



A Budget Impact Model of the Addition of Telotristat Ethyl Treatment to the Standard of Care in Patients with Uncontrolled Carcinoid Syndrome

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Abstract

Background Carcinoid syndrome, a rare condition in patients with neuroendocrine tumours, characterised by flushing and diarrhoea, severely affects patients' quality of life. The current carcinoid syndrome standard of care includes somatostatin analogues, but some patients experience uncontrolled symptoms despite somatostatin analogue therapy. Telotristat ethyl is a novel treatment approved by the European Medicines Agency (EMA) and US FDA that significantly reduces bowel movement frequency in patients with uncontrolled carcinoid syndrome.

Objective We developed a model to evaluate the 5-year budget impact of introducing telotristat ethyl to standard care in Swedish patients with uncontrolled carcinoid syndrome.

Methods Treatment response in the 12-week phase III TELESTAR trial (NCT01677910) informed telotristat ethyl efficacy; subsequently, health states were captured by a Markov model using 4-week cycles. TELESTAR open-label extension data informed telotristat ethyl discontinuation. The number of treatment-eligible patients was estimated from literature reviews reporting the prevalence, incidence and mortality of carcinoid syndrome. A Swedish database study informed real-world costs related to carcinoid syndrome and carcinoid heart disease costs. Telotristat ethyl market share was assumed to increase annually from 24% (year 1) to 70% (year 5).

Results Over the 5-year model horizon, 44 patients were expected to initiate telotristat ethyl treatment. The cumulative net budget impact of adding telotristat ethyl to current standard of care was €172,346; per-year costs decreased from €66,495 (year 1) to €29,818 (year 5). Increased drug costs from adding telotristat ethyl were offset by reduced costs elsewhere.

Conclusions The expected budget impact of adding telotristat ethyl to the standard of care in Sweden was relatively low, largely because of the rarity of carcinoid syndrome.

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Key Points for Decision Makers

The expected 5-year budget impact of introducing telotristat ethyl to the standard of care in Swedish patients with uncontrolled carcinoid syndrome was relatively low (€172,346), largely because of the rarity of carcinoid syndrome.

Per-year costs decreased from €66,495 (year 1) to €29,818 (year 5).

Increased treatment costs from adding telotristat ethyl were offset by reduced costs for other aspects of patient care.

1 Introduction

Carcinoid syndrome (CS) is a rare but serious condition that develops in some patients with neuroendocrine tumours (NETs) [1–3]. Studies from the USA have estimated the prevalence of NETs to range between 0.035 and 0.048% [4, 5]. Secretion of vasoactive peptides and amines by some NETs, including serotonin, results in the characteristic symptoms of CS, such as cutaneous flushing, diarrhoea and wheezing [1]. CS develops most commonly in patients with small intestinal NETs and hepatic metastases [3, 6] and less commonly in patients with pancreatic tumours or lung NETs; CS can also occur when secretions drain directly from tumours into the central circulation [3, 7–9]. Approximately 6–19% of patients with NETs will develop CS [1–3, 10], and 20–50% of patients with CS develop carcinoid heart disease (CaHD) [11]. In CaHD, secretion of serotonin and other vasoactive substances can cause the deposition of plaques on the right side of the heart, leading to right heart valve dysfunction and possible heart failure [12]. CS progression and response to treatment can be measured through urinary or plasma levels of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) [13, 14], with elevated urinary 5-HIAA (u5-HIAA) being associated with more severe CS and CaHD [15, 16].

The US National Comprehensive Cancer Network guidelines and European Neuroendocrine Tumor Society guidelines currently recommend somatostatin analogues (SSAs), such as lanreotide and octreotide, as treatment for patients with CS [17, 18]. These long-acting therapeutics can slow tumour progression and, importantly, reduce symptoms of CS [19–23]. In patients with particularly severe CS, symptom burden can be further reduced by dose escalation of long-acting SSAs and the addition of short-acting SSAs and anti-diarrheal therapies to the backbone long-acting SSA therapy [8, 18, 24–29]. However, despite SSA therapy, CS symptoms can persist in approximately 20–40% of patients [24, 28, 30–32], and over 60% experience sustained debilitating diarrhoea and flushing [30]. Few options exist for patients whose CS symptoms remain uncontrolled despite treatment with SSAs. The limited alternative treatment options include costly, invasive medical interventions that target tumour load and decrease serotonin secretion [30, 33].

Telotristat ethyl (TE), a novel tryptophan hydroxylase inhibitor, was approved for the treatment of diarrhoea in patients with CS by the European Medicines Agency and US Food and Drug Administration in 2017 and by Health Canada and the Australian Therapeutic Goods Administration in 2018 [34–37]. TE has been shown to reduce daily bowel movement frequency in patients whose CS diarrhoea symptoms are inadequately controlled by SSAs, subsequently improving health-related quality of life when used alongside

the current standard of care [38, 39]. Treatment guidelines in the USA were recently updated to include TE as a treatment option when CS symptoms are poorly controlled [18].

The high healthcare cost of CS, particularly for patients with CS that is uncontrolled by the current standard of care, presents a healthcare, societal, and patient burden. A 2018 Swedish study found the cost per patient with controlled CS over an 8-month period to be €15,500, rising to €21,700 per patient with uncontrolled CS [33]. Furthermore, CS symptoms can be debilitating for patients and have a marked impact on health-related quality of life [22, 40–42]; diarrhoea and flushing, in particular, have been associated with reduced physical functioning, increased pain, sleep disturbance, depression and anxiety [41].

TE has been approved for reimbursement by the Swedish Dental and Pharmaceutical Benefits Agency (TLV) [43], but the affordability of using TE in combination with SSA therapy has not yet been demonstrated at the regional level. The aim of this study was to estimate the 5-year budget impact on the Swedish healthcare system of using TE in combination with SSAs, compared with using SSAs only, in patients with inadequately controlled CS. To investigate this, we created a budget impact model, taking into account the drug acquisition cost and all healthcare costs associated with TE treatment.

2 Methods

2.1 Budget Impact Model

Base-case model analyses were performed from the perspective of the Swedish healthcare system and included direct healthcare costs only. The time horizon of the model analysis was 5 years (2018–2022). This analysis compared two scenarios: (1) a ‘world-without TE’ scenario in which only SSA therapy was available and (2) a ‘world-with TE’ scenario in which TE 250 mg was available in addition to SSA therapy. In the model, the size of the target population and the number of patients initiating treatment were estimated. A decision tree and Markov model were then used to estimate the intensity of symptoms and the associated healthcare costs.

2.1.1 Population and Market Share

The target population was patients with CS inadequately controlled by SSA therapy. The number of eligible incident cases for years 1–5 and the number of prevalent cases for year 1 were estimated using data from systematic and targeted literature reviews (Table 1) [4, 5, 26, 44–47]. Figure 1 demonstrates how these data were used to estimate incident and prevalent cases, with the resulting estimates shown in Table 2. For years 2–5, the number of prevalent cases was

calculated by the model as the patients continuing from previous years who had not died. Ten incident patients were estimated to be eligible for TE therapy in each year of the analysis (based on incidence estimates in Table 1). Additionally, 72 prevalent cases were eligible for therapy in year 1. Prevalent patients were assumed to initiate TE treatment in year 1 only.

As SSAs are the current standard of care for CS and for some stages of NETs, all patients were assumed to have received SSA treatment (lanreotide or octreotide) in both the world-with TE and world-without TE scenarios [48]. In the SSA + TE arm, both prevalent and incident cases were considered eligible to commence treatment with TE 250 mg in year 1 (2018), whereas only incident cases were considered eligible in years 2–5 (2019–2022) (Table 2). Based on the assumption that TE has just been introduced and most patients with inadequately controlled disease will receive TE, internal forecasting estimates projected that the market share of TE would increase annually, from 24% of eligible patients in year 1 to 70% in year 5 (Table 2). SSA market share did not vary, as TE is to be used in combination with SSAs.

2.1.2 Decision Tree and Markov Model Structure

The model structure used to estimate the intensity of symptoms, duration of treatment and associated costs had two components: a decision tree that tracked the response to the initial 12 weeks of TE treatment using data from TELESTAR, and a Markov model using 4-week (28-day) cycles that tracked the longer-term response to treatment for the remaining model time horizon (Fig. 2). Adverse events reported in TELESTAR were not expected to increase healthcare costs significantly or substantially affect patients' quality of life so were not included in the model.

Patients in the 'SSA Only' arm who had a durable response to SSAs during the initial 12 weeks of treatment entered the Markov model in the 'respond to SSA' health state, whereas the remaining patients in the SSA Only arm entered in the 'inadequate response' health state. Patients within the SSA Only arm were assumed to remain on SSA therapies for the entire simulation, regardless of response status. In the SSA + TE arm, patients who achieved a durable response to TE during the initial 12 weeks of treatment entered the Markov model in the 'durable response' health state, whereas patients who did not demonstrate a durable response entered in the 'discontinue TE' health state (and no longer received TE). The inadequate response health state captured patients in the SSA + TE arm who did not maintain a durable response but still continued to receive TE. All health states were stratified by whether the patient had CaHD or not, and the model allowed patients to develop

CaHD as time progressed. Patients could die in any cycle while in any of the health states.

2.1.3 Model Inputs

Initial TE treatment efficacy was informed by data from the 12-week double-blind treatment period of the phase III TELESTAR trial (NCT01677910). A total of 135 patients entered the trial and were randomised to one of three study arms: TE 500 mg, TE 250 mg, or placebo, each three times daily. All patients remained on the dose of SSA therapy that they were receiving upon entry. Full details of the TELESTAR study design and results have been published previously [38]. For this analyses, a durable response during either stage (the initial 12 weeks of treatment or the 4-week Markov cycles) was defined as a $\geq 30\%$ reduction in bowel movement frequency for $\geq 50\%$ of the time, matching the definition used in TELESTAR [38].

The target population for treatment with TE has been defined as patients who have not adequately responded to SSA treatment. In other words, patients who receive TE treatment are not expected to have further symptom reduction with SSAs alone. Therefore, for the base-case analysis, the proportion of durable responders was assumed to be 0% for patients receiving SSA treatment alone. All patients in the SSA Only arm entered the Markov model in the inadequate response health state and did not ever enter into the respond to SSA health state. Within the SSA + TE treatment arm, the proportion of patients with a durable response attributable to TE after 12 weeks of treatment was 24.4% (Table 1). This was calculated using data from the TELESTAR trial, in which 20 of the 45 (44.4%) patients randomised to SSA + TE demonstrated a durable response compared with 9 of the 45 (20%) patients randomised to SSA + placebo [38].

The 4-week probability of transitioning to the discontinue TE health state was set to 0.0321 based on data from the open-label extension period of TELESTAR, which was not placebo controlled [49]. The probability of transitioning to the inadequate response health state was set to 0 under the assumption that clinicians would discontinue TE treatment if patients stopped showing a durable response to TE. The impact of this assumption was tested in sensitivity analyses by increasing the probability that patients would transition to the inadequate response health state to 0.5, in the situation where a physician does not discontinue TE in a fragile patient even though the patient is not benefiting from treatment, given a lack of alternative options.

To incorporate CaHD into the model, the following assumptions were made: an increase in 5-HIAA levels is associated with an increase in CaHD incidence; TE reduces 5-HIAA levels regardless of durable response status [38]; and individuals with CaHD have an increased risk of death compared with those

Table 1 Base-case model inputs

Target population selection inputs		Value [source]	
Total population of Sweden, <i>n</i>		10,223,505 [46]	
NETs prevalence, <i>n</i> per 100,000 population		37 [4, 44]	
Annual NETs incidence, <i>n</i> per 100,000 population		5.25 [5, 44]	
Proportion of patients with intestinal (small bowel) NETs, %		17.2 [5, 44]	
Proportion of intestinal (small bowel) NETs that are grade 1/2, %		91.0 [44, 45]	
Proportion of patients with CS, of those with grade 1/2 intestinal NETs, %		30.0 [26, 44]	
Proportion of patients with lung NETs, %		27.0 [5]	
Proportion of lung NETs that are grade 1/2, %		5.4 [45]	
Proportion of patients with CS, of those with grade 1/2 lung NETs, %		5.0 [47]	
Proportion of patients with CS that is uncontrolled by SSAs, %		40.0 ^a	
CaHD inputs [50]		Value	
Relative mortality associated with CaHD		2.55	
Baseline incidence of CaHD, %		2.96	
Relative risk for CaHD development in patients with u5-HIAA levels > 300 µmol/24 h		2.74	
Proportion of TE-treated patients with u5-HIAA levels < 300 µmol/24 h, % ^b		82.0	
Proportion of placebo-treated patients with u5-HIAA levels < 300 µmol/24 h, % ^b		55.0	
Efficacy inputs for patients receiving TE		Value	
Proportion of patients treated with TE achieving durable response that is attributed to TE (TELESTAR), %		24.4 ^c	
Annual mortality rate for patients with and without CaHD by year of the analysis [51]			
Year of analysis	Age, years	No CaHD	With CaHD
1 (2018)	64	0.1455	0.3303
2 (2019)	65	0.1491	0.3375
3 (2020)	66	0.1491	0.3375
4 (2021)	67	0.1491	0.3375
5 (2022)	68	0.1491	0.3375
Medical cost inputs for patients receiving standard of care (SSAs) [33] ^d			
Item	Controlled CS, € per month	Uncontrolled CS, € per month	Incremental cost of CaHD, € per month ^e
Medical and surgical interventions	143.60	494.00	170.92
Examinations and imaging	78.78	264.75	87.58
Other outpatient visits	57.84	74.75	2.08
Inpatient admissions	260.13	263.75	32.75
SSAs	1257.88	1521.50	220.50
IFN-α	137.63	83.88	–
Chemotherapy	0.94	5.60	–
Other diarrhoea therapy	1.98	4.11	–
CaHD drug costs	–	–	1.83
Sum of monthly medical cost inputs for patients receiving standard of care	1938.78	2712.34	515.66
Drug costs for patients receiving SSAs + TE ^f			€ per 4 weeks
TE			982.27

CaHD carcinoid heart disease, CS carcinoid syndrome, IFN interferon, NET neuroendocrine tumour, SSA somatostatin analogue, TE telotristat ethyl, u5-HIAA urinary 5-hydroxyindoleacetic acid

^aForecasting assumption based on interviews with healthcare professionals

^bBased on a post-hoc analysis of TELESTAR clinical trial data

^cData derived from Kulke et al. [38], in which 20 of 45 (44.4%) patients randomised to SSA + TE demonstrated a durable response, compared with 9 of 45 (20%) patients randomised to SSA + placebo; therefore, for the purpose of this model, 24.4% of the response was presumed to be attributable to TE

^dValues from Lesén et al. [33], which cover an 8-month period, were divided by eight to determine per-month costs

^eAnnual CaHD incidence was assumed to be 2.96% for patients with 5-HIAA < 300 mmol/24 h [50]

^fTE not included in standard of care

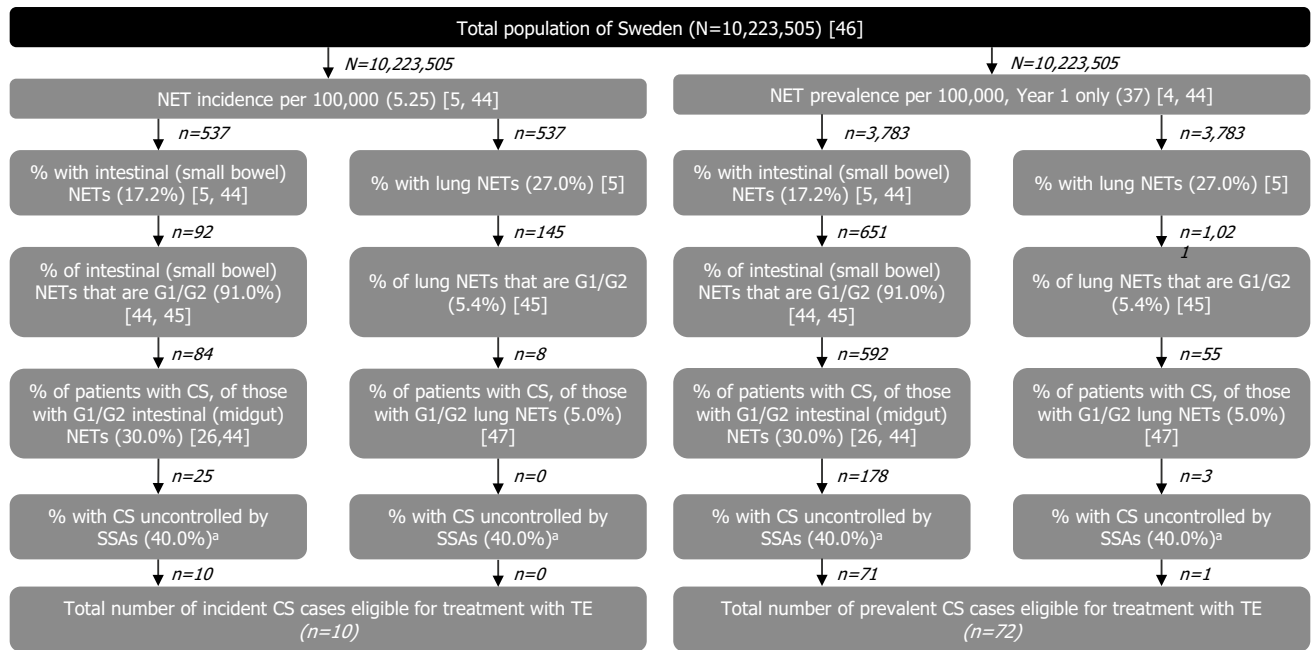


Fig. 1 Selection criteria for determining the target population (incident and prevalent CS cases eligible for treatment with TE), based on data from systematic and targeted literature reviews. Data from literature reviews were used to estimate the target population selection inputs as listed in Table 1. Resulting estimates used in the model are

shown in (parentheses), with the relevant sources in [brackets]. ^aForecasting assumption based on interviews with healthcare professionals. CS carcinoid syndrome, G1/G2 grade 1/grade 2, NET neuroendocrine tumour, SSA somatostatin analogue, TE telotristat ethyl

Table 2 Forecast base-case eligible population and market share assumptions for the world-without TE and world-with TE scenarios over 5 years

	Year 1 (2018)	Year 2 (2019)	Year 3 (2020)	Year 4 (2021)	Year 5 (2022)
Population					
Prevalent cases	72	74	71	68	66
Incident cases	10	10	10	10	10
Total cases ^a	82	84	81	79 ^b	76
Market share					
World-without TE scenario					
SSAs only, %	100	100	100	100	100
World-with TE scenario					
SSA + TEs, %	24	52	58	60	70
SSAs only, %	76	48	42	40	30

CS carcinoid syndrome, SSA somatostatin analogue, TE telotristat ethyl

Prevalence and incidence of uncontrolled CS was assumed to be the same for scenarios both with and without TE; values have been rounded to the nearest whole number

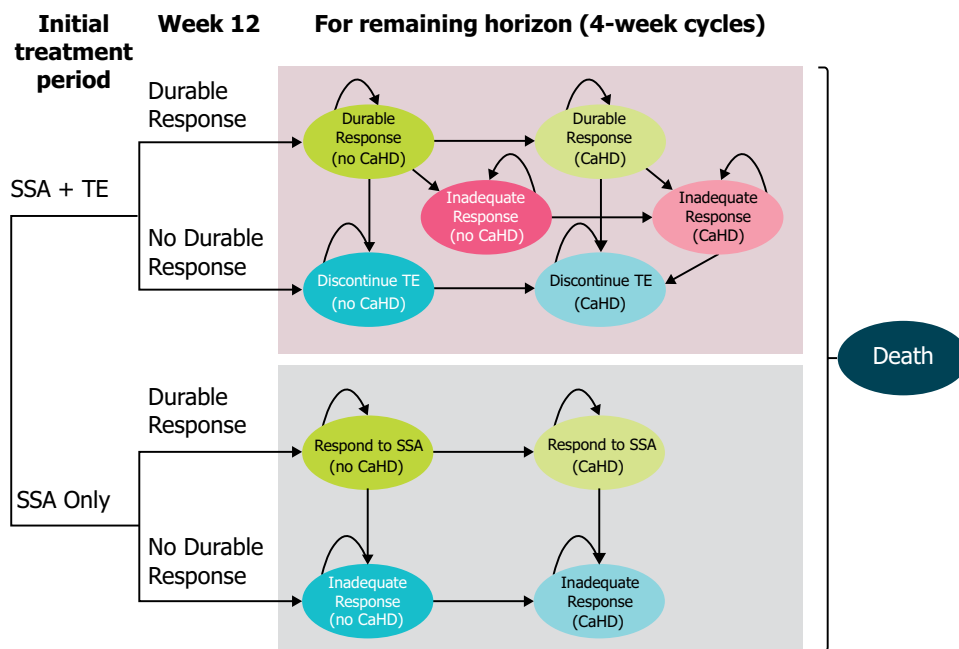
^aTotal cases decreases from year 3 as the rate of mortality for patients with prevalent CS is higher than the incidence of new patients, based on mortality estimates in Table 1

^bPrevalent and incident cases do not sum to 78 due to rounding

without. Levels of u5-HIAA were informed through analysis of data from the TELESTAR clinical trial [38]. The incidence of CaHD based on u5-HIAA was calculated using CaHD incidence as reported in Bhattacharyya et al. [50], which was the only study identified in a systematic literature review examining the link between 5-HIAA levels and CaHD incidence (Table 1).

The mean age of the cohort at the start of the simulation was assumed to be 64 years based on TELESTAR patient characteristics [38]. Relative 5-year survival rates for grade 1 and 2 tumours located in the intestinal tract were determined through application of the relative survival rates in Korse et al. [45] to the Swedish age-specific mortality rates.

Fig. 2 Markov model for treatment response after the initial 12-week treatment period. Patients with a durable response to TE begin the Markov process in the ‘SSA + TE’ arm. Patients who do not experience a durable response are assumed to discontinue TE but maintain SSA treatment and start in the ‘SSA only’ arm. The transition between durable response and inadequate response in the SSA + TE arm was set to 0 for the base-case analysis. There were no deaths during the first 12 weeks of the model (the trial period). *CaHD* carcinoid heart disease, *SSA* somatostatin analogue, *TE* telotristat ethyl



For the base case, the mortality risk associated with CaHD was calculated using data from Westberg et al. [51]. Base-case model inputs for mortality risk are shown in Table 1.

2.1.4 Cost Inputs

The unit cost of TE in Swedish krona (SEK) (10,100.00) [43] was converted to € using the European Central Bank conversion rate as of 28 November 2018 (€1 = SEK10.2823). Therefore, the unit cost of TE in Sweden is approximately €11.69 per 250 mg pill, cumulating in a total cost of €982.27 over 4 weeks (three pills per day). Patients in the SSA + TE arm during the initial treatment period and those in the durable response and inadequate response to TE health states within the Markov model incurred this cost.

Real-world CS and CaHD-related costs, including healthcare resource use (frequency per month), drug acquisition and SSA dosage (cost of average dose) for patients with controlled and uncontrolled CS were obtained from a retrospective Swedish database study [33] (Table 1). A number of symptoms not limited to diarrhoea may contribute to cost differences between responders and non-responders in the model. The costs associated with patients with controlled CS were assigned to the respond to SSA and durable response to TE health states. The costs associated with patients with uncontrolled CS were assigned to all remaining non-responder health states. Incremental costs for CaHD were determined by calculating the difference in monthly costs between patients with and without CaHD. The cost year for all model inputs was 2015, except for the Swedish total population size and TE unit cost, which used actual values as of reimbursement approval by the TLV in 2018.

2.2 Deterministic Sensitivity Analyses

Deterministic (one-way) sensitivity analyses were conducted to assess the impact of model parameters. Model parameters were varied using 95% confidence intervals (CIs) or plausible ranges as reported in the published literature. When the published study did not report 95% CIs or ranges, plausible ranges were specified or informed by clinical expert opinion, obtained through interviews with experts identified as knowledgeable about NET management and economic models. Ranges for inputs included in the sensitivity analyses are shown in electronic supplementary material 1.

3 Results

3.1 Base-Case Analysis

3.1.1 Number of Patients Treated

Based on the assumed TE market share and number of CS cases in the base population, approximately 44 patients would initiate TE therapy during the 5-year time horizon (Table 3). Because prevalent patients were assumed to initiate TE treatment in year 1 only, the number of patients expected to begin TE therapy was highest in year 1 (19.8).

3.1.2 Costs

Table 4 shows a full breakdown of costs over 5 years in the world-without TE and world-with TE scenarios. The total cost in year 1 was €2,793,111 in the world-without TE

scenario and €2,859,606 in the world-with TE scenario and subsequently declined over the 5-year period. The world-with TE scenario resulted in total drug costs €269,056 higher than in the world-without TE scenario over the 5-year period. Approximately 40% was offset by the reduced costs for other aspects of patient care in the world-with TE scenario, including medical and surgical interventions, examinations and imaging, outpatient visits, inpatient admissions, chemotherapy, other diarrhoea therapy and CaHD drug costs (Table 4).

The cumulative 5-year net budget impact of introducing TE to the current standard of care was €172,346; the cumulative cost over 5 years of treatment was €13,263,595 for the world-without TE scenario and €13,435,941 for the world-with TE scenario (Table 5). The net budget impact per year of introducing TE to the current standard of care was predicted to decrease from €66,495 in year 1 to €29,818 in year 5.

3.2 Deterministic Sensitivity Analyses

Results of the deterministic sensitivity analysis are shown in Fig. 3. The 5-year net budget impact of TE was most sensitive to the proportion of patients who continued TE therapy after 12 weeks of treatment despite lack of durable response. If 50% of patients who did not achieve a durable response continued TE therapy, the cumulative budget impact would increase to €696,661. The price of TE (250 mg) was the second biggest factor affecting the model outcomes, with a 25% increase or decrease resulting in a 5-year cumulative net budget impact of €251,668 and €92,824, respectively.

4 Discussion

Despite most patients with NETs receiving SSA therapy, many of those with CS continue to experience uncontrolled symptoms [24, 28, 30, 31, 52]. TE offers an effective, novel treatment option for patients with CS with uncontrolled diarrhoea. Used in combination with SSAs, TE has been shown to offer effective relief from CS diarrhoea and to improve the quality of life in patients who experience a durable response to treatment [38]. This study investigated the budget impact of the addition of TE to the current standard of care for CS in Sweden.

The total cost per year of treatment for patients with CS inclusive of TE therapy in Sweden declined over the 5-year time-period, from €2,859,606 in year 1 to €2,523,961 in year 5, as patients were assumed to discontinue TE due to adverse events, lack of effectiveness and CS progression. The cumulative 5-year net budget impact resulting from the addition of TE was relatively low at €172,346, with a per-year net cost of €66,495 in year 1 and decreasing thereafter.

The relatively low budget impact of adding TE to the existing standard of care in Sweden is likely due to two reasons. First, CS is a component of a rare disease, and the number of total prevalent and incident patients eligible for TE was estimated at approximately 80 patients each year over the 5 years; according to market share assumptions, only 44 patients would initiate treatment with TE by year 5. This aligns with findings from a 2014 study assessing the budget impact of orphan medicinal products in Sweden and France, in which the low overall number of annual sales made the costs associated with these treatments sustainable [53]. Further to this, the TE budget impact model assumed that patients who responded to TE would gradually discontinue treatment either as the disease progressed, TE

Table 3 Number of patients initiating TE treatment in the world-with TE scenario over 5 years

	Year 1 (2018)	Year 2 (2019)	Year 3 (2020)	Year 4 (2021)	Year 5 (2022)
Prevalent cases	17.3 ^a	0.0	0.0	0.0	0.0
Incident cases	2.5	5.3	5.9	6.1	7.2
Total cases	19.8	5.3	5.9	6.1	7.2
Number of patients discontinuing TE after initial 12-week treatment period	14.9	4.0	4.5	4.6	5.4
Number of patients continuing TE after initial 12-week treatment period	4.8	1.3	1.4	1.5	1.7

Numbers may not sum due to rounding

TE telotristat ethyl

^aTE was granted marketing authorisation in the EU prior to the start of year 1; therefore, prevalent patients were assumed to have had an opportunity to switch to TE in year 1 but were not expected to switch in following years

Table 4 Total costs over 5 years from the world-without TE and world-with TE scenarios

	Year 1 (2018)	Year 2 (2019)	Year 3 (2020)	Year 4 (2021)	Year 5 (2022)	Total
World-without TE scenario						
Total costs, €	2,793,111	2,742,376	2,659,435	2,574,530	2,494,143	13,263,595
SSA + TE drug costs	1,565,879	1,534,877	1,486,779	1,438,271	1,392,723	7,418,528
TE 250 mg	–	–	–	–	–	–
SSA only	1,565,879	1,534,877	1,486,779	1,438,271	1,392,723	7,418,528
SSA component of TE arm	–	–	–	–	–	–
Medical and surgical intervention	509,755	503,360	490,013	475,535	461,403	2,440,068
Examinations and imaging	273,139	269,564	262,319	254,508	246,908	1,306,438
Other outpatient visits	76,812	74,965	72,402	69,907	67,612	361,698
Inpatient admissions	271,369	265,792	257,330	248,851	240,919	1,284,260
IFN- α	86,157	83,998	81,069	78,239	75,648	405,112
Chemotherapy	5752	5608	5413	5224	5051	27,048
Other diarrhoea therapy	4224	4119	3975	3836	3709	19,863
CaHD drug cost	25	93	134	158	170	580
World-with TE scenario						
Total costs, €	2,859,606	2,766,700	2,684,974	2,600,700	2,523,961	13,435,941
SSA + TE drug costs	1,652,700	1,580,473	1,531,252	1,482,313	1,440,846	7,687,584
TE 250 mg	97,334	56,542	54,083	52,965	57,136	318,061
SSA only	1,190,068	1,112,025	1,017,163	927,248	828,840	5,075,343
SSA component of TE arm	365,299	411,906	460,005	502,101	554,870	2,294,180
Medical and surgical intervention	495,791	488,730	476,947	463,149	448,672	2,373,289
Examinations and imaging	265,728	261,801	255,387	247,938	240,155	1,271,009
Other outpatient visits	76,139	74,268	71,790	69,336	67,032	358,566
Inpatient admissions	271,221	265,648	257,235	248,802	240,904	1,283,811
IFN- α	88,295	86,243	83,093	80,182	77,667	415,480
Chemotherapy	5567	5415	5241	5061	4883	26,167
Other diarrhoea therapy	4139	4030	3896	3762	3633	19,461
CaHD drug cost	24	91	133	156	168	574

CaHD carcinoid heart disease, IFN interferon, SSA somatostatin analogue, TE telotristat ethyl

Table 5 Costs and net budget impact of TE for the world-without TE and world-with TE scenarios

	Year 1 (2018)	Year 2 (2019)	Year 3 (2020)	Year 4 (2021)	Year 5 (2022)	Total
World-without TE scenario						
Total costs, €	2,793,111	2,742,376	2,659,435	2,574,530	2,494,143	13,263,595
PMPM, €	0.02	0.02	0.02	0.02	0.02	–
PPPM, €	2825	2723	2727	2729	2731	–
World-with TE scenario						
Total costs, €	2,859,606	2,766,700	2,684,974	2,600,700	2,523,961	13,435,941
PMPM, €	0.02	0.02	0.02	0.02	0.02	–
PPPM, €	2892	2747	2752	2756	2763	–
Net budget impact of TE						
Total costs, €	66,495	24,323	25,539	26,171	29,818	172,346
PMPM, €	0.00	0.00	0.00	0.00	0.00	–
PPPM, €	67.26	24.06	25.74	26.85	31.29	–

PMPM per population member per month, PPPM per patient per month, TE telotristat ethyl

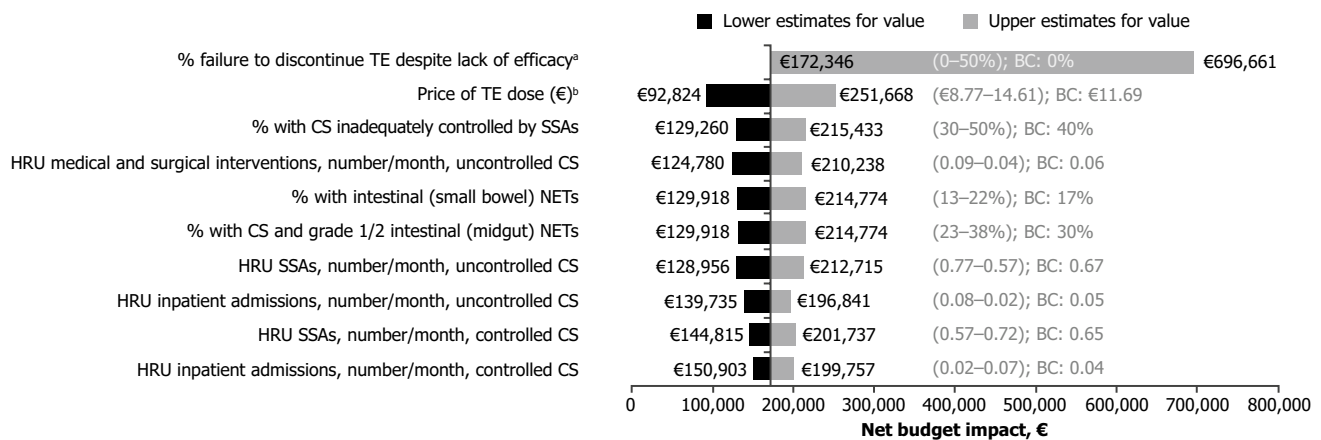


Fig. 3 Deterministic sensitivity analyses on the 5-year net budget impact. ^aFailure to discontinue treatment with TE after 12 weeks of TE treatment using data from TELESTAR. ^bParameter varied based on arbitrary ranges. Values in parentheses are the variation param-

eters for the sensitivity analyses. *BC* base case, *CS* carcinoid syndrome, *HRU* healthcare resource use, *NET* neuroendocrine tumour, *SSA* somatostatin analogue, *TE* telotristat ethyl

effectiveness decreased, adverse events occurred or patients died, which would also contribute to the small economic impact.

Second, the improved diarrhoea symptom control resulting from treatment with TE translated into overall healthcare system cost savings that offset the pharmacy cost of TE, an outcome previously reported for other treatments in rare chronic diseases [54, 55]. Although patients who respond to TE will still require ongoing monitoring for tumour progression, they would avoid the increased costs related to uncontrolled CS. The total costs per patient per year associated with medical and surgical interventions, examinations and imaging, outpatient visits, inpatient admissions, chemotherapy and other diarrhoea therapies were lower in the world-with TE scenario. This is in accordance with other studies showing that patients with CS who experience flushing and diarrhoea symptoms incur around \$US14,766–29,890 more per year in healthcare costs than those experiencing improvements in symptoms [10, 56].

Our results are consistent with those from a US study that also showed a minimal budget impact on a US health plan of adding TE to SSA therapy [57]. In this study, the budget impact of adding TE totalled \$US687,330 over 3 years. With a similar assumed market share (28% in year 1, 42% in year 2, and 55% in year 3), the net annual overall healthcare cost of TE (\$US55–109 million) was well under the Institute for Clinical and Economic Review (ICER) threshold for new molecular entities (\$US915 million per year) when the study was published in 2017 [57]. While the ICER decreased the threshold to \$US819 million in May 2019, the budget impact of adding TE to the standard of care in the USA still falls well under this amount [58].

A limitation of our study was the lack of readily available data, which is often a challenge when conducting budget impact analyses of treatments for orphan diseases [59, 60]. For example, prevalence and incidence data specific to Sweden were not available, so this analysis used data from a systematic review conducted for Europe and the USA to estimate the size of the target population [44]. The derivation of cost inputs for patients with controlled and uncontrolled CS from Swedish databases presented another limitation for this study. It was assumed that patients demonstrating a durable response to TE would have the same resource use as patients with controlled CS, and patients without a durable response to TE would have that of patients with uncontrolled CS (despite the fact that the definition of a durable response relates to reductions in symptoms of diarrhoea). The impact of this assumption on our budget impact estimate is unknown. However, because diarrhoea is the most burdensome symptom of CS, this model focused on cost outcomes associated with this symptom, though durable responders have also been shown to have improvements in other symptoms that would not be captured by this model [39]. It should be noted that this model does not account for the lost productivity to individual patients and society in general from the impact of CS on quality of life and consequences such as missed workdays.

5 Conclusions

Treatment with TE alongside SSAs more often results in durable improvement of diarrhoea symptoms than use of SSAs alone; symptomatic relief can lead to improved quality of life for patients with NETs and CS. This budget impact model demonstrated that TE could be an affordable addition

to the current standard of care for patients with NETs and CS in Sweden. Therefore, further research assessing the health and budget impacts of TE and other treatments for CS and NETs in Sweden would be beneficial and is warranted.

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Compliance with Ethical Standards

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Conflict of interest KF is employed by Optum. MM and MK were formerly employed by Optum. SS has received honoraria from Ipsen Pharma and Novartis, and research funding/fellowship support from Ipsen Pharma, Novartis, Merck EMD Serono and Pfizer. DMP has received honoraria from Advanced Accelerator Applications (AAA) and Ipsen Pharma, and research funding from Trio Medicines Ltd. FM, PM, MF are employed by Ipsen Pharma.

Data Sharing Where patient data can be anonymised, Ipsen will share all individual participant data that underlie the results reported in this article with qualified researchers who provide a valid research question. Study documents, such as the study protocol and clinical study report, are not always available. Proposals should be submitted to DataSharing@Ipsen.com and will be assessed by a scientific review board. Data are available beginning 6 months and ending 5 years after publication; after this time, only raw data may be available.

Author Contributions KF, MM, MK, SS, DMP, FM and MF made substantial contributions to the study conception/design or acquisition/analysis/interpretation of the data. KF, MM, MK, SS, DMP, FM, PM and MF drafted the publication or revised it critically for important intellectual content. MM, MK, SS, DMP, FM, PM and MF approved the manuscript for publication.

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