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Somatostatin analogue continuation upon progression in patients with gastroenteropancreatic neuroendocrine tumour (SAUNA trial): a randomised controlled trial protocol

Siddharth Chhajlani,[1,2] Jelka Kuiper ,[3] Philippe Beutels,[4] Ivan Borbath,[5] Wouter Dercksen,[6] Christophe M Deroose,[7] Stella Heemskerk,[8] Suzanne Polinder,[8] Ella Roelant,[9,10] Elke Smits ,[9,10] Iris Verhaegen,[9] Isolde Van der Massen,[1] Annemiek Walenkamp,[11] Wouter W de Herder ,[3] Marc Peeters,[2] Johannes Hofland,[3] Timon Vandamme,[1,2] for the SAUNA investigators and the Dutch Belgian Neuroendocrine Tumor Society (DBNETS)

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SC, JK, JH and TV contributed equally.

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For numbered affiliations see end of article.

Correspondence to
Professor Timon Vandamme; timon.vandamme@uza.be

ABSTRACT

Introduction Gastroenteropancreatic neuroendocrine tumours (GEP NET) are malignant neoplasms that impact survival. Somatostatin analogues (SSA) are used for treating hormonal symptoms caused by GEP NET and have antiproliferative effects. They are used as first-line therapy in patients with advanced GEP NET, but disease control is limited to a median progression-free survival (mPFS) of 14–32 months. Second-line treatment options include targeted therapy (everolimus or sunitinib), or peptide receptor radionuclide therapy (PRRT) with ^{177}Lu-DOTATATE. In patients suffering from a NET-related hormonal syndrome, SSA is generally continued life-long. However, there is no consensus on whether it is beneficial to continue SSA in non-functional NET upon disease progression. Due to the ongoing activity of the somatostatin receptor pathway in GEP NET progressing on first-line SSA, we hypothesise that SSA have an added efficacy in second-line therapy.

Methods and analysis The SAUNA trial is an international, multicentre, open-label, randomised, controlled, pragmatic clinical trial. 270 patients with advanced, non-functional GEP NET and progression under first-line SSA will be included in substudy 1 (PRRT; n=142) or substudy 2 (targeted therapy (everolimus/sunitinib); n=128) per investigator's choice of second-line therapy and will be randomised (1:1) per substudy between SSA continuation or SSA withdrawal arms. Co-primary endpoints are the difference in progression-free survival (PFS) according to the RECIST (Response Evaluation Criteria In Solid Tumours) V.1.1 criteria and difference in time to deterioration (TTD) in quality of life (QoL) per substudy after initiating second-line therapy with or without SSA. Secondary endpoints include the PFS rate at 18 months, the difference in pooled PFS and TTD combining both substudies, overall survival, response rates, QoL, costs, cost-effectiveness and toxicity. The study design was developed in cooperation with the Belgium and Dutch patient organisations.

Ethics and dissemination The study has been approved on 31 May 2023 by the Ethical Committees and Regulatory Authorities of the concerned member states (EU CT number 2022-502703-30-00). Both the trial management group and the steering committee will oversee good governance of this trial. Results of the study will be published in peer-reviewed international journals and presented at international conferences.

Trial registration number NCT05701241.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Binational, multicentre, pragmatic trial that reflects real-world clinical settings, ensuring representativeness across different types of medical centres.
⇒ Active involvement of Belgian and Dutch patient organisations throughout the course of the trial.
⇒ Randomised trial design to prevent confounding based on patient and physician preferences.
⇒ Open-label design, which could potentially lead to bias, but makes the trial more practical and reflective of real-world situations.
⇒ Real-life limitation: more patients eligible and randomised for substudy 1 (peptide receptor radionuclide therapy) than for substudy 2 (targeted therapy).

INTRODUCTION

Neuroendocrine neoplasms (NEN) commonly originate from the gastrointestinal tract and lungs[1 2] and display a heterogeneous biological profile. NEN can clinically and histologically be divided into poorly differentiated neuroendocrine carcinomas and well-differentiated neuroendocrine tumours (NET).[3] Among NEN, gastroenteropancreatic (GEP) NET impact survival with a cancer-related mortality in 60% of the patients.[4] In

the past years, the incidence and prevalence rates for GEP NET are rising steadily across Europe and globally.[2 5 6] Pancreatic NET (panNET) and small intestinal NET (siNET) are most common among GEP NET and often present with distant metastases, impeding curative surgical resection. Metastatic panNET or siNET exhibit 5-year overall survival (OS) rates of 34% and 59%, respectively.[5] In addition, a minority of GEP NET are functional NET, secreting bioactive peptides and amines, leading to specific hormonal syndromes that subsequently impair quality of life (QoL) and OS.[7] Moreover, several studies reveal that patients with NET have a lower health-related QoL on various domains, compared with the general population[8] and other cancer types.[9]

Treatment of newly diagnosed, locally advanced or metastatic GEP NET is based on various patient and tumour characteristics. One of the treatment modalities is somatostatin analogues (SSA),[10] which mainly bind to the somatostatin receptor type 2 (SSTR2) expressed by the majority of NET cells,[10] inhibiting tumour hormone release and growth. Initially, SSA were predominantly used for treating hormonal symptoms of GEP NET, such as the carcinoid syndrome.[10] Recently, studies have also proven the antiproliferative effects of SSA in GEP NET. In the phase III PROMID[11] and CLARINET trials,[12] SSA octreotide long-acting release (LAR) and lanreotide increased time to progression and progression-free survival (PFS) in siNET and in GEP NET, respectively, compared with placebo. Both octreotide LAR[13] and lanreotide[14 15] are approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) for advanced GEP NET. Furthermore, SSAs have a favourable tolerability and a limited adverse event profile and are thus advocated as the first-line therapy of choice in patients with advanced GEP NET in international clinical guidelines.[16–18] Despite their efficacy, disease control on SSA was limited to a median PFS (mPFS) of 14–32 months in phase III clinical trials.[11 12]

Second-line FDA-registered and EMA-registered treatment options for non-functional GEP NET include the following: tyrosine kinase inhibitor sunitinib for panNET, mTOR inhibitor everolimus for all GEP NET and peptide receptor radionuclide therapy (PRRT) with radiolabelled SSA ^{177}Lu-DOTATATE for SSTR2-positive GEP NET.[17] Therapy with sunitinib[19] or everolimus[17 19 20] resulted in an mPFS of 11 months, whereas PRRT with ^{177}Lu-DOTATATE resulted in an mPFS of 28 months.[21 22] Due to their toxicity and costs, European Society of Medical Oncology guidelines recommend targeted therapy and PRRT as second-line treatment for GEP NET after progression on SSA.[17] In functional NET, SSA are often continued life-long, in monotherapy or alongside second-line therapy,[23 24] to avoid a rebound of the hormonal syndrome.[16] Throughout the registration trials with these second-line therapies, the inclusion criteria varied, resulting in a heterogeneous overall population of patients with functional and non-functional tumours, with or without SSA continuation. Although the investigation of the interaction of SSA and targeted therapy was not part of the study design, the concomitant use of SSA was permitted in the registration trials of both sunitinib and everolimus. This resulted in SSA use in 27–44% of the patients included in these trials, evenly distributed over intervention and placebo arms.[19] In the NETTER-1 trial, all patients in the ^{177}Lu-DOTATATE arm were treated with 30 mg octreotide LAR every 4 weeks, leading to a much-adopted strategy of continuation of SSA alongside PRRT in both functional and non-functional GEP NET.[25] Hence, the evidence on the benefit of SSA addition in second-line treatment of non-functional GEP NET is inconclusive, and that is why there is no consensus whether SSA should be continued on progressive disease (PD) in patients with non-functional NET.

Trial rationale: should SSA be continued in second-line in case of PD under first-line SSA?

In oncology, the classical paradigm advises discontinuing a certain therapy on documented PD during treatment. However, this does not necessarily apply to SSA continuation in GEP NET. For instance, sustained functional SSTR2 expression on progression under SSA indicates ongoing suppression of hormonal activity, supporting the efficacy of second-line PRRT. Moreover, on progression, disease control could be reobtained through dose escalation of SSA, suggesting continued antiproliferative effects of SSA.[25 26] Additionally, GEP NET exhibit low tumour growth rates, resulting in slow progression under SSA, suggesting sustained intracellular effects of SSA. Finally, a retrospective study (n=168) showed that SSA continuation alongside second-line PRRT yielded a survival benefit (mPFS and median OS (mOS) of 91 months each in PPRT+SSA arm (n=87), compared with mPFS of 27 months and mOS of 47 months in the PRRT monotherapy arm (n=81)).[27]

Conversely, some reports question the benefits of SSA continuation in combination therapy. In the COOPERATE-2 trial, pasireotide LAR (pan-SSTR-targeting ligand) with everolimus did not improve PFS versus everolimus monotherapy. However, since the clinical efficacy of pasireotide in NET is not established, these results may not extend to lanreotide or octreotide LAR.[28] Moreover, post-hoc analyses of the sunitinib and everolimus registration trials did not show the benefit of SSA continuation. However, SSA administration was not randomised, nor stratified upfront, and likely selects for functional NET.[28 29]

These considerations above, combined with the tolerability of SSA, the lack of high-grade evidence from clinical trials, and its continued use in functional NET have fuelled the controversy of continuing SSA in advanced, non-functional GEP NET during second-line systemic therapy. Moreover, the current guidelines[16–18] provide insufficient support in this area. Consequently, routine clinical practice differs between NET centres in both Belgium and the Netherlands. Feasibility questionnaires in SAUNA-participating centres revealed a high degree

of intercountry and intracountry variability in current clinical practice regarding SSA use in this setting. During second-line therapy with everolimus, 58% of all centres (n=19) would continue SSA (77% of the Belgian centres (n=13) and 17% of the Dutch centres (n=6)). A similar trend was seen for sunitinib as second-line treatment. For patients treated with PRRT, 47% of all centres (n=19) would continue SSA (46% of the Belgian centres (n=13) and 50% of the Dutch centres (n=6)). This divergence in clinical practice is mirrored by an emerging dichotomy in ongoing clinical research: the STARTER-NET trial investigates the potential benefit of concomitant SSA with first-line targeted therapy, whereas the STOPNET trial explores the counter-hypothesis that concomitant SSA with PRRT has no added value.[30–32]

Due to the ongoing activity of the SSTR pathway in GEP NET progressing during first-line SSA, we hypothesise that SSA has added efficacy in second-line treatment alongside PRRT or targeted therapy. With the SAUNA trial, we aim to investigate the efficacy of SSA continuation in terms of PFS and QoL in advanced, non-functional GEP NET patients during second-line therapy, compared with SSA withdrawal. This will provide the necessary high-grade evidence for guidelines and inform the NET specialists on the preferred strategy. We additionally aim to perform a cost-effectiveness analysis, so policymakers can be informed about the costs, health outcomes and efficiency of the treatment options under consideration. In case of a proven benefit of SSA, this could help patients directly in terms of expected OS and QoL outcomes. Furthermore, these health gains can be related to the incremental costs they require to help policy makers shape their decisions.

METHODS AND ANALYSIS

The aim, design and setting of the study

Trial design

The SAUNA trial is an international, multicentre, open-label, randomised, controlled, pragmatic clinical trial. It will be conducted across 20 participating centres in Belgium and the Netherlands. Figure 1 gives an overview of the trial design. Patients with advanced, non-functional, grade 1 or 2 GEP NET with progression under first-line SSA will be divided into two substudies according to the choice of second-line therapy at the discretion of the local principal investigator (PI). Substudy 1 will include patients receiving PRRT with four cycles of ^{177}Lu-DOTATATE, and substudy 2 will include patients receiving targeted therapy

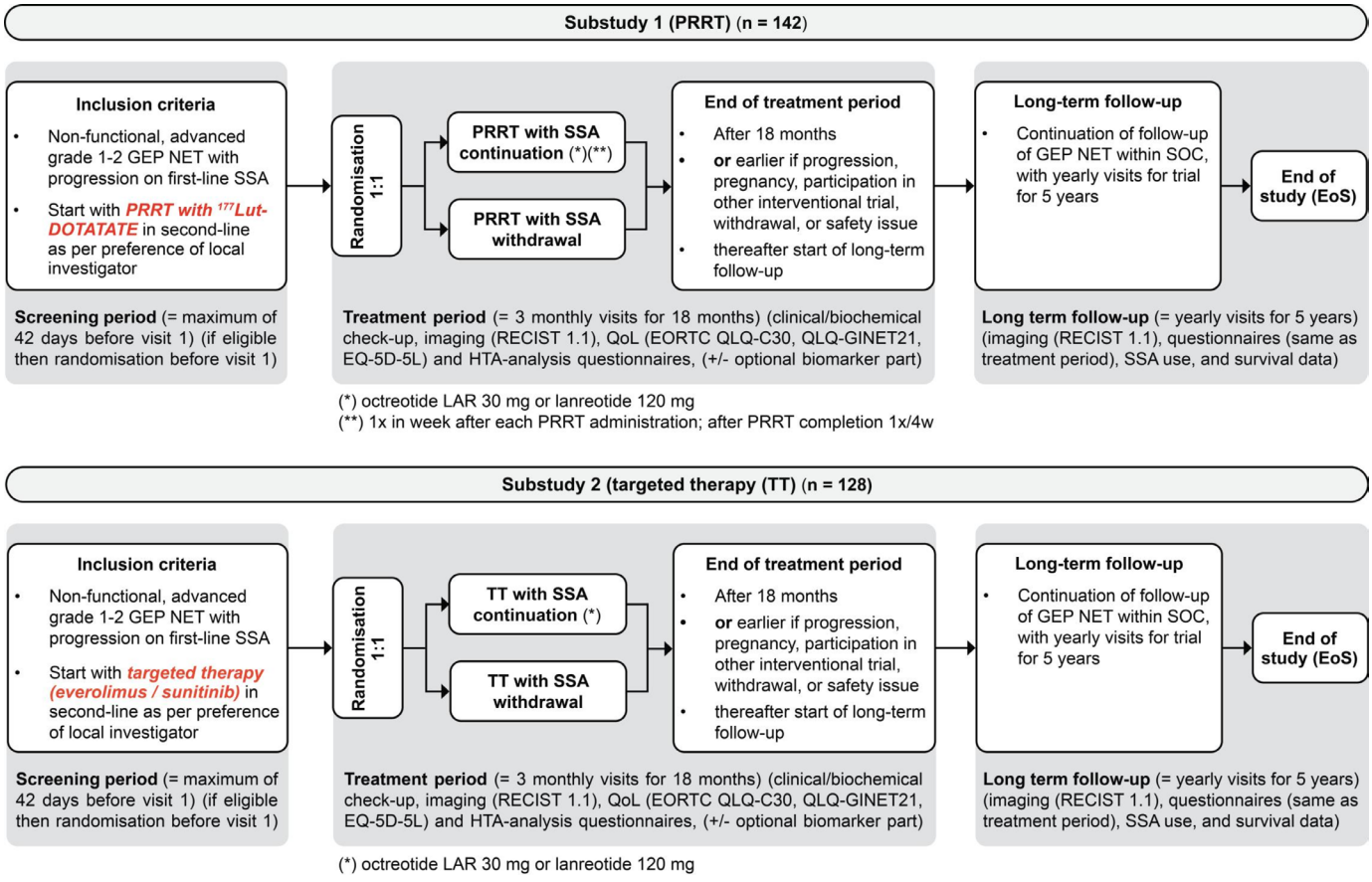

Figure 1 Overview of trial design. EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D-5L, generic 5-level EuroQoL 5D; GEP, gastroenteropancreatic; HTA, health technology assessment; LAR, long-acting release; NET, neuroendocrine tumour; PRRT, peptide receptor radionuclide therapy; QLQ-C30, Quality of Life Questionnaire Core 30; QLQ-GINET21, Quality of Life Questionnaire Gastrointestinal Neuroendocrine Tumours 21; QoL, quality of life; RECIST, Response Evaluation Criteria In Solid Tumours; SOC, standard of care; SSA, somatostatin analogues.

(everolimus or sunitinib). Patients within each substudy will be randomised 1:1 to the SSA continuation or the SSA withdrawal arm. Follow-up will be performed every 3 months until 18 months after the start of second-line therapy. After the treatment phase, participants will be followed up for 5 years (long-term follow-up). Follow-up will consist of imaging and Response Evaluation Criteria In Solid Tumours (RECIST) V.1.1 assessment, validated QoL and healthcare usage questionnaires and optional blood collection for biomarker analysis.

Patient and public involvement statement

The trial was set-up in collaboration with patient organisations 'vzw NET & MEN Kanker (Belgium)' and 'Stichting NET-NEC (the Netherlands)'. These groups contributed to the trial design, ensuring patient-centric outcome measures. They evaluated the intervention's burden and the time commitment required for participation. Furthermore, all the study information provided to the patients was reviewed and approved by the patient organisations. Finally, continued patient involvement is foreseen during all phases of the trial, including the dissemination of results, as representatives from the patient organisations are part of the trial steering committee.

Endpoints

Co-primary endpoints

The trial aims to demonstrate the superiority of SSA continuation compared with SSA withdrawal during second-line therapy. This trial is divided into two substudies, using either PRRT (substudy 1) or targeted therapy (substudy 2) as second-line therapy. Each participant is further allocated to the SSA continuation or SSA withdrawal arm through 1:1 randomisation per substudy.

The first co-primary endpoint assesses the difference in PFS between SSA continuation and SSA withdrawal arm per substudy after initiating second-line therapy, as assessed by blinded local radiologists on cross-sectional imaging. Progression is defined through RECIST V.1.1[33] after initiating second-line therapy with PRRT or targeted therapy. The second co-primary endpoint assesses the difference in time to deterioration (TTD) in QoL between SSA continuation and SSA withdrawal arm per substudy after initiating second-line therapy with PRRT or targeted therapy. TTD is defined as the time from the start of second-line therapy to the first decrease from baseline on the Global Health component of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) questionnaire by at least 10 points (on a 100-point scale),[34] with no further increase above this threshold, or death.

The trial will only be considered positive if superiority can be demonstrated for PFS and TTD in QoL for SSA continuation alongside second-line therapy compared with SSA withdrawal. This is because proving the benefits of SSA continuation, both in terms of survival and QoL benefit, could help patients directly. Subsequently, this will help NET experts and policymakers to shape their decisions.

Secondary endpoints

Secondary endpoints are PFS according to RECIST V.1.1 at 18 months, OS, response rates, overall QoL via Quality of Life Questionnaire Gastrointestinal Neuroendocrine Tumours 21 (QLQ-GINET21), EORTC QLQ-C30 and the generic 5-level EuroQoL 5D (EQ-5D-5L) questionnaires, costs, cost-effectiveness and toxicity. The primary and secondary endpoints will be considered per substudy and in the full data set combining both substudies.

Exploratory endpoints

Exploratory endpoints are exploratory biomarker analyses (eg, circulating tumour DNA, circulating transcripts, circulating non-malignant DNA) via multiomics analysis in a subset of participants to discover additional blood-based biomarkers for prediction of response to therapy in order to better select patients that will benefit from SSA therapy. To test whether the level of a biomarker from our multiomics approach is associated with tumour progression, an association between tumour fraction evolution and PFS will be evaluated using a joint modelling approach with the R package 'JM'. A joint model will be fitted for the data using a linear mixed model for the longitudinal data and a Cox survival model for PFS.

Study population

Eligibility criteria

A total of 270 adult patients with GEP NET will be included as per the eligibility criteria (table 1).

Study procedures

Study screening and randomisation

Potential participants will first be scheduled for a screening visit, where the eligibility criteria (see table 1) will be checked and written informed consent form will be obtained (see online supplemental files 1 and 2). A unique study identification number will then be assigned to the participant, and the relevant data collection and study procedures (as outlined in table 2) will be performed during the screening period of 42 days before eventual randomisation. Within 8 days before visit 1, eligibility criteria will be rechecked and after completion of the study questionnaires, participants within each substudy will be randomised 1:1 through Qminim, a web-based minimisation tool, to the SSA continuation or the SSA withdrawal arm. Stratification will occur according to the study centre and the Ki67 value (<10% (grade 1 and low grade 2), ≥10% (high grade 2)) in accordance with the cut-off criteria established by the CLARINET trial.[12]

Participants that are determined as not eligible will be listed as screen failure together with the reason for screen failure. They will continue to be followed-up according to the standard of care.

Table 1 Eligibility criteria of the SAUNA trial

Inclusion criteria	Exclusion criteria
For eligibility to participate in this study, a potential participant must meet all of the following criteria:	A potential participant who meets any of the following criteria will be excluded from participation in this trial:
Age≥18 years	Indication for second-line treatment of GEP NET with chemotherapy
Written informed consent prior to any study-related procedure	Presence of poorly-differentiated grade 3 neuroendocrine carcinoma, well-differentiated grade 3 NET or rapidly progressive NET
Eastern Cooperative Oncology Group performance status≤2	Prior treatment with everolimus, sunitinib or PRRT
Histologically-proven diagnosis of locally advanced or metastatic, non-functional, well-differentiated WHO 2019 grade 1–2 GEP NET	Contraindication, proven allergy or other indication than functional NET for the use of an SSA
Documented radiological PD on first-line SSA treatment	Patient showing PD while being on a lower than the registered dose of SSA
► Indication, according to the local PI, to start with second-line treatment with: ► PRRT with ^{177}Lu-DOTATATE (substudy 1) ► Either sunitinib or everolimus (substudy 2)	Functional NET, defined as the presence of clinical and biochemical evidence of a hormonal NET-related syndrome
	Patient undergoing palliative, systemic oncological treatment for other malignancy than GEP NET
	Concurrent anticancer treatment in another investigational trial
	Any abnormal findings at baseline, clinical finding, including psychiatric and behavioural problems, or any other medical condition(s) or laboratory findings that, in the PI's opinion, might jeopardise the participants' safety or decrease the chance of obtaining satisfactory data needed to achieve the objective(s) of the study
	Pregnant or lactating participant at screening or if the participant wishes to get pregnant during the treatment phase of the trial

GEP, gastroenteropancreatic; NET, neuroendocrine tumour; PD, progressive disease; PI, principal investigator; PRRT, peptide receptor radionuclide therapy; SAUNA, Continuing Somatostatin Analogues Upon progression in Neuroendocrine tumour pAtients; SSA, somatostatin analogues.

Therapeutic schedules

After randomisation, the participants will start the second-line therapy of choice of the local PI according to the registered label (PRRT or targeted therapy). Following international guidelines and the SAUNA feasibility questionnaire among participating centres, participant treatment is estimated to be split evenly between PRRT and targeted therapy. As the efficacy between everolimus[35] and sunitinib[36] is not different in randomised phase III clinical trials (as measured by PFS), further stratification based on the type of drug within the targeted treatment subgroup is not warranted. However, a post-hoc analysis for the effect of the type of drug is planned.

Participants who are randomised in the SSA continuation arm will continue SSA at its registered dose for first-line treatment: octreotide LAR 30 mg or lanreotide 120 mg. In participants previously using an above-label frequency (ie, every 2–3 weeks, instead of every 4 weeks) or an above-label dose, the dosing schedule will be reduced to octreotide LAR 30 mg or lanreotide 120 mg every 4 weeks. Participants randomised in the SSA withdrawal arm will stop SSA after randomisation.

Participants in arm 1 (PRRT) who are randomised to the SSA continuation arm will receive the SSA injection in the week following each administration of ^{177}Lu-DOTATATE,[37] which will be administered every 8 weeks, followed by dosing every 4 weeks after completion of PRRT. Participants in substudy 2 (targeted therapy) who are randomised in the SSA continuation arm will receive an injection of the first dose of SSA within the study, 28±7 days after their final SSA dose before visit 1. Participants will continue this dose every 4 weeks. For targeted therapy, the local PI will prescribe daily oral doses of everolimus 10 mg or sunitinib 37.5 mg. Dose reductions after initiation of everolimus, sunitinib and PRRT will be performed according to local guidelines.

After the end of treatment/early termination visit, it is advised that the participants continue the allocated treatment. Nonetheless, should the local PI have clinical reasons to continue or resume SSA treatment, either option is acceptable.

Follow-up

All patients are followed up at 3, 6, 9, 12, 15 and 18 months (±14 days) from the day they started the second-line treatment. The details of follow-up and the respective study procedures are given in table 2. After the end of treatment or early termination, long-term follow-up (yearly (±3 months)) will initiate and continue for 5 years.

Patient withdrawal and study termination

Participants may leave the study at any time without any consequences. The PI can also withdraw a participant for urgent medical or valid reasons. Follow-up will continue for participants who stopped study treatment unless consent is withdrawn. The available data until the withdrawal of consent or loss to follow-up will be used and will be censored at the last time point available in the absence of progression or death.

Health-related QoL measurements and health care-related cost-estimation tools

Health-related QoL will be measured using a generic and two disease-specific instruments. The EQ-5D-5L is a valid instrument and is recommended for economic evaluation, clinical and public health studies.[38] Country-specific versions of the EQ-5D-5L will be used (BE-Dutch and BE-French version for Belgian participants, and NL-Dutch version for Dutch participants). This will be

Table 2 The details of follow-up and the respective study procedures

	Screening period	Treatment period			Early termination visit or end of treatment visit	
	Visit −1	Visit 1	Visit 2	Visit 3–6	Visit 7	Long-term follow-up
	Max 42 days before visit 1	Day 1	Month 3±14 days	Month 6, 9, 12 and 15±14 days	Month 18±14 days or in case of radiological progression per RECIST 1.1, pregnancy or participation in interventional trial	Yearly (±3 months) after early termination visit or end of treatment visit for 5 years
Informed consent	X					
Eligibility assessment	X	X				
Registration demographics and medical history*	X					
Randomisation		X				
First treatment with PRRT/targeted therapy		X				
Radiological imaging CT/MRI	X†		X	X	X	X‡
Radiological assessment RECIST 1.1	X		X	X	X	X‡
Registration ECOG	X	X	X	X	X	X
Registration physical examination/ vital signs§	X	X	X	X	X	
Registration prior GEP NET treatment	X					
Registration concomitant medication/surgery	X	X	X	X	X	
Registration hospitalisation-related records (healthcare resource use)	X	X	X	X	X	
Registration SSA use (if applicable)						X
Quality of life questionnaires¶		X**	X	X	X††	X
Questionnaire regarding medical consumption and productivity costs¶		X**	X	X	X††	X
Adverse events review and serious adverse events reporting‡‡	X	X	X	X	X	
Collection of survival data		X	X	X	X	X

Continued

Table 2 Continued

	Screening period	Treatment period			Early termination visit or end of treatment visit	
	Visit −1	Visit 1	Visit 2	Visit 3–6	Visit 7	Long-term follow-up
	Max 42 days before visit 1	Day 1	Month 3±14 days	Month 6, 9, 12 and 15±14 days	Month 18±14 days or in case of radiological progression per RECIST 1.1, pregnancy or participation in interventional trial	Yearly (±3 months) after early termination visit or end of treatment visit for 5 years
Registration of blood haematology/biochemistry values (if done per standard of care)§§	X	X¶¶	X	X	X	
Optional blood collection biomarker substudy		X¶¶	X		X***	X†††
Registration NET related hospitalisations (healthcare resource use)‡‡‡		X	X	X	X	

*Year of birth, age at the time of inclusion, sex, race, length, significant medical history, NET history, date of diagnosis and stage.
†If the last cross-sectional imaging (consisting of abdominal or thoracoabdominal CT scan/MRI) were performed more than 42 days before Visit 1, participants will undergo a thoracoabdominal CT at screening.
‡Only applicable for study participants who did not yet progress radiologically per RECIST 1.1 during treatment phase. Registration of all RECIST measurements by a blinded local investigator on radiological imaging (CT/MRI) per SOC.
§Blood pressure, pulse and weight.
¶EORTC QLQ-C30, QLQ-GINET21, EQ-5D-5L and questionnaire regarding medical consumption and productivity costs collection online via an email sent using the eCRF prior to the hospital visit (these will be sent out after inclusion maximum 42 days prior to visit 1, and for subsequent visits (visits 2–7) these will be sent out maximum 2 weeks prior to the visit). If not done prior to the visit, participants will be asked to complete the questionnaires during the visit.
**The Visit 1 questionnaires need to be completed prior to the start of the second-line therapy.
††Participants who had an early termination visit will be asked to complete the questionnaires. This can be done during the visit or within the window of +14 days. Participants will continue to receive the questionnaires every 3 months until 18 months after the start of the second-line therapy and will then receive the questionnaires yearly.
‡‡AEs (grade 3 or more) and SAEs will need to be reported since ICF signature until end of treatment/early termination visit. Only related SAEs will need to be reported until 42 days after last SSA administration or until start new treatment.
§§If a blood collection is done per routine clinical practice ±14 days of the visit, then registration of the following parameters (clinical chemistry and haematology) is required: blood count: haemoglobin, thrombocytes, leucocytes with differential; kidney function: sodium, potassium, creatinine; calcium; liver function: albumin, bilirubin, aspartate aminotransferase/alanine transaminase, gamma-glutamyl transferase, alkaline phosphatase, lactate dehydrogenase (mandatory), international normalised ratio, chromogranin A, neuron specific enolase (optional)). If the last blood levels were performed more than 42 days before Visit 1, participants will undergo a venipuncture at screening.
¶¶These procedures do not need to be reperformed on the D1 visit if they were already performed within 8 days prior to the D1 visit.
***The blood sample needs to be taken prior to starting third-line therapy.
†††Only for the participants who are included in the biomarker analysis subset who exhibit radiological progression per RECIST 1.1.
‡‡‡This also includes planned NET-related hospitalisations, such as hospitalisations for therapy administration (eg, PRRT administration).
AEs, adverse events; D1, Day 1; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; EORTC, European Organisation for Research and Treatment of Cancer; EQ-5D-5L, generic 5-level EuroQoL 5D; GEP, gastroenteropancreatic; ICF, informed consent form; NET, neuroendocrine tumour; PRRT, peptide receptor radionuclide therapy; QLQ-C30, Quality of Life Questionnaire Core 30; QLQ-GINET21, Quality of Life Questionnaire Gastrointestinal Neuroendocrine Tumours 21; RECIST 1.1, Response Evaluation Criteria In Solid Tumours version 1.1; SAEs, serious AEs; SOC, standard of care; SSA, somatostatin analogues.

supplemented by the disease-specific EORTC QLQ-C30 (co-primary endpoint) and QLQ-GINET21 questionnaires, which both have been developed and validated for patients with cancer and patients with GEP NET, respectively.[8]

Total costs will be measured based on intervention costs and costs for healthcare utilisation (in both countries) and productivity loss (only in the Netherlands) until the primary endpoint will be measured in accordance with economic guidelines. Healthcare costs will be calculated using data from electronic hospital registries, electronic case report form (eCRF), InterMutualistic Agency administrative data for Belgian participants (if applicable), and data from the questionnaire on medical consumption and production consumption, which is an adapted version of the Medical Consumption Questionnaire and Production Consumption Questionnaire developed and validated by the Institute for Medical Technology Assessment (Erasmus University, Rotterdam, the Netherlands).[39–43] Both questionnaires are adapted to only include relevant healthcare-related questions to reduce patient burden. The cost price of SSAs will be determined by the bottom-up micro-costing method. These data will be collected in the trial database and will be used for a cost-effectiveness analysis.

Sample size calculation and statistical analysis plan

Sample size calculation

Substudy 1: PRRT

To assess the PFS co-primary endpoint in this substudy, a total of 142 participants will be randomised. The phase III NETTER-1 trial[25] showed a HR of 0.21 for PFS for PRRT with SSA versus double-dose SSA monotherapy in midgut NET. Based on these findings and assuming an mPFS of 15.4 months in the SSA withdrawal arm, an overall total of 96 events or an overall sample size of 134 participants would be needed in the PRRT arm to detect an HR of 0.54 using a log-rank test (85% power and α=0.05). The assumed mPFS of 15.4 months in the SSA withdrawal group was not taken directly from empirical data, but was mathematically inferred from the reported median PFS of 29 months for the SSA continuation group in the NETTER-1 trial.[44] Accounting for a 5% dropout rate, 142 participants will need to be randomised. For the TTD co-primary endpoint, this foreseen sample size of 142 participants would allow the detection of an HR of 0.55 in TTD using a log-rank test with 102 events (85% power and α=0.05). This assumes a median TTD of 13.5 months in the SSA withdrawal arm, based on the findings of the NETTER-1 trial,[25] which showed an HR of 0.41 with a median TTD of 28.8 months in the SSA continuation arm, and the CLARINET trial,[12] which showed an HR of 0.47 in the SSA arm.

Substudy 2: targeted therapy (everolimus or sunitinib)

To assess the PFS co-primary endpoint in this substudy, a total of 128 participants will be randomised. Three large phase III trials[19–21] demonstrated an mPFS of 11 months during treatment with everolimus or sunitinib. The RADIANT-3 trial,[29] evaluating everolimus in panNET, reported an HR of 0.35 for PFS was reported, while the RADIANT-4 trial[20] reported an HR of 0.48 for the extra-pancreatic NET. The SUN-111 trial,[19] studying sunitinib in panNET, reported an HR of 0.42 for PFS for treatment with sunitinib. In addition, the STARTER-NET trial with a randomisation between lanreotide (SSA) in combination with everolimus and everolimus monotherapy in first-line showed an HR of 0.38 for PFS favouring the lanreotide+everolimus arm.[30–32] Based on these findings and assuming an mPFS of 11 months in the SSA withdrawal arm (=group considered in RADIANT trials), an overall total of 97 events or an overall sample size of 120 participants will be needed to detect an HR of 0.54 using a log-rank test (85% power and α=0.05). Accounting for a 5% dropout rate, 128 participants will be randomised in total for this substudy. For the TTD co-primary endpoint, this foreseen sample size of 128 participants would allow the detection of an HR of 0.55 in TTD using a log-rank test with 103 events (85% power and α=0.05), assuming a median TTD of 9 months in the SSA withdrawing arm.

Pooled analysis

In a pre-planned analysis, the co-primary endpoints PFS and TTD will be considered in the 270 included participants of both substudies 1 and 2, allowing for the detection of superiority of continued SSA treatment with an HR of 0.66 for PFS (assuming an mPFS of 13 months in the SSA withdrawal arm) and an HR of 0.67 for TTD (assuming a median TTD of 11 months in the SSA withdrawal arm) a total of 210 events and 227 events (85% power and α=0.05) are needed, respectively.

Although the results of the trials[12 19 22 44] used for sample size calculations cannot necessarily be extrapolated to the SAUNA trial, it does highlight the importance and potential effect size of continuation of SSA and therefore supports our HR assumptions.

Statistical analysis plan

The intention-to-treat (ITT) population is considered the main analysis population for both the co-primary and secondary endpoints. For the co-primary study endpoints, the difference in PFS and respectively in TTD in QoL between SSA continuation or withdrawal will be estimated using the Kaplan-Meier method and compared using a log-rank test. HRs and 95% CIs will be reported using a Cox-proportional hazard model. As a sensitivity analysis, the co-primary outcomes will also be assessed in the per-protocol (PP) population with the same analysis methods.

For the secondary endpoints, the PFS at 18 months between SSA continuation or withdrawal will be calculated using the χ^2 test per substudy. ORs with 95% CI will be reported. The intervention effect of SSA continuation compared with withdrawal with the adjustment for clinicopathological variables (primary tumour type (defined as pancreatic vs extra-pancreatic NET), age,

presence of extra-hepatic metastases at screening, duration of SSA during first-line, Ki67 level and use of everolimus or sunitinib in the targeted treatment substudy) will be evaluated using a logistic regression model for the PFS at 18 months. The 18-month follow-up is based on the RADIANT trial, where 80% of patients treated with everolimus had progression at 18 months.[22] The median PFS in the NETTER-1 study in patients treated with PRRT was 28 months.[44] Through the long-term follow-up of 5 years, PFS events beyond the 18-month timeframe will be captured. When the last patient reaches 18 months follow-up, the estimated median follow-up will be 33 months for the overall population. Within this timeframe, there will be a sufficient number of PFS events to allow analysis of this primary outcome when the last patient included has reached his or her 18 months of follow-up.

A time-to-event analysis comparing PFS and respectively TTD between SSA continuation and withdrawal with the inclusion of the same clinicopathological data will be performed using a Cox-proportional hazard model (HR and 95% CIs will be reported). The same analysis will be done for OS.

Furthermore, response rates will be described according to RECIST V.1.1 criteria, and QoL measures will be measured at different time points to compare evolution over time between the two study arms using a linear mixed model with the participant as a random effect. Finally, secondary survival endpoints will be assessed in the PP population with the same analytical methods, and a pooled analysis of the whole sample (using the data of the ITT population of both substudies), PFS, TTD and OS will be estimated using the Kaplan-Meier method and compared using a log-rank test. HR and 95% CIs will be reported using a Cox proportional hazard model.

Health technology assessment analysis

As part of the health technology assessment (HTA) analysis, an economic evaluation study will be performed according to the Belgian and Dutch guidelines.[38 45–49] A cost-effectiveness analysis (CEA) and a cost-utility analysis (CUA) will be performed. The cost-related data will be collected as defined in the methods section.

The CEA will be performed using PFS at 18 months as the primary endpoint. In accordance with the economic evaluation guidelines, in the Netherlands, this analysis will be performed from a societal perspective to include costs for healthcare and lost productivity until 5 years after treatment initiation. In Belgium, this analysis will be done from the perspective of the healthcare payer. The CUA will be performed using quality-adjusted life years as the outcome, based on the Dutch and Belgian tariff for the EQ-5D-5L.

During the economic evaluation, as well as the CEA and CUA, the Incremental Cost-Effectiveness Ratio of SSA continuation versus SSA withdrawal will be calculated by dividing the difference in costs by the difference in effects, while accounting appropriately for uncertainty. Missing data will be imputed using multiple imputation by changed equations. Special caution will be given for possible clustering of data, as this might lead to inaccurate levels of uncertainty and inaccurate point estimates. To account for this, the analyses will be performed using linear multilevel analyses.

Other study parameters: blood samples for future multiomics research

The ITT population subset that will provide blood samples for future multiomics research is considered the main analysis population for the exploratory endpoints. To test whether the level of a biomarker from our multiomics approach is associated with tumour progression, an association between tumour fraction evolution and PFS will be evaluated using a joint modelling (JM) approach using the R-package 'JM'.[50]

ETHICS AND DISSEMINATION

Ethics approval and consent to participate

The study has been approved by the Ethical Committees and Regulatory Authorities of the concerned member states through the CTIS procedure (approval obtained on 31 May 2023; EU CT number 2022-502703-30-00). It has also been registered at the ClinicalTrials.gov database (NCT05701241). The study will be carried out in accordance with the protocol, with Clinical Trials Regulation No 536/2014 with principles enunciated in the current version of the Declaration of Helsinki and the guidelines of GCP issued by the International Conference on Harmonisation. The first patient was enrolled in July 2023, and the study will remain open for inclusion until July 2027.

Monitoring, quality assurance and safety considerations

A trial management group will oversee daily management, and alongside the steering committee ensure good governance of this trial. This trial may undergo internal or external monitoring, auditing or inspections to ensure compliance with good clinical practice, protocol, eligibility criteria, proper implementation, informed consent procedures and data verification. Furthermore, adequate reporting of AEs, SAEs and suspected unexpected serious adverse reactions (SUSARs) will be monitored and graded using the Common Terminology Criteria for Adverse Events (CTCAE) V.5.0, and reported to the Regulatory Authority and Ethics Committee according to national regulations. All reported or observed grade 3 or more AEs, SAEs or SUSARs will be recorded in the eCRF and will be monitored throughout the treatment phase until resolution or stabilisation, with appropriate medical intervention if required. Only related SAEs need reporting until 42 days after the last SSA administration or until the start of a new treatment. The PI assesses the grade of the (S)AE/SUSAR and its relatedness to SSA. The sponsor will submit an annual safety report to all Member States (via Clinical Trials Information System) regarding the safety of the investigated product.

Dissemination

This trial aims to evaluate the impact of SSA on PFS and TTD of QoL in second-line therapy alongside PRRT (with ^{177}Lu-DOTATATE) or targeted therapy (with everolimus or sunitinib) in patients with advanced, non-functional GEP NET with progression under first-line SSA. According to the current literature, no trial has specifically studied these endpoints, and the current international guidelines provide insufficient support in this area. Therefore, this trial has the potential to change the treatment paradigm for these patients. The results will be disseminated through multiple channels: they will be published in peer-reviewed international journals, presented at international conferences and scientific meetings for clinicians and researchers and communicated to patients via patient organisations and their NET physicians.

Author affiliations
[1]Department of Medical Oncology - NETwerk, University Hospital Antwerp, Edegem, Flanders, Belgium
[2]Integrated Personalized and Precision Oncology Network (IPPON) – Center for Oncological Research (CORE), University of Antwerp, Antwerp, Flanders, Belgium
[3]Department of Internal Medicine, Section of Endocrinology, Erasmus MC Cancer Center, Rotterdam, Netherlands
[4]Centre for Health Economics Research and Modelling Infectious Diseases (CHERMID), University of Antwerp, Antwerp, Flanders, Belgium
[5]Department of Gastroenterology, Cliniques universitaires Saint-Luc, Brussels, Belgium
[6]Department of Internal Medicine, Maxima Medical Centre, Veldhoven, Netherlands
[7]Nuclear Medicine, University Hospitals Leuven, Leuven, Flanders, Belgium
[8]Department of Public Health, Erasmus MC Cancer Center, Rotterdam, Netherlands
[9]Clinical Trial Center (CTC), University Hospital Antwerp, Edegem, Flanders, Belgium
[10]Clinical Research Center (CRC), University Hospital Antwerp, Edegem, Flanders, Belgium
[11]Department of Medical Oncology, University Medical Centre Groningen, Groningen, Netherlands

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Collaborators SAUNA investigators and the Dutch Belgian Neuroendocrine Tumor Society (DBNETS).

Contributors SC and JK contributed equally, and drafted the manuscript and contributed in the conceptualisation and design of the trial and research protocol. PB, SH and SP conceptualised and designed the health technology assessment part, and reviewed the research protocol and manuscript. ER conceptualised and designed the statistical analyses, and contributed in the conceptualisation and design of the trial and research protocol, and reviewed the manuscript. IB, WD, CMD, ES, IV and AW contributed in the conceptualisation and design of the trial and research protocol, and reviewed the manuscript. IVdM, WWdH (national coordinator) and MP conceptualised and designed the trial and research protocol; coordinated funding, regulatory permission and approval processes; and reviewed the manuscript. JH (steering committee chair) and TV (chief investigator and guarantor) contributed equally; they conceptualised and designed the trial and research protocol; coordinated funding, regulatory permission and approval processes; and reviewed the manuscript. SAUNA investigators and DBNETS contributed in the conceptualisation and design of the trial and research protocol.

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ORCID iDs
Jelka Kuiper http://orcid.org/0009-0003-3169-2599
Elke Smits http://orcid.org/0000-0002-8129-2193
Wouter W de Herder http://orcid.org/0000-0003-1463-5165

REFERENCES

1 Chauhan A, Kohn E, Del Rivero J. Neuroendocrine Tumors-Less Well Known, Often Misunderstood, and Rapidly Growing in Incidence. *JAMA Oncol* 2020;6:21–2.
2 Dasari A, Shen C, Halperin D, *et al*. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. *JAMA Oncol* 2017;3:1335–42.
3 Rindi G, Mete O, Uccella S, *et al*. Overview of the 2022 WHO Classification of Neuroendocrine Neoplasms. *Endocr Pathol* 2022;33:115–54.
4 Low SK, Giannis D, Bahaie NS, *et al*. Competing Mortality in Patients With Neuroendocrine Tumors. *Am J Clin Oncol* 2019;42:668–74.
5 Poleé IN, Hermans BCM, van der Zwan JM, *et al*. Long-term survival in patients with gastroenteropancreatic neuroendocrine neoplasms: A population-based study. *Eur J Cancer* 2022;172:252–63.
6 White BE, Rous B, Chandrakumaran K, *et al*. Incidence and survival of neuroendocrine neoplasia in England 1995-2018: A retrospective, population-based study. *Lancet Reg Health Eur* 2022;23:100510.
7 Hofland J, Kaltsas G, de Herder WW. Advances in the Diagnosis and Management of Well-Differentiated Neuroendocrine Neoplasms. *Endocr Rev* 2020;41:371–403.
8 Fröjd C, Larsson G, Lampic C, *et al*. Health related quality of life and psychosocial function among patients with carcinoid tumours. A longitudinal, prospective, and comparative study. *Health Qual Life Outcomes* 2007;5:18.
9 Beaumont JL, Cella D, Phan AT, *et al*. Comparison of health-related quality of life in patients with neuroendocrine tumors with quality of life in the general US population. *Pancreas* 2012;41:461–6.
10 Stueven AK, Kayser A, Wetz C, *et al*. Somatostatin Analogues in the Treatment of Neuroendocrine Tumors: Past, Present and Future. *Int J Mol Sci* 2019;20:3049.
11 Rinke A, Müller H-H, Schade-Brittinger C, *et al*. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with

metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. *J Clin Oncol* 2009;27:4656–63.
12 Caplin ME, Pavel M, Ćwikła JB, *et al*. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med* 2014;371:224–33.
13 Agency EM. SANDOSTATIN lar and associated names - summary of product characteristics. EMA; 2022.
14 Somatuline autogel 60, 90, and 120 mg, solution for injection in a pre-filled syringe. Summary of Product Characteristics for Belgium; 2022.
15 Somatuline autogel 60, 90, and 120 mg, solution for injection in a pre-filled syringe. Summary of Product Characteristics for the Netherlands; 2019.
16 Pavel M, O"Toole D, Costa F, *et al*. ENETS Consensus Guidelines Update for the Management of Distant Metastatic Disease of Intestinal, Pancreatic, Bronchial Neuroendocrine Neoplasms (NEN) and NEN of Unknown Primary Site. *Neuroendocrinology* 2016;103:172–85.
17 Pavel M, Öberg K, Falconi M, *et al*. Gastroenteropancreatic neuroendocrine neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2020;31:844–60.
18 Strosberg JR, Halfdanarson TR, Bellizzi AM, *et al*. The North American Neuroendocrine Tumor Society Consensus Guidelines for Surveillance and Medical Management of Midgut Neuroendocrine Tumors. *Pancreas* 2017;46:707–14.
19 Raymond E, Kulke MH, Qin S, *et al*. Efficacy and Safety of Sunitinib in Patients with Well-Differentiated Pancreatic Neuroendocrine Tumours. *Neuroendocrinology* 2018;107:237–45.
20 Yao JC, Fazio N, Singh S, *et al*. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. *The Lancet* 2016;387:968–77.
21 Yao JC, Shah MH, Ito T, *et al*. Everolimus for advanced pancreatic neuroendocrine tumors. *N Engl J Med* 2011;364:514–23.
22 Pavel ME, Hainsworth JD, Baudin E, *et al*. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. *Lancet* 2011;378:2005–12.
23 Grozinsky-Glasberg S, Davar J, Hofland J, *et al*. European Neuroendocrine Tumor Society (ENETS) 2022 Guidance Paper for Carcinoid Syndrome and Carcinoid Heart Disease. *J Neuroendocrinol* 2022;34:e13146.
24 Hofland J, Falconi M, Christ E, *et al*. European Neuroendocrine Tumor Society 2023 guidance paper for functioning pancreatic neuroendocrine tumour syndromes. *J Neuroendocrinol* 2023;35:e13318.
25 Strosberg J, El-Haddad G, Wolin E, *et al*. Phase 3 Trial of. *N Engl J Med* 2017;376:125–35.
26 Ruszniewski P, CwiklaJ, Lombard-BohasC, *et al*. Quality of life, tumour heterogeneity and biomarker levels in patients with progressive pancreatic or midgut neuroendocrine tumours: baseline data from clarinet forte. 17th Annual ENETS Concerence (2020) ENETS; 2020.
27 Yordanova A, Wicharz MM, Mayer K, *et al*. The Role of Adding Somatostatin Analogues to Peptide Receptor Radionuclide Therapy as a Combination and Maintenance Therapy. *Clin Cancer Res* 2018;24:4672–9.
28 Kulke MH, Ruszniewski P, Van Cutsem E, *et al*. A randomized, open-label, phase 2 study of everolimus in combination with pasireotide LAR or everolimus alone in advanced, well-differentiated, progressive pancreatic neuroendocrine tumors: COOPERATE-2 trial. *Ann Oncol* 2019;30:1846.
29 Shah MH, Lombard-Bohas C, Ito T, *et al*. Everolimus in patients with advanced pancreatic neuroendocrine tumors (pNET): Impact of somatostatin analog use on progression-free survival in the RADIANT-3 trial. *JCO* 2011;29:4010.
30 Faggiano A, Di Maio S, Mocerino C, *et al*. Therapeutic sequences in patients with grade 1-2 neuroendocrine tumors (NET): an observational multicenter study from the ELIOS group. *Endocrine* 2019;66:417–24.
31 Shimoyama R, Hijioka S, Mizuno N, *et al*. Study protocol for a multi-institutional randomized phase III study comparing combined everolimus plus lanreotide therapy and everolimus monotherapy in patients with unresectable or recurrent gastroenteropancreatic neuroendocrine tumors; Japan Clinical Oncology Group Study JCOG1901 (STARTER-NET study). *Pancreatology* 2020;20:1183–8.
32 AGITG. Cessation of somatostatin analogues after prrt in mid, hind-gut and pancreatic neuroendocrine tumours (STOPNET). ClinicalTrials.gov; 2025. Available: https://clinicaltrials.gov/study/NCT06345079
33 Eisenhauer EA, Therasse P, Bogaerts J, *et al*. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228–47.
34 Strosberg J, Wolin E, Chasen B, *et al*. Health-Related Quality of Life in Patients With Progressive Midgut Neuroendocrine Tumors Treated With ^{177}Lu-Dotatate in the Phase III NETTER-1 Trial. *J Clin Oncol* 2018;36:2578–84.
35 Agency EM. Afinitor, inn-everolimus - summary of product characteristics. EMA; 2019.
36 Agency EM. Sutent, inn-sunitinib - summary of product characteristics. EMA; 2016.
37 Agency EM. Lutathera, INN-lutetium (177Lu) oxodotreotide - SUMMARY OF PRODUCT CHARACTERISTICS. EMA; 2017.
38 M Versteegh M, M Vermeulen K, M A A Evers S, *et al*. Dutch Tariff for the Five-Level Version of EQ-5D. *Value Health* 2016;19:343–52.
39 Cleemput I, Neyt M, Sande S, *et al*. Belgian guidelines for economic evaluations and budget impact analyses. 2015.
40 Bouwmans C, Krol M, Severens H, *et al*. The iMTA Productivity Cost Questionnaire: A Standardized Instrument for Measuring and Valuing Health-Related Productivity Losses. *Value Health* 2015;18:753–8.
41 Van Roijen LH, Van Der LindenN, Bouwmans C, *et al*. Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg. 2016.
42 Erasmus University Rotterdam iPaHRG. Manual iMTA Medical Cost Questionnaire (iMCQ). Rotterdam iMTA; 2018.
43 Erasmus University Rotterdam iPaHRG. Manual of the iMTA Productivity Cost Questionnaire (iPCQ). Rotterdam iMTA; 2018.
44 Strosberg J, Krenning E. 177Lu-Dotatate for Midgut Neuroendocrine Tumors. *N Engl J Med* 2017;376:1391–2.
45 Cleemput I, NeytM, Van de sandeS, *et al*. *Belgian guidelines for economic evaluations and budget impact analyses*. 2nd edn. KCE, 2015.
46 Fenwick E, O'Brien BJ, Briggs A. Cost-effectiveness acceptability curves--facts, fallacies and frequently asked questions. *Health Econ* 2004;13:405–15.
47 Gomes M, Ng ES-W, Grieve R, *et al*. Developing appropriate methods for cost-effectiveness analysis of cluster randomized trials. *Med Decis Making* 2012;32:350–61.
48 RoijenL, LindenN, Bouwmans C, *et al*. Kostenhandleiding: methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg. 2016.
49 Stinnett AA, Mullahy J. Net health benefits: a new framework for the analysis of uncertainty in cost-effectiveness analysis. *Med Decis Making* 1998;18:S68–80.
50 Rizopoulos D. JM: An R Package for the Joint Modelling of Longitudinal and Time-to-Event Data. *J Stat Softw* 2010;35:1–33.