	1159,1426	Gamma	25	32,4598
Support besides PS administration, nurse	580,8068	116,1614	375,8676	829,6267	Gamma	25	23,2323
Hospitalisation (outpatient incl. visits to hepatologic clinic)	2343,0000	468,6000	1516,2661	3346,7503	Gamma	25	93,7200
Hospitalisation (outpatient incl. visits to hepatologic clinic)	98,5600	19,7120	63,7828	140,7835	Gamma	25	3,9424
Hospitalisation (inpatient) (avrg. inpatient stay: 7 days)	22992,0000	4598,4000	14879,2101	32841,8626	Gamma	25	919,6800
Hospitalisation (inpatient) transportation cost	98,5600	19,7120	63,7828	140,7835	Gamma	25	3,9424
General practitioner visits	143,4400	28,6880	92,8268	204,8903	Gamma	25	5,7376

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Appendix K

UK Delphi panel report

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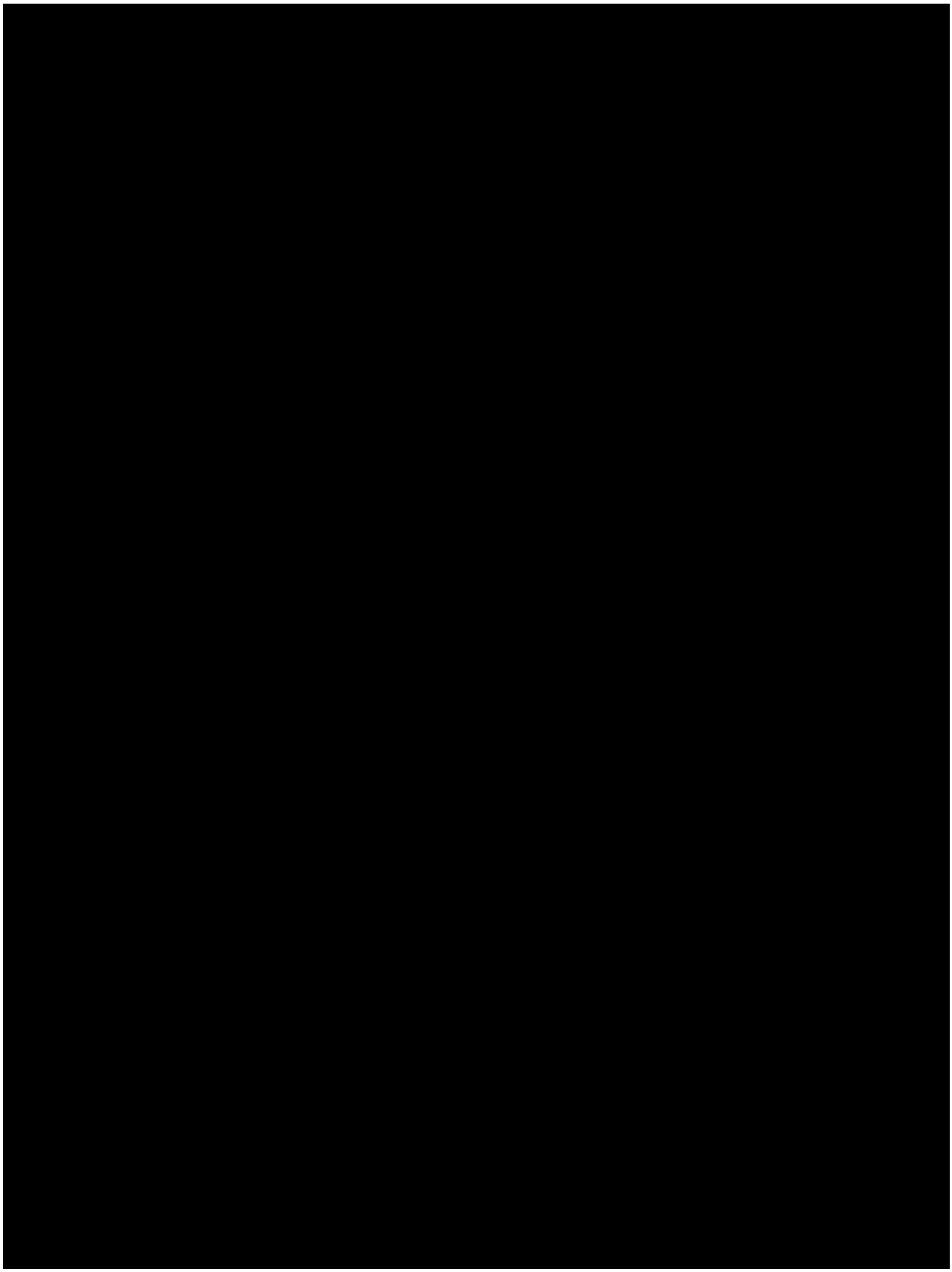

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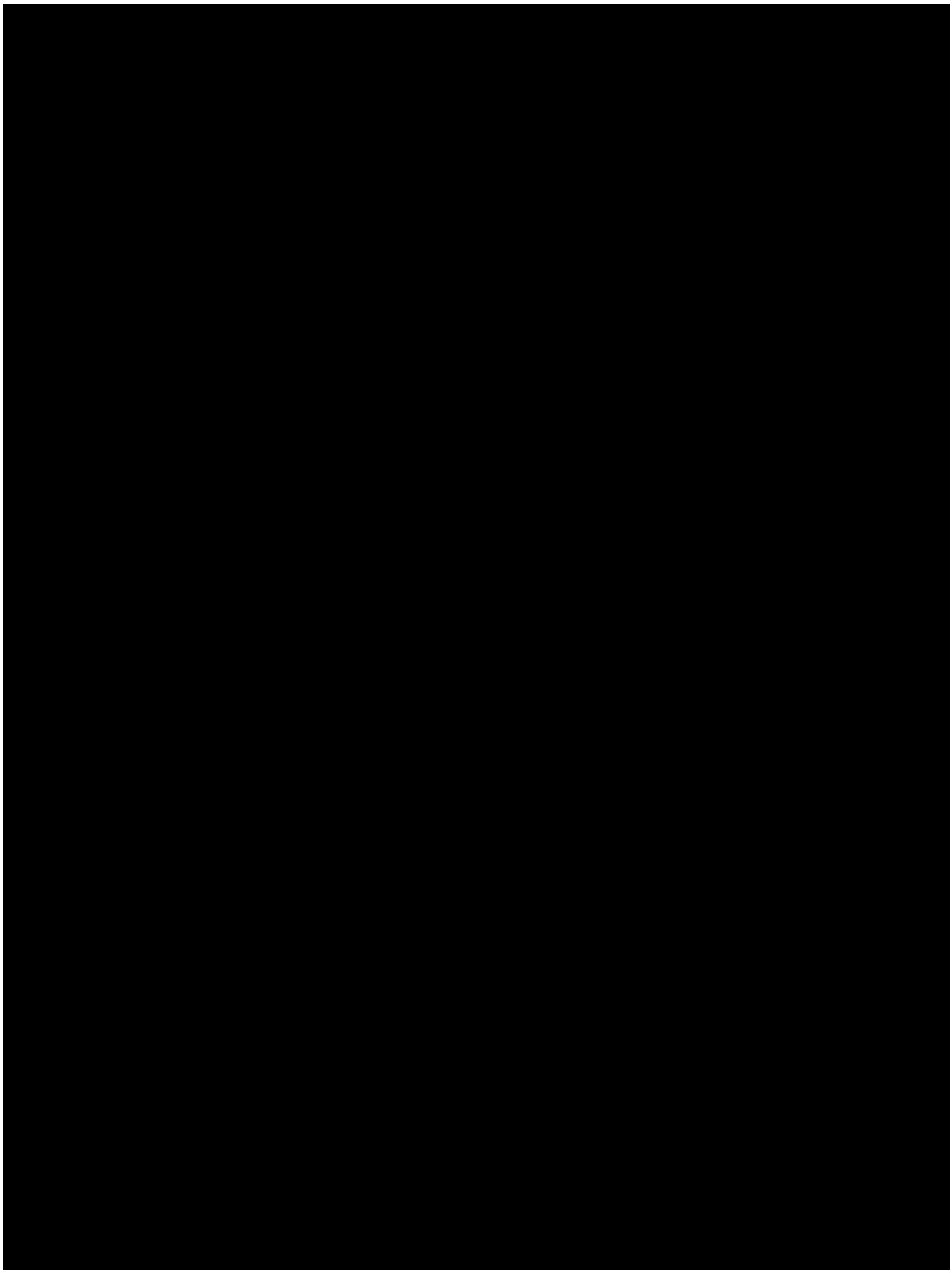

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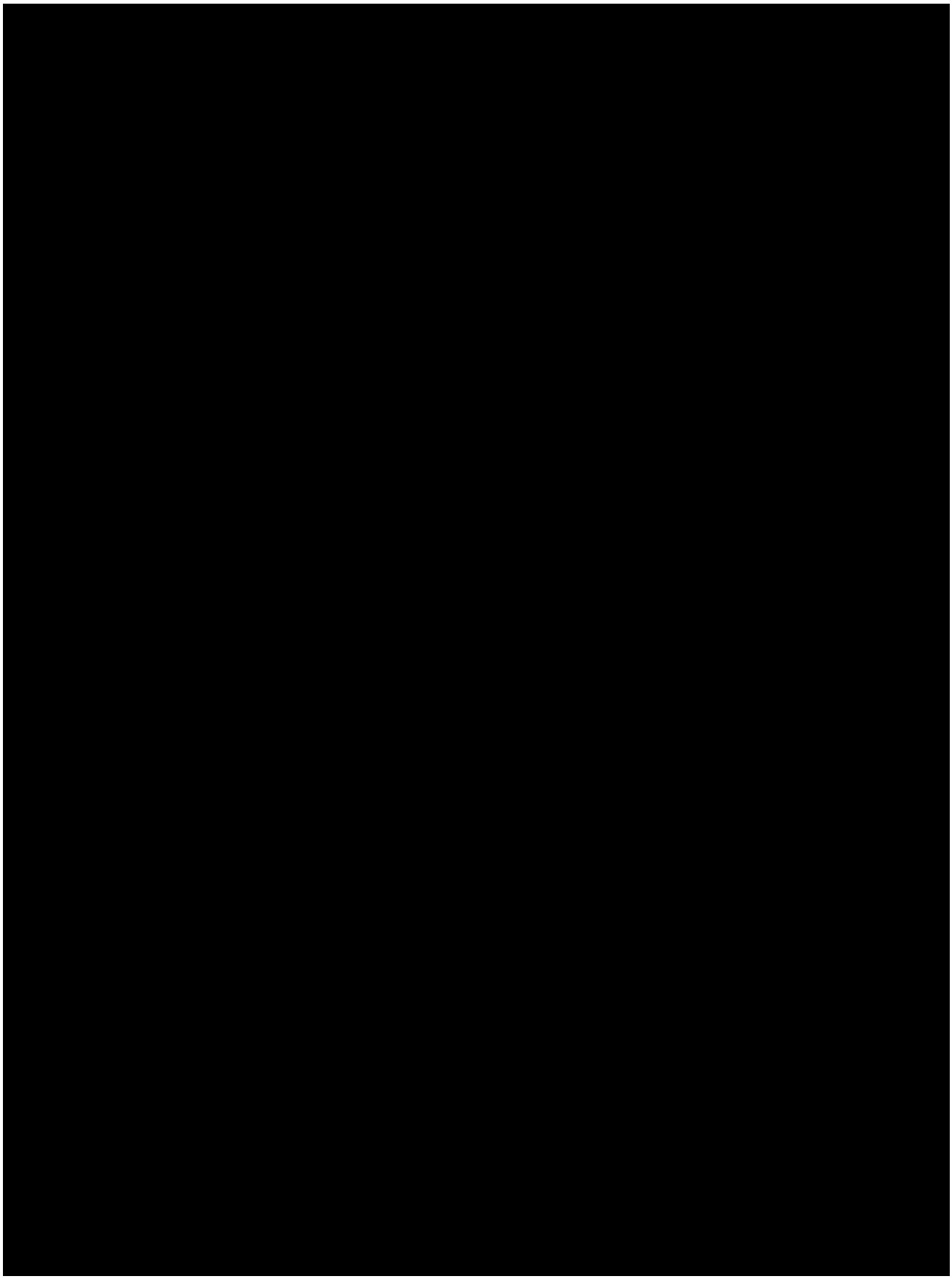

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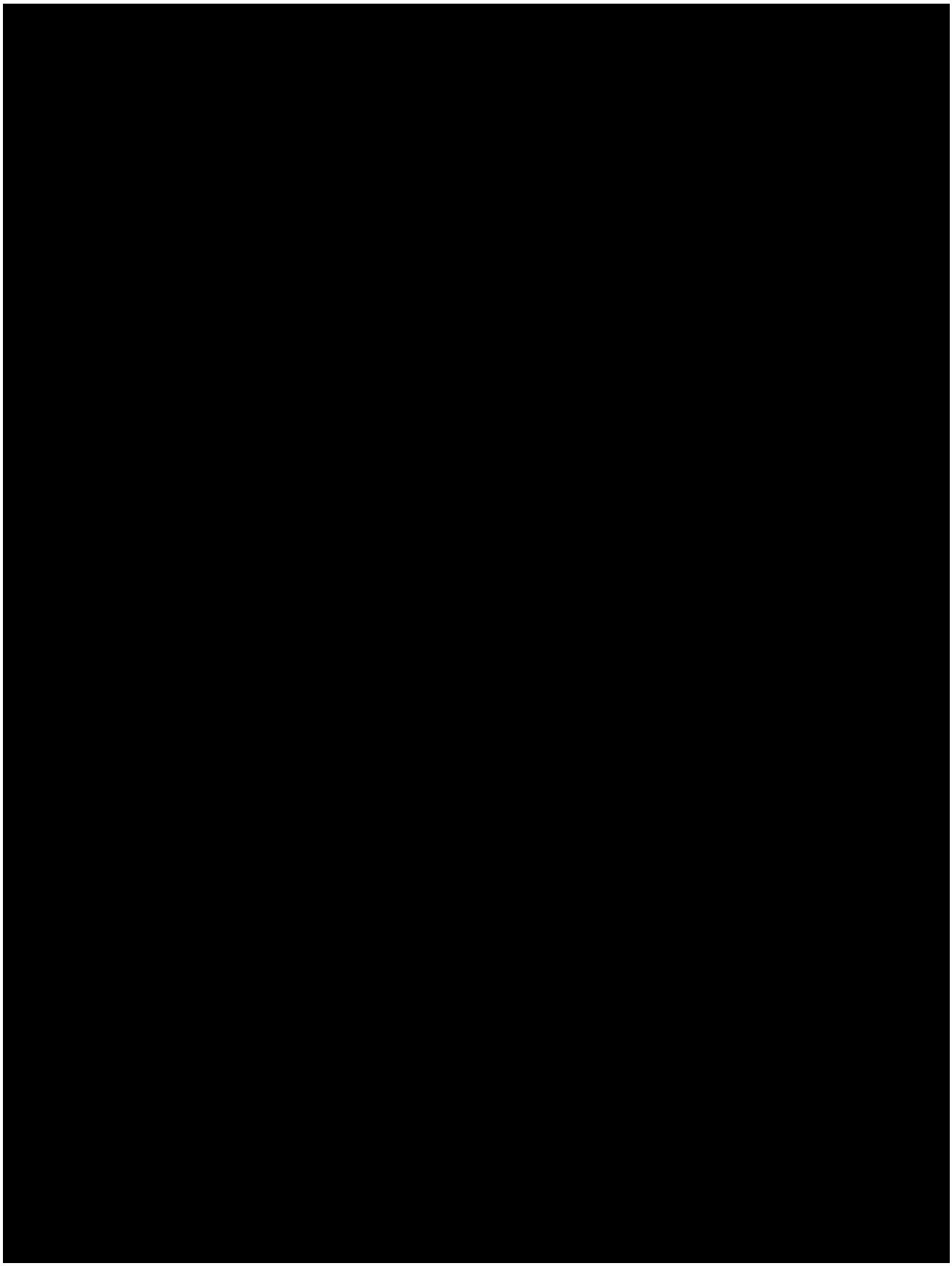

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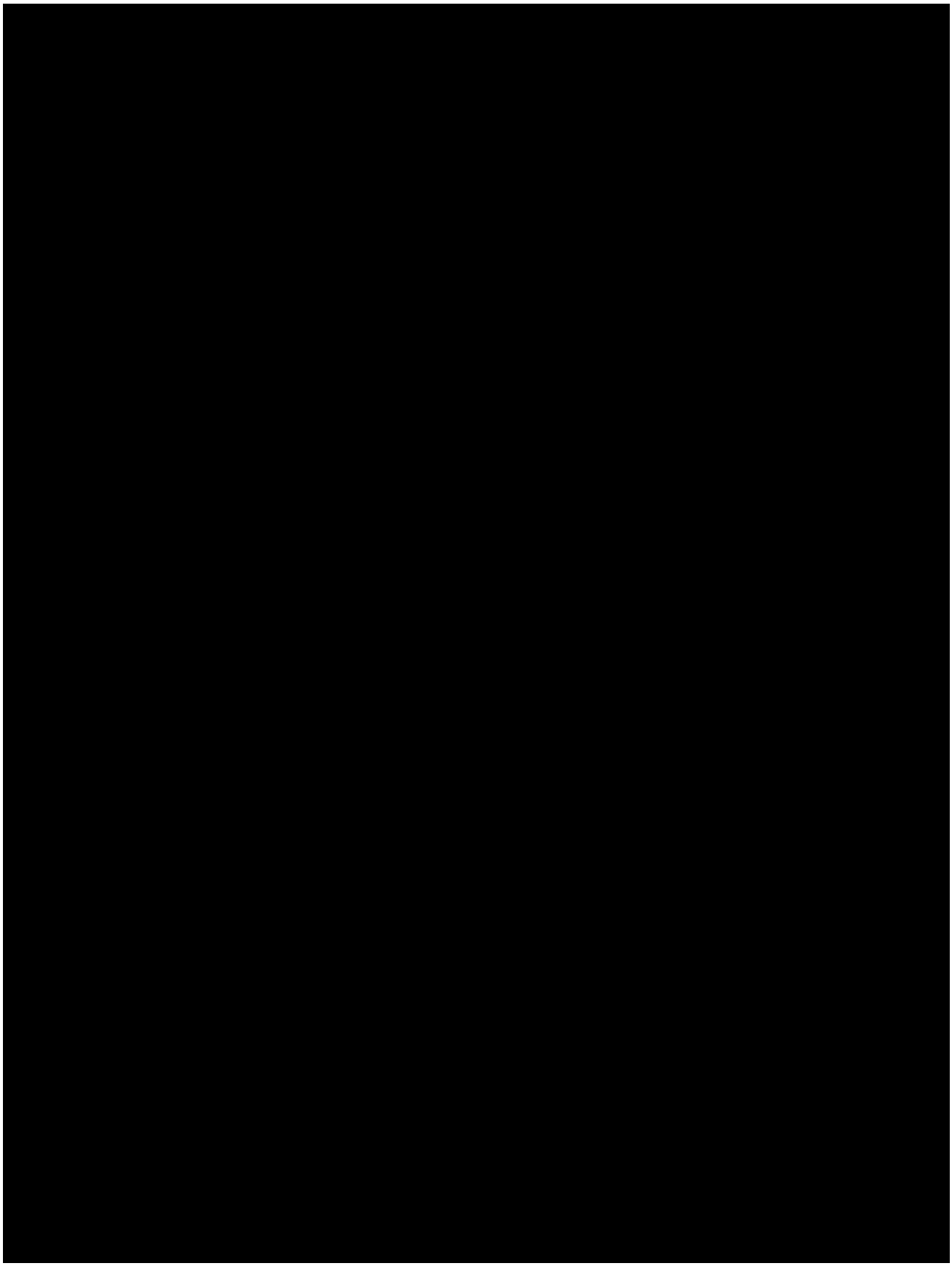

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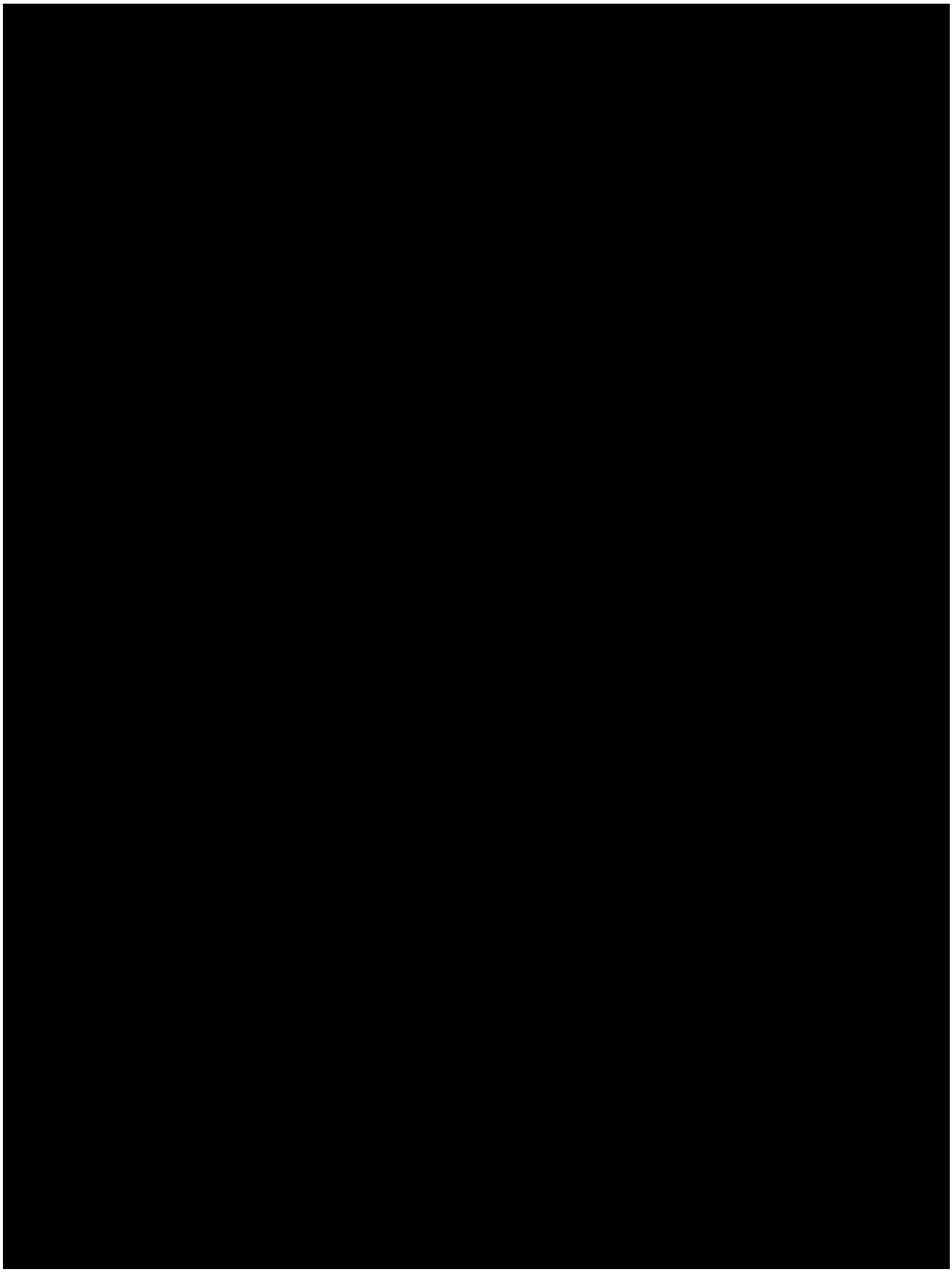

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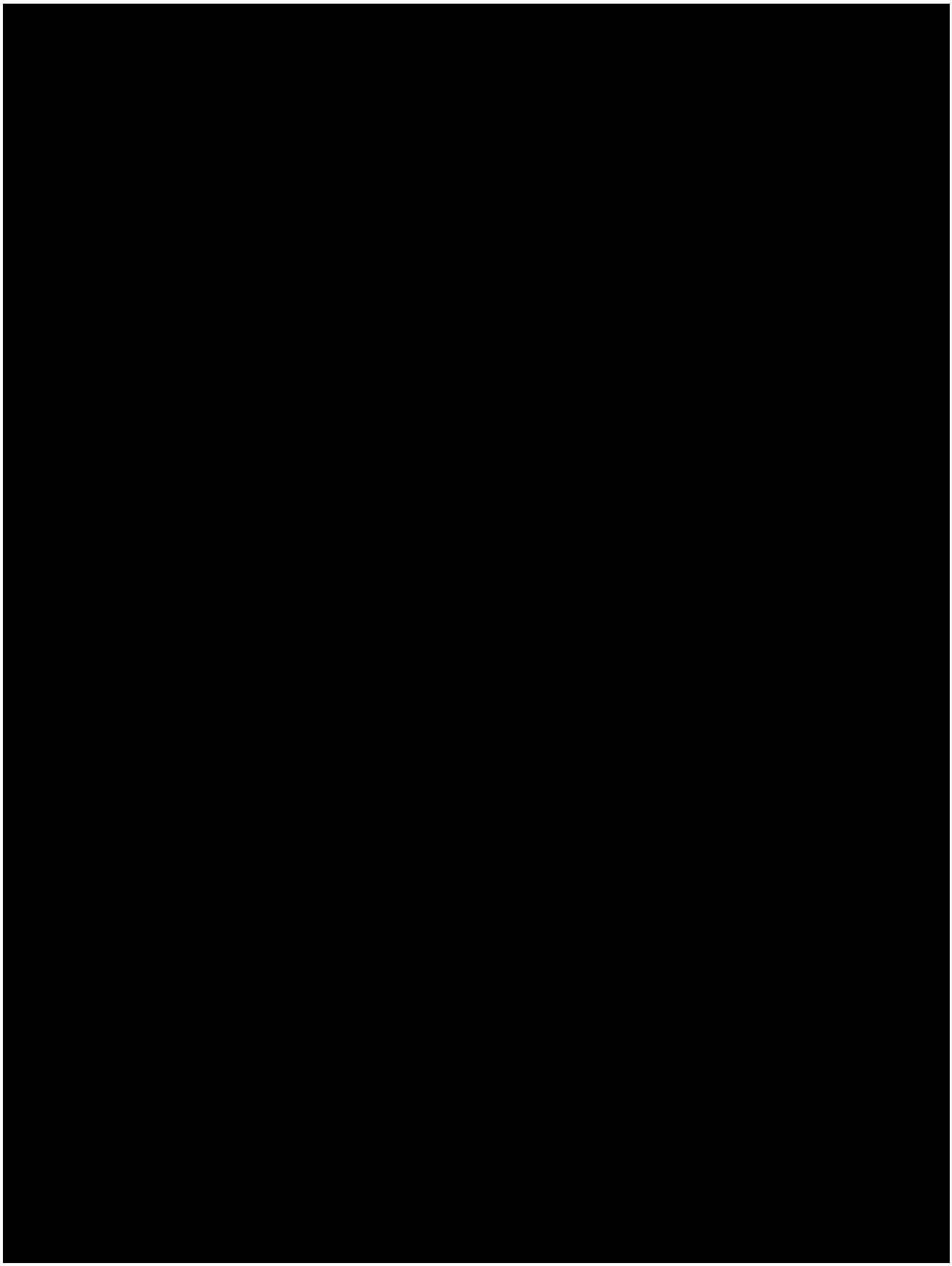

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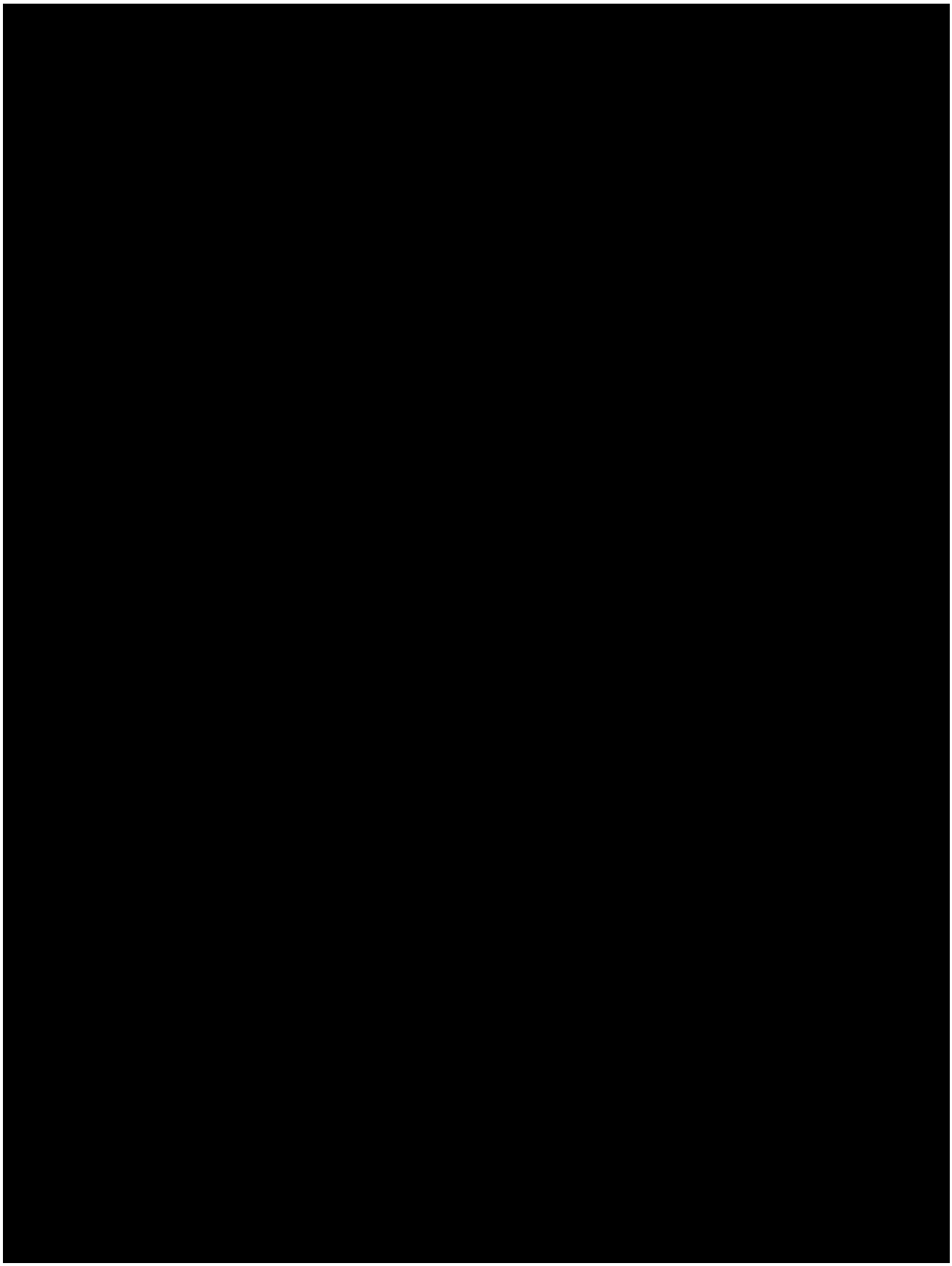

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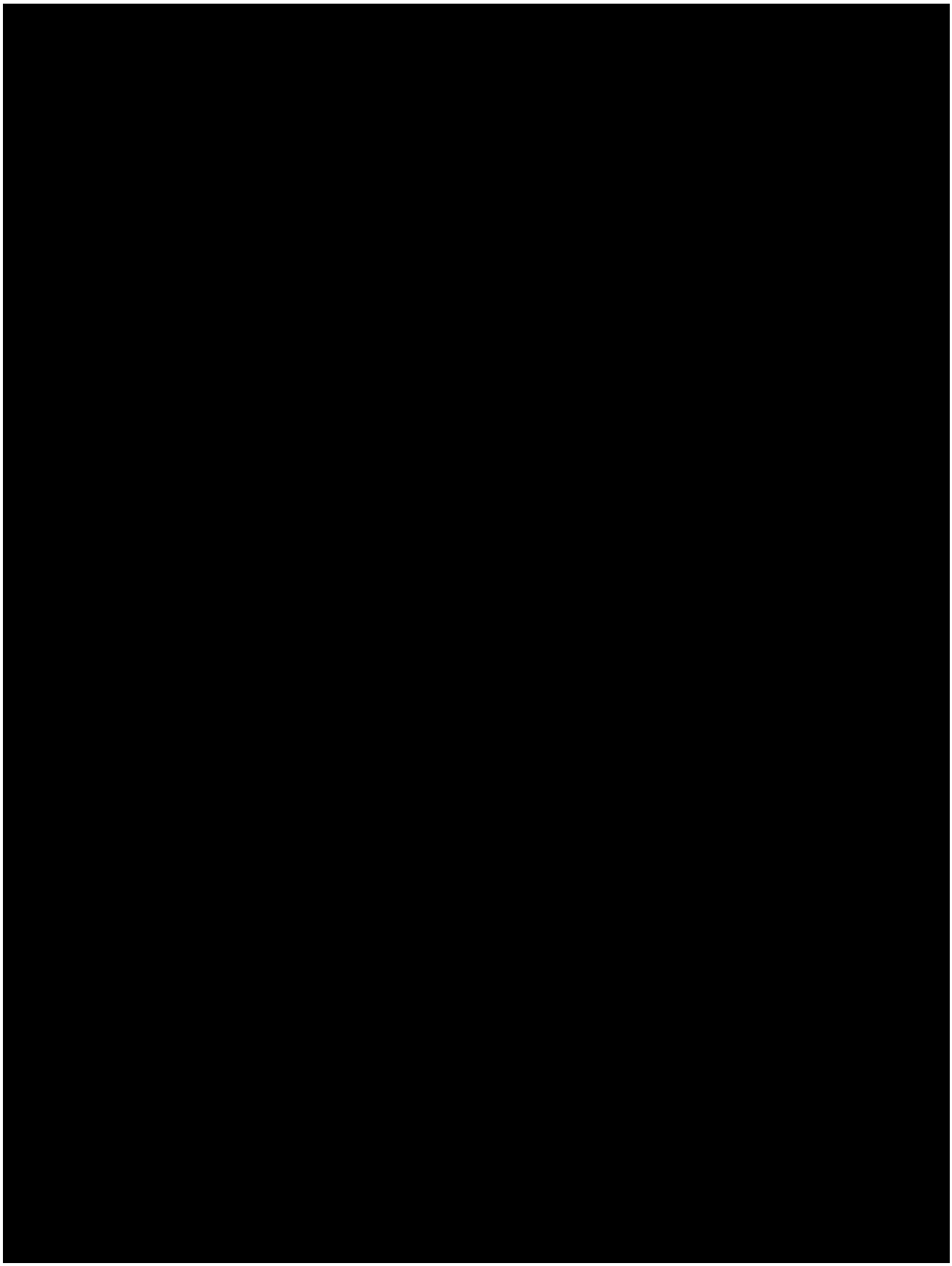

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Appendix L

Transition probabilities

Baseline transition probabilities (based on STEPS and STEPS-2), teduglutide

Teduglutide

Cycle 0-1	To							
From	0	1	2	3	4	5	6	7
0	1,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000
1	0,000	1,000	0,000	0,000	0,000	0,000	0,000	0,000
2	0,000	0,000	1,000	0,000	0,000	0,000	0,000	0,000
3	0,000	0,000	0,167	0,833	0,000	0,000	0,000	0,000
4	0,000	0,000	0,000	0,000	1,000	0,000	0,000	0,000
5	0,000	0,000	0,000	0,000	0,250	0,250	0,500	0,000
6	0,000	0,000	0,000	0,000	0,000	0,143	0,857	0,000
7	0,000	0,000	0,000	0,000	0,000	0,000	0,056	0,944

Cycle 1-2	To							
From	0	1	2	3	4	5	6	7
0	1,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000
1	0,000	1,000	0,000	0,000	0,000	0,000	0,000	0,000
2	0,000	0,000	0,000	1,000	0,000	0,000	0,000	0,000
3	0,000	0,000	0,200	0,800	0,000	0,000	0,000	0,000
4	0,000	0,000	0,000	0,167	0,667	0,167	0,000	0,000
5	0,000	0,000	0,000	0,000	0,000	1,000	0,000	0,000
6	0,000	0,000	0,000	0,000	0,111	0,222	0,667	0,000
7	0,000	0,000	0,000	0,000	0,000	0,000	0,059	0,941

Cycle 2-3	To							
From	0	1	2	3	4	5	6	7
0	1,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000
1	0,000	1,000	0,000	0,000	0,000	0,000	0,000	0,000
2	0,000	0,000	1,000	0,000	0,000	0,000	0,000	0,000
3	0,000	0,000	0,000	0,600	0,200	0,200	0,000	0,000
4	0,000	0,000	0,000	0,600	0,400	0,000	0,000	0,000
5	0,000	0,000	0,000	0,000	0,400	0,400	0,200	0,000
6	0,000	0,000	0,000	0,000	0,167	0,167	0,500	0,167
7	0,000	0,000	0,000	0,000	0,000	0,125	0,063	0,813

Cycle 3-4	To							
From	0	1	2	3	4	5	6	7
0	1,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000

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1	0,000	1,000	0,000	0,000	0,000	0,000	0,000	0,000
2	0,000	0,000	1,000	0,000	0,000	0,000	0,000	0,000
3	0,000	0,000	0,167	0,833	0,000	0,000	0,000	0,000
4	0,000	0,000	0,167	0,167	0,667	0,000	0,000	0,000
5	0,000	0,000	0,000	0,200	0,400	0,000	0,200	0,200
6	0,000	0,000	0,000	0,000	0,000	0,600	0,400	0,000
7	0,000	0,000	0,000	0,000	0,000	0,000	0,071	0,929

Cycle 4-5	**To**							
From	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
0	1,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000
1	0,000	1,000	0,000	0,000	0,000	0,000	0,000	0,000
2	0,000	0,000	0,667	0,333	0,000	0,000	0,000	0,000
3	0,000	0,000	0,286	0,571	0,143	0,000	0,000	0,000
4	0,000	0,000	0,000	0,167	0,833	0,000	0,000	0,000
5	0,000	0,000	0,000	0,000	0,333	0,667	0,000	0,000
6	0,000	0,000	0,000	0,000	0,000	0,200	0,600	0,200
7	0,000	0,000	0,000	0,000	0,000	0,000	0,077	0,923

Cycle 5-6	**To**							
From	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
0	1,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000
1	0,000	1,000	0,000	0,000	0,000	0,000	0,000	0,000
2	0,000	0,250	0,500	0,250	0,000	0,000	0,000	0,000
3	0,000	0,000	0,167	0,833	0,000	0,000	0,000	0,000
4	0,000	0,000	0,000	0,000	1,000	0,000	0,000	0,000
5	0,000	0,000	0,000	0,000	0,250	0,500	0,250	0,000
6	0,000	0,000	0,000	0,000	0,250	0,250	0,500	0,000
7	0,000	0,000	0,000	0,000	0,000	0,000	0,231	0,769

Cycle 6-7	**To**							
From	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
0	1,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000
1	1,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000
2	0,000	0,333	0,667	0,000	0,000	0,000	0,000	0,000
3	0,000	0,000	0,167	0,833	0,000	0,000	0,000	0,000
4	0,000	0,000	0,000	0,222	0,778	0,000	0,000	0,000
5	0,000	0,000	0,000	0,000	0,333	0,333	0,333	0,000
6	0,000	0,000	0,000	0,000	0,000	0,200	0,600	0,200
7	0,000	0,000	0,000	0,000	0,000	0,100	0,000	0,900

Cycle 7-8	**To**

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From	0	1	2	3	4	5	6	7
0	1,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000
1	1,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000
2	0,000	0,000	1,000	0,000	0,000	0,000	0,000	0,000
3	0,000	0,143	0,000	0,714	0,143	0,000	0,000	0,000
4	0,000	0,000	0,000	0,375	0,625	0,000	0,000	0,000
5	0,000	0,000	0,000	0,000	0,667	0,333	0,000	0,000
6	0,000	0,000	0,000	0,000	0,000	0,250	0,750	0,000
7	0,000	0,000	0,000	0,000	0,000	0,000	0,100	0,900

Cycle 8-9	To							
From	0	1	2	3	4	5	6	7
0	1,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000
1	0,000	1,000	0,000	0,000	0,000	0,000	0,000	0,000
2	0,000	0,000	0,667	0,333	0,000	0,000	0,000	0,000
3	0,000	0,000	0,286	0,714	0,000	0,000	0,000	0,000
4	0,000	0,000	0,000	0,125	0,750	0,125	0,000	0,000
5	0,000	0,000	0,000	0,000	0,000	1,000	0,000	0,000
6	0,000	0,000	0,000	0,000	0,000	0,250	0,750	0,000
7	0,000	0,000	0,000	0,000	0,000	0,000	0,000	1,000

Cycle 9-12	To							
From	0	1	2	3	4	5	6	7
0	1,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000
1	0,000	0,000	0,000	0,000	0,000	0,000	0,000	1,000
2	0,000	0,250	0,500	0,000	0,000	0,000	0,000	0,250
3	0,000	0,000	0,286	0,429	0,286	0,000	0,000	0,000
4	0,000	0,000	0,000	0,167	0,667	0,167	0,000	0,000
5	0,000	0,000	0,000	0,000	0,000	1,000	0,000	0,000
6	0,000	0,000	0,000	0,000	0,000	0,333	0,000	0,667
7	0,000	0,000	0,000	0,000	0,000	0,000	0,000	1,000

Cycle 12-15	To							
From	0	1	2	3	4	5	6	7
0	1,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000
1	0,000	1,000	0,000	0,000	0,000	0,000	0,000	0,000
2	0,000	0,000	1,000	0,000	0,000	0,000	0,000	0,000
3	0,000	0,000	0,250	0,500	0,250	0,000	0,000	0,000
4	0,000	0,000	0,000	0,333	0,667	0,000	0,000	0,000
5	0,000	0,000	0,000	0,000	0,400	0,600	0,000	0,000
6	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000
7	0,000	0,000	0,000	0,000	0,000	0,000	0,083	0,917

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Cycle 15-18	To							
From	0	1	2	3	4	5	6	7
0	1,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000
1	0,000	1,000	0,000	0,000	0,000	0,000	0,000	0,000
2	0,200	0,400	0,400	0,000	0,000	0,000	0,000	0,000
3	0,000	0,000	0,500	0,250	0,250	0,000	0,000	0,000
4	0,000	0,000	0,000	0,000	0,714	0,286	0,000	0,000
5	0,000	0,000	0,000	0,000	0,000	1,000	0,000	0,000
6	0,000	0,000	0,000	0,000	0,000	0,000	1,000	0,000
7	0,000	0,000	0,000	0,100	0,100	0,000	0,100	0,700

Cycle 18-21	To							
From	0	1	2	3	4	5	6	7
0	1,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000
1	0,667	0,000	0,333	0,000	0,000	0,000	0,000	0,000
2	0,000	0,000	0,500	0,500	0,000	0,000	0,000	0,000
3	0,000	0,000	0,500	0,500	0,000	0,000	0,000	0,000
4	0,143	0,000	0,000	0,143	0,571	0,143	0,000	0,000
5	0,000	0,000	0,000	0,000	0,200	0,800	0,000	0,000
6	0,000	0,000	0,000	0,000	0,000	0,000	1,000	0,000
7	0,000	0,000	0,000	0,000	0,000	0,000	0,000	1,000

Cycle 21-24	To							
From	0	1	2	3	4	5	6	7
0	1,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000
1	0,000	1,000	0,000	0,000	0,000	0,000	0,000	0,000
2	0,250	0,000	0,750	0,000	0,000	0,000	0,000	0,000
3	0,250	0,000	0,250	0,250	0,250	0,000	0,000	0,000
4	0,000	0,000	0,000	0,200	0,800	0,000	0,000	0,000
5	0,000	0,000	0,000	0,000	0,400	0,600	0,000	0,000
6	0,000	0,000	0,000	0,000	0,000	0,000	1,000	0,000
7	0,000	0,000	0,000	0,000	0,000	0,000	0,000	1,000

Cycle 24-27	To							
From	0	1	2	3	4	5	6	7
0	1,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000
1	0,000	1,000	0,000	0,000	0,000	0,000	0,000	0,000
2	0,000	0,250	0,750	0,000	0,000	0,000	0,000	0,000
3	0,000	0,000	0,000	1,000	0,000	0,000	0,000	0,000
4	0,143	0,000	0,000	0,286	0,571	0,000	0,000	0,000
5	0,000	0,000	0,000	0,000	0,000	1,000	0,000	0,000

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6	0,000	0,000	0,000	0,000	0,000	0,000	0,500	0,500
7	0,000	0,000	0,000	0,000	0,000	0,000	0,000	1,000

Cycle 27-30	**To**							
From	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
0	1,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000
1	1,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000
2	0,000	0,333	0,667	0,000	0,000	0,000	0,000	0,000
3	0,000	0,000	0,000	1,000	0,000	0,000	0,000	0,000
4	0,000	0,000	0,000	0,000	1,000	0,000	0,000	0,000
5	0,000	0,000	0,000	0,000	0,333	0,333	0,000	0,333
6	0,000	0,000	0,000	0,000	0,000	0,000	1,000	0,000
7	0,000	0,000	0,000	0,000	0,000	0,000	0,000	1,000

Baseline transition probabilities (based on STEPS), standard care

Standard Care

Cycle 0-1	**To**							
From	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
0	1,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000
1	0,000	1,000	0,000	0,000	0,000	0,000	0,000	0,000
2	0,000	0,000	1,000	0,000	0,000	0,000	0,000	0,000
3	0,000	0,000	0,000	1,000	0,000	0,000	0,000	0,000
4	0,000	0,000	0,000	0,500	0,500	0,000	0,000	0,000
5	0,000	0,000	0,000	0,000	0,000	1,000	0,000	0,000
6	0,000	0,000	0,000	0,000	0,000	0,250	0,750	0,000
7	0,000	0,000	0,000	0,000	0,000	0,000	0,200	0,800

Cycle 1-2	**To**							
From	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
0	1,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000
1	0,000	1,000	0,000	0,000	0,000	0,000	0,000	0,000
2	0,000	0,000	1,000	0,000	0,000	0,000	0,000	0,000
3	0,000	0,000	0,200	0,800	0,000	0,000	0,000	0,000
4	0,000	0,000	0,000	0,000	1,000	0,000	0,000	0,000
5	0,000	0,000	0,000	0,000	0,000	1,000	0,000	0,000
6	0,000	0,000	0,000	0,000	0,000	0,091	0,545	0,364
7	0,000	0,000	0,000	0,000	0,000	0,000	0,050	0,950

Cycle 2-3	**To**							
From	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**

0	1,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000
1	0,000	1,000	0,000	0,000	0,000	0,000	0,000	0,000
2	0,000	0,000	1,000	0,000	0,000	0,000	0,000	0,000
3	0,000	0,000	0,000	1,000	0,000	0,000	0,000	0,000
4	0,000	0,000	0,000	0,000	1,000	0,000	0,000	0,000
5	0,000	0,000	0,000	0,000	0,000	1,000	0,000	0,000
6	0,000	0,000	0,000	0,000	0,000	0,143	0,857	0,000
7	0,000	0,000	0,000	0,000	0,000	0,000	0,000	1,000

Cycle 3-4	**To**							
From	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
0	1,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000
1	0,000	1,000	0,000	0,000	0,000	0,000	0,000	0,000
2	0,000	0,000	1,000	0,000	0,000	0,000	0,000	0,000
3	0,000	0,000	0,000	1,000	0,000	0,000	0,000	0,000
4	0,000	0,000	0,000	0,000	1,000	0,000	0,000	0,000
5	0,000	0,000	0,000	0,000	0,250	0,500	0,000	0,250
6	0,000	0,000	0,000	0,000	0,000	0,167	0,667	0,167
7	0,000	0,000	0,000	0,000	0,000	0,000	0,087	0,913

Cycle 4-5	**To**							
From	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
0	1,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000
1	0,000	1,000	0,000	0,000	0,000	0,000	0,000	0,000
2	0,000	0,000	1,000	0,000	0,000	0,000	0,000	0,000
3	0,000	0,000	0,000	1,000	0,000	0,000	0,000	0,000
4	0,000	0,000	0,000	0,000	1,000	0,000	0,000	0,000
5	0,000	0,000	0,000	0,000	0,333	0,667	0,000	0,000
6	0,000	0,000	0,000	0,000	0,000	0,000	1,000	0,000
7	0,000	0,000	0,000	0,000	0,000	0,000	0,130	0,870

Cycle 5-6	**To**							
From	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**
0	1,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000
1	0,000	1,000	0,000	0,000	0,000	0,000	0,000	0,000
2	0,000	1,000	0,000	0,000	0,000	0,000	0,000	0,000
3	0,250	0,000	0,250	0,500	0,000	0,000	0,000	0,000
4	0,000	0,000	0,000	0,500	0,250	0,250	0,000	0,000
5	0,000	0,000	0,000	0,000	0,500	0,000	0,500	0,000
6	0,000	0,000	0,000	0,000	0,000	0,000	0,889	0,111
7	0,000	0,000	0,000	0,000	0,000	0,000	0,000	1,000

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Appendix M

Carer utilities

Carer utilities are not included in the base case scenario, as per the DMC methods guide. However, we have kept the option to include carer utilities in the model, as we believe it to provide useful information.

To quantify the impact of SBS on carer utilities, experts in a Delphi process (**Appendix K**) were asked to give an estimate of the utility of carers of patients with SBS-IF with 0-7 days of PS requirements (they were given the instructions that 0 equals death and 1 equals perfect health). These are provided below in Table 131.

Table 131 Carer dis-utility values based on Delphi panel

Disutility PS 1 day per week	-0,11
Disutility PS 2 days per week	-0,11
Disutility PS 3 days per week	-0,11
Disutility PS 4 days per week	-0,23
Disutility PS 5 days per week	-0,23
Disutility PS 6 days per week	-0,33
Disutility PS 7 days per week	-0,33

Source: Delphi Panel (**Appendix K**)

Scenarios are included in the model to make an assumption of the underlying value of the carer's utility:

- Perfect health (base 0) – Assuming no baseline utility for carers, only a decrement, and basing this on the utility decrements directly from the source data, without adjusting for age-matched individuals in the general population.
- Perfect health (base 1) – Assuming a baseline utility of 1 (perfect health) for carers, with a decrement applied to it. And basing this on the utility decrements directly from the source data, without adjusting for age-matched individuals in the general population

If carer utilities were to be included, we suggest 0,8 carer per adult patient and 1,8 carer per pediatric patient.

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Appendix N

Here, we present cost-effectiveness results for 2 alternative pricing scenarios for adults and pediatrics.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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Appendix O

European public assessment report (EPAR) for Revestive

revestive-epar-product-information_en.

Appendix P

Clinical and real-world evidence systematic literature review report

Appendix P - Clinical and RWE SLR report.c

Appendix Q

Real-world evidence meta-analysis report (confidential)

[redacted]

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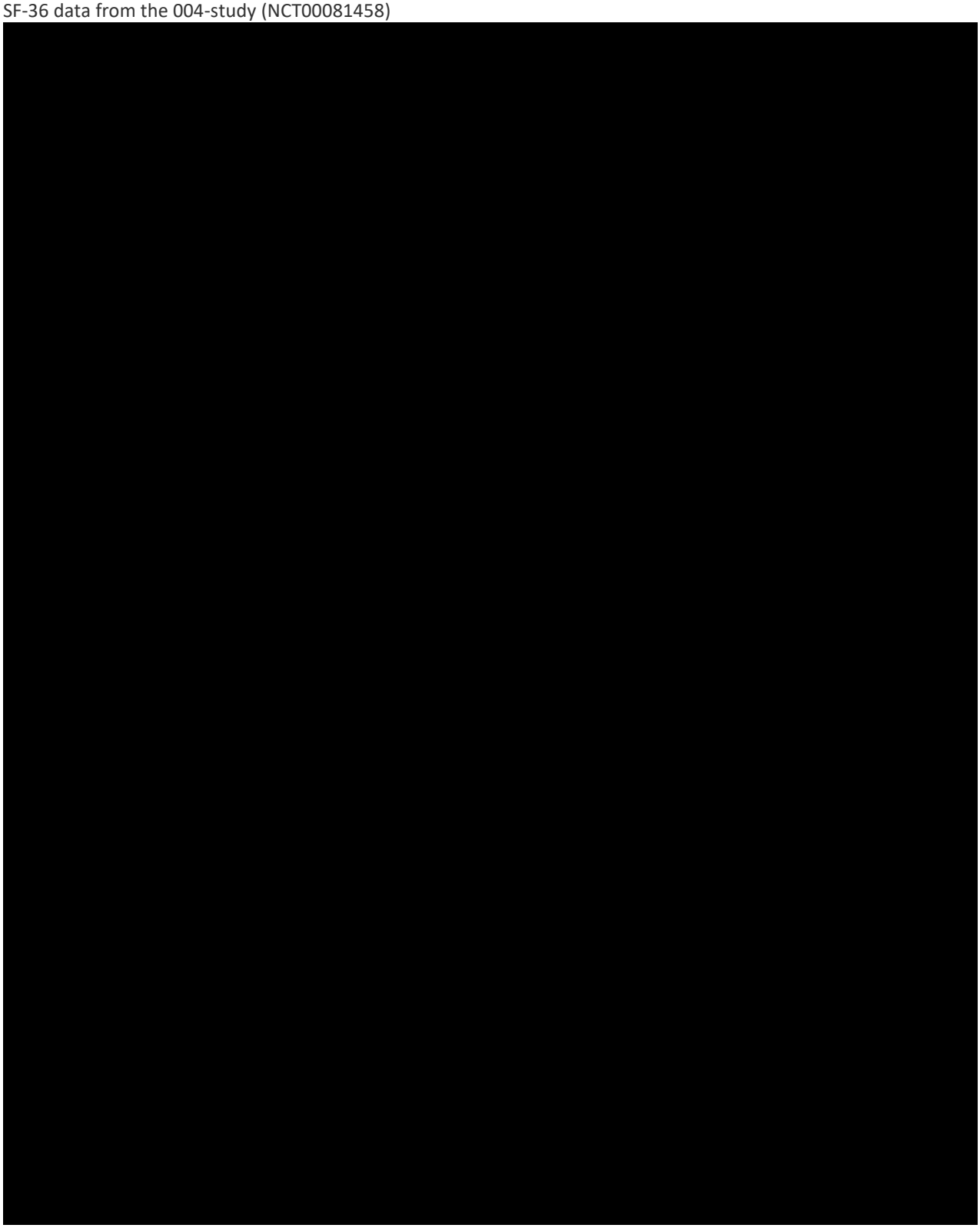
Appendix R

Quality of life data from

SF-36 data from the 004-study (NCT00081458)



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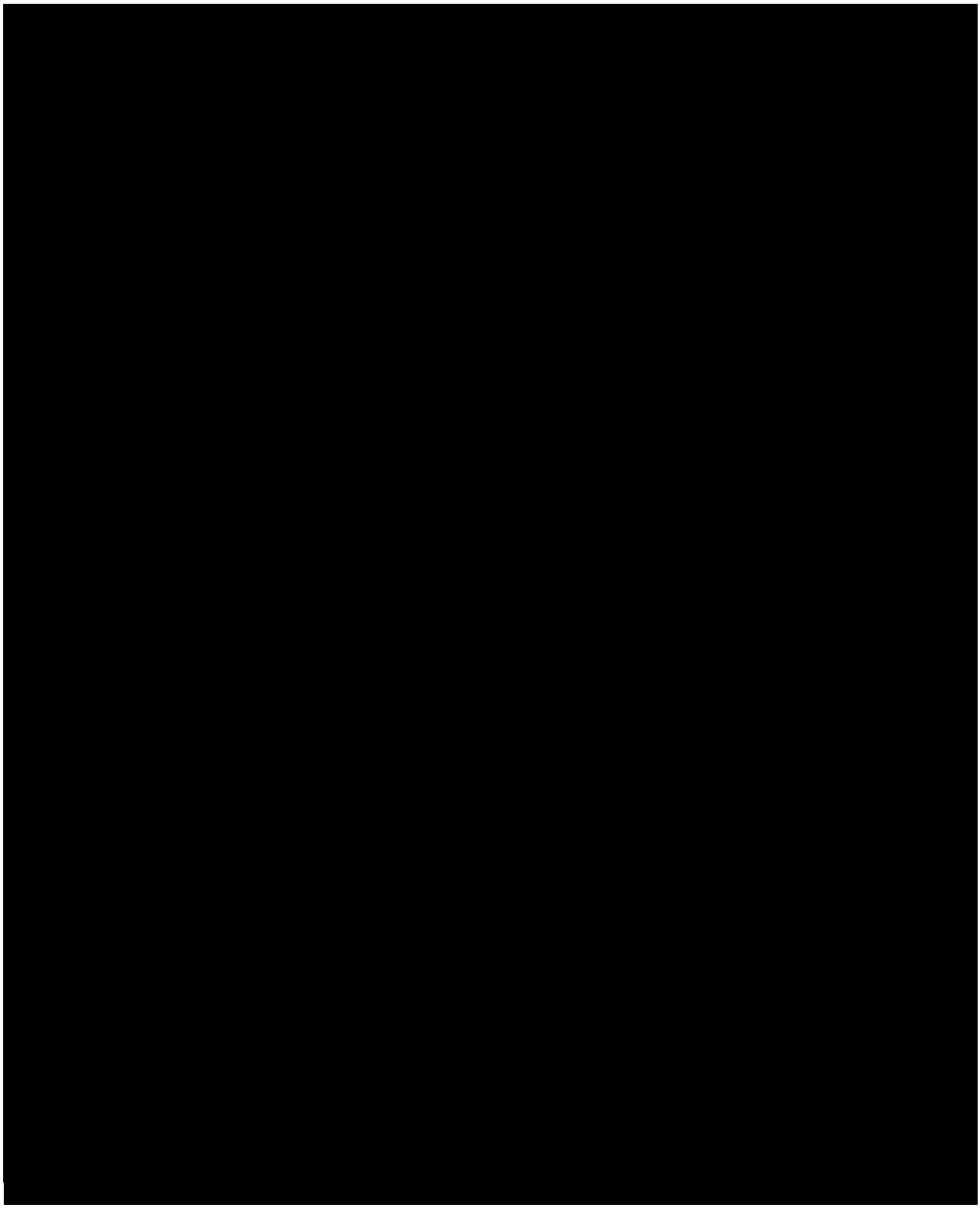

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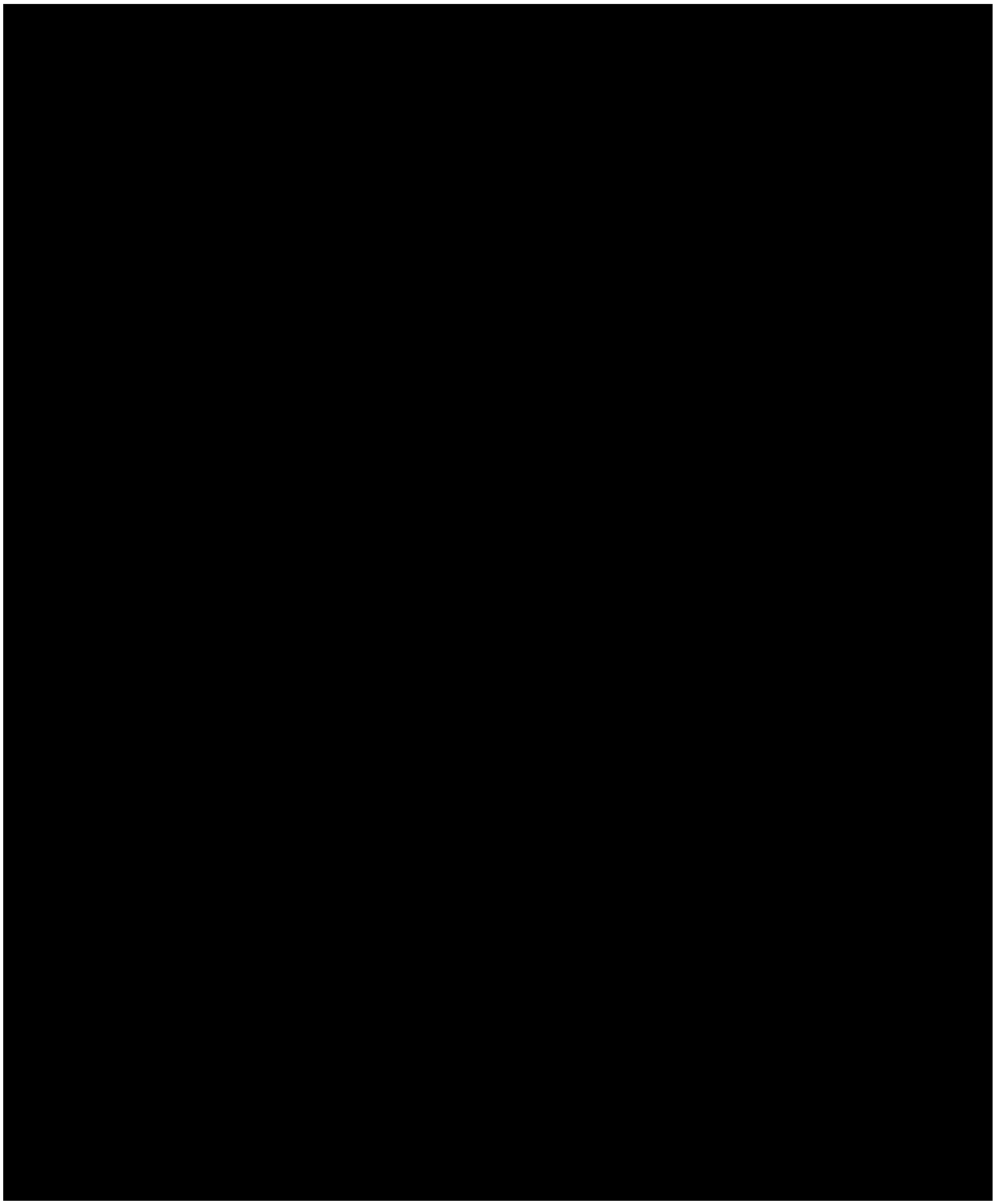

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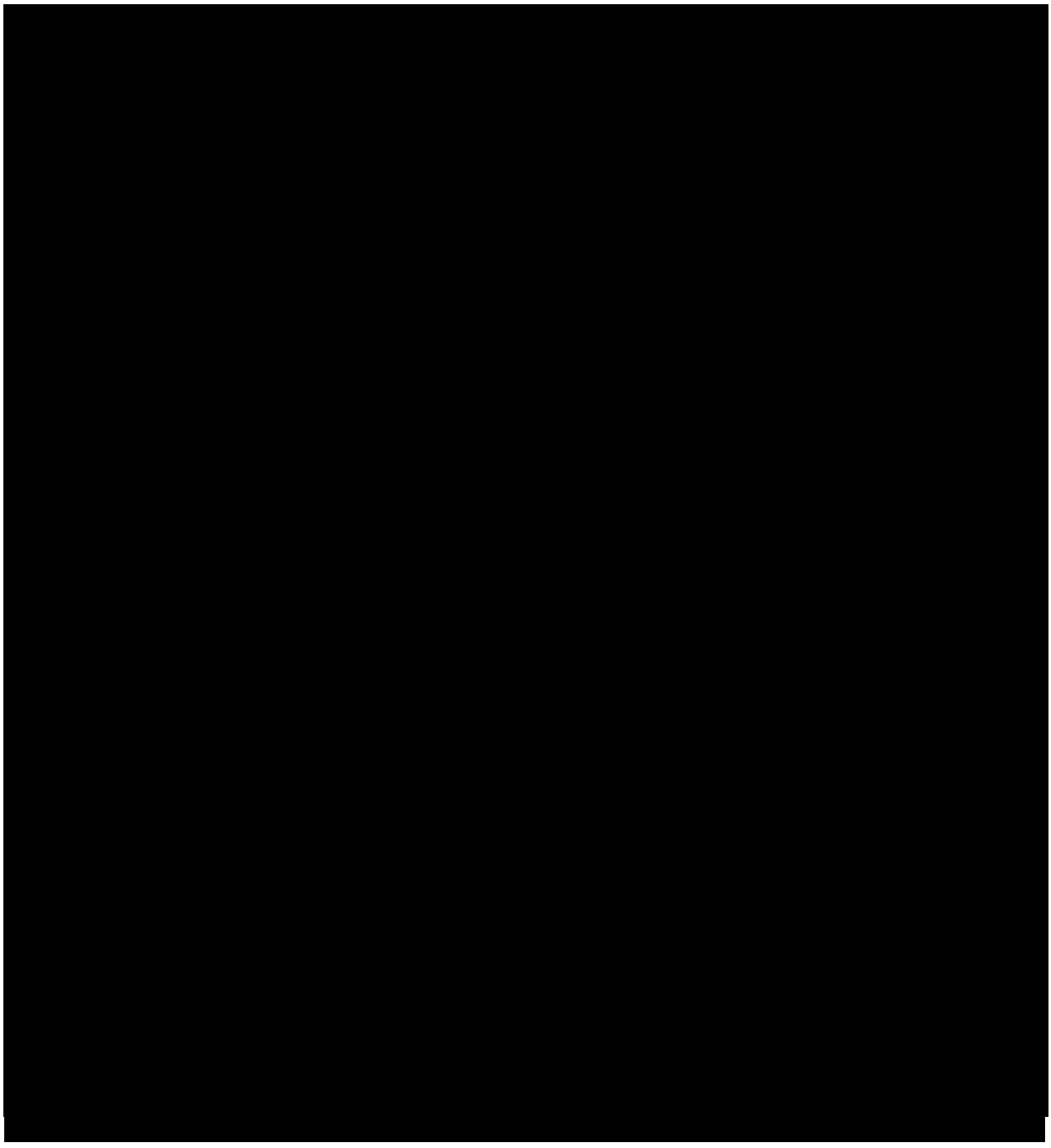

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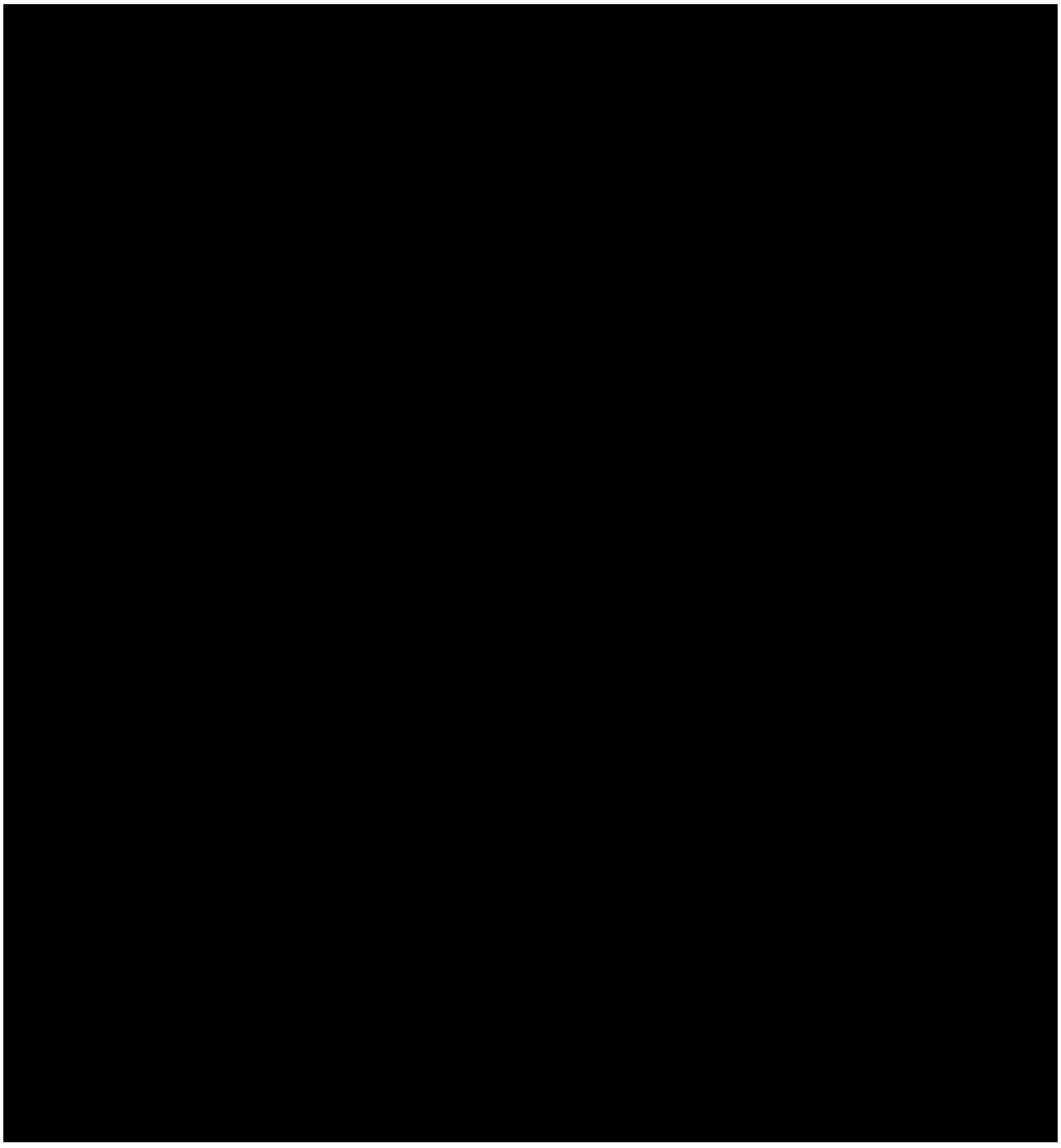

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Appendix S

Expert statement on high placebo effect

Appendix S - Expert statement on high p

Appendix T

Meta analysis of 004 and STEPS

Appendix T Takeda META statistical calcul

Appendix U

Teduglutide approved for treatment of infants

Appendix U 14012022_Revestive

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