pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Lutetium Lu 177 dotatate (Lutathera) for Gastroenteropancreatic Neuroendocrine Tumors

August 1, 2019

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The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories with the exception of Quebec, which does not participate in pCODR at this time.

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LIST OF ABBREVIATIONS

AAA	Advanced Accelerator Applications
AEs	Adverse events
BICR	Blinded independent central review
CGP	Clinical Guidance Panel
CI	Confidence intervals
CR	Complete response
CT	Computed tomography
DLT	Dose limiting toxicity
DOR	Duration of response
EMA	European Medicines Agency
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
FDA	U.S. Food and Drug Administration
GI-NET-21	Gastrointestinal-Neuroendocrine-21 Questionnaire
GEP-NETs	Gastroenteropancreatic neuroendocrine tumours
GI-NET	Gastrointestinal tract neuroendocrine tumours
HR	Hazard ratio
HRQoL	Health-related quality of life
ITT	Intention-to-treat
KM	Kaplan Meier
LAR	Long acting repeatable
^{177}Lu	lutetium-177
MAA	Marketing authorization application
MCID	Minimal clinically important difference
MRI	Magnetic resonance imaging
NDA	New drug application
NICE	National Institute for Health and Care Excellence
OS	Overall survival
P-NET	Pancreatic neuroendocrine tumours
pCODR	pan-Canadian Oncology Drug Review
PR	Partial response
pERC	pCODR Expert Review Committee
ORR	Objective response rate
OS	Overall survival
PFS	Progression-free survival
QLQ-C30	Quality of Life Questionnaire C30
RECIST	Response Evaluation Criteria in Solid Tumors
RCT	Randomized controlled trial
SAP	Statistical analysis plan
SAE	Serious adverse event
TRAEs	Treatment-related adverse events
TTD	Time-to-deterioration
TTP	Time-to-progression

1 GUIDANCE IN BRIEF

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding lutetium-177 (^{177}Lu-Dotatate) for gastroenteropancreatic neuroendocrine tumors (GEP-NETs), The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the CADTH website (www.cadth.ca/pcodr).

This Clinical Guidance is based on: a systematic review of the literature regarding lutetium-177 ^{177}Lu-Dotatate for GEP-NETs conducted by the Gastrointestinal Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; input from Registered Clinicians; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. A background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on lutetium-177 ^{177}Lu-Dotatate for GEP-NETs, and a summary of submitted Provincial Advisory Group Input on lutetium-177 ^{177}Lu-Dotatate for GEP-NETs and are provided in Sections 2, 3, and 4, respectively.

1.1 Introduction

The purpose of this review is to evaluate the efficacy and safety of lutetium-177 ^{177}Lu-Dotatate (Lutathera) for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut, and hindgut neuroendocrine tumors in adults whose disease has progressed and is unresectable.

Lutetium-177 ^{177}Lu-Dotatate (Lutathera) was issued the notice of compliance from Health Canada in January 2019 and is indicated for the treatment of unresectable or metastatic, well-differentiated, somatostatin receptor-positive GEP-NETs in adults with progressive disease. The recommended dose in adults is 7.4 GBq (200 mCi) as an intravenous infusion over 30 minutes every 8 weeks for a total of 4 doses.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

One clinical trial was identified that met the eligibility criteria of the pCODR systematic review. NETTER-1 is an ongoing, open-label, randomized, multicentre (41 centres), international (eight countries) phase 3 trial that evaluated the efficacy and safety of ^{177}Lu-Dotatate compared to high-dose octreotide long-acting repeatable (LAR) in patients with advanced, progressive, somatostatin-receptor positive GEP-NETs of the midgut (defined as the jejunoileum and proximal colon).[1] The trial was funded by the manufacturer, Advanced Accelerator Applications (AAA), who also jointly designed and oversaw conduct of the trial in collaboration with trial authors.

The primary endpoint of NETTER-1 was progression-free survival (PFS) by blinded independent central review (BICR). Key secondary outcomes included objective response rate (ORR), time-to-progression (TTP), duration of response (DOR), overall survival (OS), health-related quality of life (HRQoL) and safety.

Eligible patients were randomized in a 1:1 ratio to receive ^{177}Lu-Dotatate or high-dose octreotide LAR using a centralized randomization scheme that was stratified by somatostatin receptor scintigraphy (OctreoScan) tumour uptake score (grade 2, 3 and 4),

and by length of time patients had been on a constant dose of octreotide (≤ 6 months versus > 6 months).

Treatment with ^{177}Lu-Dotatate consisted of four administrations at a dose of 7.4 GBq (200 mCi) infused intravenously over a 30 minute period every eight weeks, equating to a cumulative radioactivity of 29.6 GBq [800 mCi], unless unacceptable toxicities occurred, centrally confirmed progression was present on imaging, or the patient was unable or unwilling to adhere to trial procedures, withdrawal of consent or patient death. In addition to ^{177}Lu-Dotatate, patients in the experimental group received best supportive care with octreotide LAR, which was administered intramuscularly 24 hours (30 mg) after each ^{177}Lu-Dotatate infusion and then monthly after completion of all four infusions. Patients treated with ^{177}Lu-Dotatate also received intravenous amino acid solution administered concomitantly for renal protection. In the control group, patients received high-dose (60 mg) octreotide LAR intramuscularly every four weeks. In both treatment groups patients continued the four-week interval administrations of octreotide LAR until the primary outcome was reached or until 72 weeks from randomization after the primary outcome was reached, unless patients progressed or died. Patients in both treatment groups were also permitted to receive rescue injections of subcutaneous octreotide for hormonal symptoms associated with carcinoid syndrome. Patient crossover was not permitted per protocol; however, for ethical reasons patients who had progressed were free to receive other available treatments outside of the trial, which included ^{177}Lu-Dotatate. For details on the specific eligibility criteria used in the trial refer to Table 4 in Section 6 of this report.

There were a total of 229 patients randomized into the NETTER-1 trial. The median age of patients was approximately 64 years and most trial patients were white (82%), had a mean Karnofsky performance status score of approximately 88%, primary tumours located in the ileum (73%), and presented with metastases in the liver (83%), lymph nodes (62%), or both (typically in the mesentery or retroperitoneum). The majority of patients in both treatment groups had tumours considered low grade by the Ki67 proliferation index (66% in the ^{177}Lu-Dotatate group, and 72% in the control group) and highest grade in terms of uptake of tumour somatostatin radiotracer (grade 4: 61% in the ^{177}Lu-Dotatate group, and 59% in the control group). Most patients had undergone prior surgical resection (80% in ^{177}Lu-Dotatate group, 82% in control group); and a significant proportion of patients had received systemic therapy other than somatostatin analogue therapy (41% in ^{177}Lu-Dotatate group, 45% in control group). In the last 12 weeks prior to trial enrolment, the most recent constant dose of octreotide LAR received by patients was 30 mg (3-4 week intervals) in both treatment groups (94% in each group).

Limitations

The NETTER-1 trial had several limitations, which mainly stemmed from issues with trial conduct and data collection, and inappropriate data analysis approaches. These limitations were considered significant in terms of their potential to affect the internal validity of the trial and prompted reanalyses of the NETTER-1 trial data that incorporated data corrections, more rigorous approaches of analysis and multiple sensitivity analyses. The reanalyses performed, however, confirmed the validity of the highly statistically significant large effect size that was obtained for the primary outcome at the primary analysis with ^{177}Lu-Dotatate relative to control therapy with octreotide LAR. The magnitude of treatment benefit in the ITT population was observed across all patient subgroups examined. The secondary efficacy outcomes examined in the trial also demonstrated the superiority of ^{177}Lu-Dotatate compared with control therapy. Notwithstanding the magnitude of treatment benefit observed with ^{177}Lu-Dotatate in the trial, consideration should be given to the following limitations when interpreting the results of the trial:

- The trial limited enrollment to patients with GEP-NETS of the midgut and did not evaluate the efficacy of ^{177}Lu-Dotatate in patients with other GI-NET tumours (foregut, hindgut) and other GEP-NET tumour locations (pancreas, lung). Refer to Sections 7 and 8 of this report for a summary of the evidence on the use of ^{177}Lu-Dotatate in other tumour locations.
- The dose of octreotide LAR used in the control group (60 mg) is not consistent with the approved dose in Canada, which is 30 mg. Whether the dose of octreotide control therapy affects the relative magnitude of the treatment benefit observed with ^{177}Lu-Dotatate is unclear.
- It's possible that the use of an open-label trial design, where patients were aware of their treatment assignment, influenced the reporting of HRQoL outcomes in favour of the experimental treatment group. Additional limitations of the HRQoL analysis include a lack of adjustment for multiple testing which raises the possibility of type 1 error for the HRQoL outcomes assessed in the trial; uncertainty related to the clinical significance of some of the statistically significant results; and concerns over the reliability of the estimates obtained given the small numbers of patients at risk in both treatment groups for the majority of time points (across domain scales).

Outcomes

The efficacy outcomes in the NETTER-1 trial are summarized in Table 1.

Table 1: Highlights of key outcomes in the NETTER-1 trial.

Outcomes	Netter-1 Treatment Groups			
	^{177}Lu-Dotatate n=116	Control n=113	^{177}Lu-Dotatate n=116	Control n=113
	Primary Trial Publication[1]		CSR version 2.0[2]	
Analysis data cut-off date	July 24, 2015		July 24, 2015	
Median follow-up, months	9.2	5.5	9.2	5.5
Primary efficacy outcome				
PFS by BICR				
Median in months (95% CI)	Not reached	8.4 (5.8-9.1)	Not reached	8.5 (5.8-9.1)
HR (95% CI); p-value	0.21 (0.13-0.33); 0.001		0.18 (0.11-0.29); <0.0001	
Secondary efficacy outcomes				
ORR by BICR - ITT				
n	NR		15	4
% (95% CI)			15 (7.8-21.6)	4 (0.2-7.8)
p-value			0.0141	
DOR				
Median, months (95% CI)	Not reached	1.9 (1.9-NE)	Not reached	1.9 (1.9-NE)
Time-to-progression by BICR				
Median, months (95% CI)	NR		Not reached	8.7 (6.0-11.1)
HR (95% CI)			0.14 (0.08-0.24)	
OS				
Median, months (95% CI)	NR	NR	Not reached	27.4 (20.1-NE)
HR (95% CI); p-value	0.40 (0.21-0.77); 0.004		0.46 (0.25-0.83); 0.0083	
Updated OS analysis data cut-off date	NA		July 30, 2016[2,3]	
Medium follow-up, months			14.4	6.0
Median, months (95% CI)			Not reached	27.4 (23.1-NE)
HR (95% CI)			0.54 (0.33-0.86)[4]	
Harms[1]				
AE grade ≥3	46 (41)		36 (33)	
AE (any grade)	106 (95)		95 (86)	
TRAE	95 (86)		34 (31)	
SAE	29 (26)		26 (24)	
WDAE	7 (6)		10 (9)	

Abbreviations: AE - adverse events; **BICR** - blinded independent central review; **CI** confidence interval; **CR** - complete response; **DOR** - duration of response; **HR** - hazard ratio; **ITT** - intent-to-treat; **NA** - not applicable; **NE** - not estimable; **NR** - not reported; **OS** - overall survival; **PFS** - disease-free survival; **PR** - partial response; **SAE** - serious adverse events; **TRAE** = treatment-related adverse event; **WDAE** = withdrawal due to adverse events.

Notes:
[a] - The ORR was defined as the percentage of patients who had a response according to RECIST (sum of CR and PR). Patients for whom no post-baseline CT or MRI or central response data were available (n=15 in ^{177}Lu-Dotatate groups and 13 patients in the control group) were excluded from the analysis of ORR (trial is still ongoing).
* Unstratified HR < 1.00 favours treatment with ^{177}Lu Dotatate.

Primary Efficacy Outcome - PFS by BICR

Based on the trial publication,[1] at the time of the primary efficacy analysis a total of 91 PFS events had occurred in the trial; 23 in the ^{177}Lu-Dotatate group and 68 in the control group. Median PFS had not been reached in the ^{177}Lu-Dotatate group and was 8.4 months (95% CI, 50.0-76.8) in the control group. The HR for PFS by BICR was 0.21 (95% CI, 0.13-0.33; p<0.001), which indicated a statistically significant improvement in PFS (or a 79% reduction in the risk of a PFS event) in the ^{177}Lu-Dotatate group compared to the control group. Correcting for data errors had a limited impact on the HR (HR=0.18, 95% CI, 0.11-0.29; p; <0.0001)[2], and the results remained statistically significant in favour of treatment with ^{177}Lu-Dotatate compared to control therapy. The results of exploratory subgroup analyses performed by baseline characteristics demonstrated a consistent treatment benefit in favour of ^{177}Lu-Dotatate compared to control, where the magnitude of HRs (treatment effect) ranged from 0.14-0.24, with no upper bounds of associated CIs crossing unity.

Secondary Efficacy Outcomes

Based on the primary outcome obtaining statistical significance at the primary analysis, the secondary outcomes ORR and OS were formally and sequentially tested (Table 1).

At the primary efficacy analysis (interim OS analysis), and prior to data corrections, an HR of 0.40 (95% CI, 0.21-0.77; p=0.004) was obtained that did not reach the level of statistical significance pre-specified by the O'Brien-Fleming alpha spending boundary (p=0.0085%).[1] A corrected interim analysis of OS produced an HR of 0.46 (95% CI, 0.25-0.83; p<0.0083) based on 48 deaths; 17 and 31 in the ^{177}Lu-Dotatate and control groups, respectively.[2] An updated exploratory analysis of OS was performed based on 71 deaths; median OS was still unreached in the ^{177}Lu-Dotatate group and was 27. 4 months in the control group (HR=0.54, 95% CI, 0.33-0.86).[3,4] The final analysis of OS is expected after 158 deaths have accrued.

The remaining secondary outcomes (DOR, TTP) were analyzed descriptively and therefore should be considered exploratory in nature (Table 1).

Health-related Quality of Life

HRQoL was assessed using the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ-C30) and the Gastrointestinal (GI)-NET-21, which is a module specific to NET-related symptoms.[5] Trial patients completed questionnaires at baseline and every 12 weeks until centrally confirmed progression or until a maximum of 72 weeks from randomization had elapsed. The primary objective of the HRQoL analysis was to compare between treatment groups the time-to-deterioration (TTD) in a particular domain scale, which was defined as the time from randomization to the first deterioration of ≥ 10 points compared with the baseline score for the domain. Compliance rates for patients completing questionnaires were reported as high (>80%) in both treatment groups for all assessment visits, and baseline domain scores appeared balanced between the treatment groups.

At the June 30, 2016 data cut-off date, TTD (≥ 10 points change compared with baseline score) was significantly longer in the 177Lu-Dotatate treatment group compared to control for domain scales including global health status, physical functioning, role functioning, diarrhea, pain, body image, disease-related worries, and fatigue (Figure 3); the statistically significant differences in median TTD between the treatment groups were as follows:[6]

- Global health status scale – 22.7 months (HR=0.41, 95% CI, 0.24-0.69; p<0.001)
- Physical functioning – 13.7 months (HR=0.52, 95% CI, 0.30-0.89; p=0.015)

- Role functioning – not estimable due to median not reached in the 177Lu-Dotatate group (HR=0.58, 95% CI, 0.35-0.96; p=0.03)
- Diarrhea - not estimable due to median not reached in either treatment group (HR=0.47, 95% CI, 0.26-0.85; p=0.011)
- Pain - 3.7 months (HR=0.57, 95% CI, 0.34-0.94; p=0.025)
- Body image - not estimable due to median not reached in control group (HR=0.43, 95% CI, 0.23-0.80; p=0.006)
- Disease-related worries – 5.8 months (HR=0.57, 95% CI, 0.36-0.91; p=0.018)
- Fatigue – 0.9 months (HR=0.62, 95% CI, 0.42-0.96; p=0.030)

There remaining scales showed no significant differences between the treatment groups. After adjustment for the influence of other important baseline factors in a covariate analysis, the impact of treatment remained statistically significant for the following scales: global health status, physical functioning, diarrhea, and body image.

Harms

The safety analysis included all patients who received at least one dose of study medication.[1]

Based on the primary analysis data cut-off date of July 24, 2015, adverse events (AEs) of any grade occurred in 95% of patients in the ^{177}Lu-Dotatate and 86% of patients in the control group. AEs judged by investigators to be related to study treatment occurred in higher frequency in the ^{177}Lu-Dotatate group at 86% versus 31% in the control group. Treatment-related SAEs were also higher in the ^{177}Lu-Dotatate group (9% versus 1% in the control group). Treatment discontinuation due to treatment-related AEs occurred in 5% of patients in the ^{177}Lu-Dotatate group compared to 0% in the control group. A total of 16 patients (7%) in the trial experienced a treatment-emergent AE leading to death; 7 (6%) occurred in the ^{177}Lu-Dotatate group and 9 (8%) in the control group; however, none of the deaths in either group were deemed related to study drug.[2]

The most common class of AEs observed in both treatment groups was gastrointestinal disorders (GI); however, the incidence of nausea and vomiting were significantly higher in patients treated with ^{177}Lu-Dotatate occurring in 59% and 47% of patients, respectively, versus 12% and 10% in control patients. The majority of these events were low grade in severity and were attributed to amino acid infusions administered concomitantly with ^{177}Lu-Dotatate. Other GI AEs including diarrhea (29%), abdominal pain (26%) and distension (13%) occurred with less frequency in the ^{177}Lu-Dotatate group and were not significantly different from the rates observed in the control group. Other common AEs in the ^{177}Lu-Dotatate group included fatigue/asthenia (40%), musculoskeletal pain (29%), thrombocytopenia (25%), lymphopenia (18%), decreased appetite (18%), headache (16%) and anemia (14%). With the exception of musculoskeletal pain, the frequency of these AEs was significantly higher in the ^{177}Lu-Dotatate group compared to the control group. Similarly, the incidence of grade 3-4 AEs was also higher in patients treated with ^{177}Lu-Dotatate (41%) compared with patients in the control group (33%). Of note, grade 3-4 hematologic events were only observed in the 177Lu-Dotatate group and included lymphopenia (9%), thrombocytopenia (2%), and neutropenia (1%). Myelodysplastic syndrome (MDS), an AE of special interest, was suspected in one patient with a history of monoclonal gammopathy who underwent bone marrow biopsy and had significant cytopenias consistent with MDS.

1.2.2 Additional Evidence

See Section 3, and Section 4 for a complete summary of patient advocacy group input, and Provincial Advisory Group (PAG) Input.

Patient Advocacy Group Input

Patient input indicated that fatigue, weakness and low energy levels had the most impact on patients' quality of life. When asked about aspects of the disease that are more important to control than others, the majority of respondents reported disease progression as the most important aspect.

Patient input indicated that current treatments address symptom control, but that they were slightly or not effective at stopping disease progression, shrinking/stopping tumour growth and preventing the spread to other organs. Patient input reported that the benefit of current treatments include temporarily slowing disease progression and control of symptoms. Patients who were treated with or are currently on treatment with the drug under review expressed that the biggest advantages of treatment with ^{177}Lu-Dotatate that they did *not* get from other treatments include slowing or stopping disease progression, tumour shrinkage, and improving quality of life and wellbeing. Patient input reported that access and travel time and costs were disadvantages to treatment with lutetium. Overall, the core patient values included a desire for treatments that reduce or stop disease progression, treatments that provide long-term disease free survival, greater treatment options, improved quality of life or wellbeing, and fewer side effects.

Provincial Advisory Group (PAG) Input

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Types of neuroendocrine tumours eligible for treatment, whether limited to gut NET
- Sequencing with tyrosine kinase inhibitors and somatostatin analogues
- Treatments after progression
- Use of other sources of lutetium

Economic factors:

- Resources, infrastructure and human, required to administer radiopharmaceutical
- Administration of first dose is inpatient (hospital admission), followed by outpatient administration for the remaining three doses

Registered Clinician Input

pCODR did not receive input from registered clinicians.

Summary of Supplemental Questions

Critical Appraisal of a manufacturer-submitted mixed treatment comparison (MTC) of the relative efficacy of ^{177}Lu-Dotatate versus other comparators in patients with progressed gastrointestinal tract NETs (GI-NETs)

In the absence of head-to-head trials comparing ^{177}Lu-Dotatate to other comparators (everolimus, octreotide) for the GI-NET subgroup, the submitter conducted an MTC comparing ^{177}Lu- Dotatate to other comparators including everolimus, sunitinib and best supportive care. The results demonstrated that there were no significant differences between ^{177}Lu-Dotatate and relevant comparators in terms of PFS and OS. The overall conclusions are limited because of the substantial heterogeneity in the studies and patient characteristics among the included studies as well as the number of assumptions made in the analysis. Given these limitations, the comparative efficacy of ^{177}Lu- Dotatate to other treatments is uncertain. See section 7.1 for more information.

Critical Appraisal of a manufacturer-submitted matching adjusted indirect comparison (MAIC) of the relative efficacy of ^{177}Lu-Dotatate versus other comparators in patients with progressed pancreatic NETs (P-NETs)

In the absence of head-to-head trials comparing ^{177}Lu- Dotatate to other comparators for the P-NET subgroup, such as everolimus, sunitinib and placebo, the submitter conducted an ITC in the form of a MAIC. After adjustment of baseline characteristics, this analysis demonstrated that ^{177}Lu- Dotatate was superior to everolimus, sunitinib and placebo in terms of OS and PFS. However, the overall conclusions of the ITC are limited because of substantial heterogeneity in the studies and patient characteristics among the included studies. Given these limitation, the comparative efficacy of ^{177}Lu- Dotatate to other treatments is uncertain. See section 7.2 for more information.

Comparison with Other Literature

The CGP identified the ERASMUS study as a relevant study, which evaluated the safety and efficacy of ^{177}Lu-dotatate in patients with somatostatin receptive positive GEP-NETS (i.e., not limited to midgut tumours) that included multiple tumour types. The objective response rate was 41.2% (95%CI, 37.2-45.2) and PFS 28.0 months (95%CI, 25.0-30.3). The investigators concluded that that ^{177}Lu-Dotatate were beneficial to patients with GEP-NETs. While the data from the ERASMUS trial indicates that ^{177}Lu-dotatate may be efficacious for multiple GEP-NET subtypes, the results should be interpreted with caution due to the many trial-related limitations.

See Section 8 for further details on the comparison with other literature section.

1.2.3 Factors Related to Generalizability of the Evidence

Table 2 addresses the generalizability of the evidence and an assessment of the limitations and sources of bias can be found in Sections 6.3.2.1a and 6.3.2.1b (regarding internal validity).

[Table 2]: Assessment of generalizability of evidence for ^{177}Lu-Dotatate (Lutathera) for GEP-NETs

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence
(NETTER-1 trial)[1]</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td>Population</td><td>Primary tumour location</td><td>The trial enrolled patients with locally advanced or metastatic, histologically confirmed and centrally verified, inoperable NETs of only the midgut. The reimbursement request includes other GEP-NETs including the foregut and hindgut. The ERASMUS trial included patients with broader NETs.</td><td>Are the results of the trial generalizable to other GEP-NETs including foregut and hindgut?</td><td>Yes, the results of the NETTER-1 trial are generalizable to primary tumour location beyond mid-gut to include foregut, and hindgut.</td></tr>
<tr><td>Population</td><td>Stage of disease</td><td>The trial did not limit eligibility by stage of disease; patients with advanced/metastatic unresectable NETs of the midgut were included.

The number (percentages) of patients in each disease stage were as follows[6]:
<table>
<tr><th>Disease stage, %</th><th>^{177}Lu n=116</th><th>Control n=113</th></tr>
<tr><td>IV</td><td>105 (91)</td><td>89 (79)</td></tr>
<tr><td>Other</td><td>4 (3)</td><td>11 (10)</td></tr>
</table>
Subgroup analyses were conducted by stage of disease, which produced the following treatment estimates[6]:
<table>
<tr><th>Disease stage</th><th>^{177}Lu versus Control, HR (95% CI)</th></tr>
<tr><td>IV</td><td>0.19 (0.11, 0.32)</td></tr>
<tr><td>Other</td><td>Not estimable</td></tr>
</table></td><td>Does stage limit the interpretation of the trial results with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?</td><td>No, the interpretation of the trial is not limited by stage of disease as long as they fit the criteria of advanced/metastatic or unresectable disease.</td></tr>
</table>

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence
(NETTER-1 trial)[1]</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td></td><td>Performance Status</td><td>The trial limited eligibility to patients with a Karnofsky performance status of at least 60. The percentages of patients in each performance status category at baseline were as follows[6]:

<table><tr><th>Karnofsky PS, %</th><th>^{177}Lu n=116</th><th>Control n=113</th></tr><tr><td>≤ 80</td><td>31 (27)</td><td>33 (29)</td></tr><tr><td>90</td><td>51 (44)</td><td>48 (42)</td></tr><tr><td>100</td><td>33 (28)</td><td>31 (27)</td></tr></table>
Subgroup analyses were conducted by performance status, which produced the following treatment estimates[6]:

<table><tr><th>Karnofsky PS category</th><th>^{177}Lu versus Control, HR (95% CI)</th></tr><tr><td>≤ 80</td><td>0.15 (0.07, 0.35)</td></tr><tr><td>90</td><td>0.16 (0.07, 0.34)</td></tr><tr><td>100</td><td>0.15 (0.05, 0.46)[4]</td></tr></table></td><td>Does performance status limit the interpretation of the trial results (efficacy or toxicity) with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?</td><td>The eligible patient population would be ECOG PS 0-2.</td></tr>
<tr><td></td><td>Age</td><td>The trial did not limit eligibility by patient age; the mean age of patients in the trial was approximately 64 years. The proportion of patients older than 65 years was approximately 49%.

Subgroup analyses were conducted by age group, which produced the following treatment estimates[6]:

<table><tr><th>Age group</th><th>^{177}Lu versus Control HR (95% CI)</th></tr><tr><td><65 years</td><td>0.22 (0.11, 0.43)</td></tr><tr><td>≥65 years</td><td>0.15 (0.07, 0.31)</td></tr></table></td><td>Does the age restriction in the trial limit the interpretation of the trial results with respect to the target population?</td><td>No, the results of the NETTER-1 trial are not limited by age.</td></tr>
</table>

Domain	Factor	Evidence (NETTER-1 trial)[1]	Generalizability Question	CGP Assessment of Generalizability
	Organ dysfunction	The trial excluded patients based on the following laboratory values at baseline (and subsequent treatment): • Serum creatinine level of >150 µmol per liter (1.7 mg per deciliter) or a creatinine clearance <50 ml per minute • Hemoglobin level <8.0 g per deciliter • White-cell count <2000 per cubic millimeter • Platelet count <75,000 per cubic millimeter • Total bilirubin >3 times ULN • Serum albumin level >3.0 g per deciliter, unless the prothrombin time is within the normal range • Uncontrolled diabetes mellitus as defined by a fasting blood glucose >2 ULN	Does the exclusion of patients with organ dysfunction limit the interpretation of the trial results with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?	Assessment of end-organ function is required for treatment eligibility. The exclusion criteria are appropriate as stated, and results would not be generalizable to patients with compromised end organ function (particularly hematologic and renal function).
	Metastatic Sites	The trial included patients with metastases but excluded patients with known brain metastases unless treated and stabilized for at least 24 weeks prior to randomization.	Did the exclusion of patients with certain sites of metastatic disease limit the interpretation of the trial results with respect to the target population (e.g., Canadian clinical practice, patients without the factor, etc.)?	The exclusion of patients with untreated and/or uncontrolled brain metastases is appropriate and would not be generalizable to this patient population.
	Ethnicity or Demographics	The trial was conducted in in the US (59% of patients) and Europe (41%). The demographics of included patients were as follows:	Are the demographics in the trial similar to the Canadian setting?	The demographics are consistent with the demographics that would be observed in Canada.

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence (NETTER-1 trial)[1]</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>Race, n (%)</td><td>^{177}Lu n=116</td><td>Control n=113</td></tr>
<tr><td>Caucasian/White</td><td>92 (79)</td><td>96 (85)</td></tr>
<tr><td>Black or African American</td><td>5 (4)</td><td>5 (4)</td></tr>
<tr><td>Asian</td><td>1 (1)</td><td>0</td></tr>
<tr><td>Hispanic</td><td>6 (5)</td><td>2 (2)</td></tr>
<tr><td>Other</td><td>0</td><td>1 (1)</td></tr>
<tr><td>Not available</td><td>12 (10)</td><td>9 (8)</td></tr>
</table>
</td><td></td><td></td></tr>
<tr><td></td><td>Biomarkers</td><td>The trial included patients who were somatostatin receptor positive.

Somatostatin receptor positivity was determined on the basis of the lesion that had the highest update of radiotracer observed on planar somatostatin receptor scintigraphy (OctreoScan) within 24 weeks before randomization.</td><td>Is the biomarker an effect modifier (i.e., differences in effect based on biomarker status)? Are the results of the trial applicable to all subgroups equally? Is there a substantial group of patients excluded from the trial to whom the results could be generalized?</td><td>Somatostatin receptor positivity is a predictive biomarker and the results would not be generalized to patients who were excluded with SSR negative disease.</td></tr>
</table>

<table>
<tr><th>Domain</th><th>Factor</th><th>Evidence
(NETTER-1 trial)[1]</th><th>Generalizability Question</th><th>CGP Assessment of Generalizability</th></tr>
<tr><td></td><td>Well-differentiated, moderately differentiated histologic features,
- Ki67 < 20%</td><td>The trial included patients with a Ki67 proliferative index of ≤ 20% at baseline, with 0-2% considered low grade 1 and 3-20% considered intermediate grade 2[1].

<table><tr><th>Ki67 index - grade , n (%)</th><th>^{177}Lu n=116</th><th>Control n=113</th></tr><tr><td>0-2%, grade 1</td><td>76 (66)</td><td>81 (72)</td></tr><tr><td>3-20%, grade 2</td><td>40 (35)</td><td>32 (28)</td></tr></table>
Subgroup analyses were conducted by Ki67 index, which produced the following treatment estimates:

<table><tr><th>Age group</th><th>^{177}Lu versus Control HR (95% CI)</th></tr><tr><td>0-2%, grade 1</td><td>0.19 (0.10, 0.36)</td></tr><tr><td>3-20%, grade 2</td><td>0.15 (0.07, 0.34)</td></tr></table></td><td></td><td>The results of the trial are not generalizable to patients with poorly-differentiated neuroendocrine carcinoma (NEC). The results are generalizable for well to moderately differentiated disease, and for Ki67 greater than 20% in well-differentiated disease.</td></tr>
<tr><td></td><td>Line of therapy</td><td>^{177}Lu-Dotatate was evaluated as second-line treatment in patients who had progressed while receiving an uninterrupted dose of octreotide LAR (20-30 mg every 3-4 weeks for at least 12 weeks before randomization).</td><td>Are the results of the trial generalizable to other lines of therapy?</td><td>The results are generalizable to second-line therapy and beyond, and would not be limited to second line therapy alone.</td></tr>
<tr><td></td><td>Administration of intervention</td><td>^{177}Lu-Dotatate was administered at 7.4 GBq (200 mCi) IV infused over 30 minutes for four infusions every 8 weeks for a total cumulative radioactivity of 29.6 GBq (800 mCi); and combined with BSC consisting of octreotide LAR IM 30 mg, 24 hours after each infusion of ^{177}Lu-Dotatate, then monthly after completion of the four infusions.</td><td>Are the results of the trial generalizable to a different dose or administration schedule?</td><td>No, results are not generalizable to a different dose or schedule.</td></tr>
</table>

Domain	Factor	Evidence (NETTER-1 trial)[1]	Generalizability Question	CGP Assessment of Generalizability
Comparator	Standard of Care	The comparator intervention was high-dose octreotide LAR administered IM 60 mg every 4 weeks. PAG input noted that octreotide LAR is funded. Sunitinib and everolimus is funded in all provinces for P-NET. Everolimus is funded for GI-NET.	Was the comparator in the trial a standard of care in Canada?	While not the only option, SSA dose-escalation is often employed as a treatment strategy in progressing disease, hence is an acceptable control and the results would be applicable in the Canadian setting.
Outcomes	Appropriateness of Primary and Secondary Outcomes	The primary outcome was PFS by BICR. Secondary outcomes included ORR, DOR, OS, TTP, and HRQOL.	Were the primary and secondary outcomes appropriate for the trial design?	Yes, PFS as a primary endpoint is appropriate in NET disease given the long follow-up required for OS. This is a widely accepted primary endpoint in this setting. The secondeary outcomes are appropriate.
Setting	Countries participating in the Trial	The trial was conducted in the following countries (% of patients): US (59), UK (10), France (9), Germany (7), Italy (6), Spain (5), Belgium (3), and Portugal (<1).[7]	If the trial was conducted in other countries, is there any known difference in the practice pattern between those countries and Canada? Differences in the patterns of care might impact the clinical outcomes or the resources used to achieve the outcomes.	Yes, the results obtained in other countries in this trial are generalizable to the Canadian population.
	Location of the participating centres	The trial was primarily conducted in academic centres (with the exception of a few participating sites that included a limited number of patients)[6]	If the trial was conducted only in academic centres are the results applicable in the community setting?	Yes, the results obtained in the academic setting are generalizable to broader settings with infrastructure with radiopharmaceuticals.
	Supportive medications, procedures, or care	For renal protection, IV amino acid solution (Aminosyn II 10% [21.0 g of lysine and 20.4 g of arginine in 2 liters of	Are the supportive medications, procedures, or care	There are no differences in the supportive medications, procedures or care given in the

Domain	Factor	Evidence (NETTER-1 trial)[1]	Generalizability Question	CGP Assessment of Generalizability
		solution] or VAMIN-18 [18 g of lysine and 22.6 g of arginine in 2 liters of solution]) was administered concomitantly for at least 4 hours, starting 30 minutes before infusions of ^{177}Lu-Dotatate. In both treatment groups patients were permitted to receive subcutaneous rescue injections of octreotide in the event of hormonal symptoms (diarrhea, flushing) associated with carcinoid syndrome.	used with the intervention in the trial the same as those used in Canadian clinical practice?	trial compared to Canadian practice would not affect the generalizability of the trial results.

1.2.4 Interpretation

^{177}Lu-Dotatate (Lutathera^{TM})is indicated for the treatment of unresectable or metastatic, well-differentiated, somatostatin receptor-positive GEP-NETs in adults with progressive disease.

Burden of Illness and Need

NET is an uncommon malignancy. In Canada, specific cancer statistics are not reported for NETs as they are most often included with the statistics based on where the primary tumour was located. Data from the Ontario Cancer Registry indicates that the incidence of NETs among adult patients increased from 2.48 to 5.86 per 100,000 per year from 1994 to 2009, with metastatic disease documented in 20.8% at presentation and developing subsequent to diagnosis in an additional 38%.[8]

NETs most commonly arise in the gastrointestinal tract (48%), lung (25%) and pancreas (9%) and may also be classified by embryologic site of origin as follows: foregut (thymus, esophagus, lung, stomach, duodenum, pancreas), midgut (appendix, ileum, cecum, ascending colon) and hindgut (distal bowel and rectum). They may be functional or non-functional depending upon their hormone-secreting status. NETs are further classified into low-grade (G1), intermediate-grade (G2), and high-grade (G3) categories based upon mitotic count and proliferative index (Ki-67). Additionally, over 90 percent of GEP-NETs have high concentrations of somatostatin receptors (SSR-positive) and can be imaged using a radiolabeled form of the somatostatin analog octreotide (111-In pentetreotide [OctreoScan]) or, more recently by PET-based Gallium Ga-68 DOTATATE with a greater sensitivity.

In a US NCI SEER database study of NETs diagnosed between 2000 and 2012, the median survival for patients with well to intermediate grade pancreatic NETs was 50 months, and for well-intermediate grade small intestinal NETs, median survival was 103 months.[9] As such, patients may live with advanced disease which progresses over time and is ultimately incurable. The current accepted clinical practice in Canada is summarized in the Clinical Background Information Section (Section 2) of this report and includes locoregional therapies, somatostatin analogies (octreotide LAR and lanreotide autogel), everolimus (funded across Canada for pancreatic NET and in selected provinces for GI NETs), and chemotherapy (most commonly capecitabine/temozolomide for pancreatic NETs). There is a continued need for more efficacious and better tolerated therapies. Input from the Patient Advocacy Group emphasizes the unmet need for therapies which control NET disease progression.

Effectiveness

For patients with somatostatin-receptor-positive (SSR+) GEP-NETs that are progressive despite standard therapy, the use of peptide radioreceptor radionuclide therapy (PRRT) has emerged as a meaningful therapeutic option.

The ERASMUS single-institution non-randomized phase I/II experience of 1,214 patients with SSR+ GEP-NETs and bronchial NETs treated from January 2000 to December 2012 with ^{177}Lu- Dotatate demonstrated the feasibility, efficacy and tolerability of PRRT in progressing NETs.

The most compelling evidence of the efficacy of PRRT comes from the NETTER- 1 study[1] ,an open label, multicentre, international phase 3 trial conducted at 41 centres in 8 countries including the US, UK, Belgium, France, Germany, Italy, Portugal, and Spain. Eligible patients had inoperable, locally advanced or metastatic GEP-NETs of the midgut (defined as the jejunoileum and the proximal colon), and met the following key eligibility criteria:

- Disease progression with octreotide LAR (20 to 30 mg every 3 to 4 weeks)
- Karnofsky performance status of at least 60; (equivalent to ECOG PS 0-2)
- Well-differentiated histologic tumour features, defined as a Ki67 index of 20% or less;
- Somatostatin receptors present on all target lesions observed on somatostatin receptor scintigraphy (OctreoScan).

229 eligible patients were randomized to a control arm of dose-escalated octreotide LAR 60mg every 4 weeks versus an interventional arm of ^{177}Lu-Dotatate x 4 administrations at a dose of 7.4 GBq (200 mCi) infused intravenously over a 30 minute period every eight weeks, plus best supportive care with octreotide LAR 30mg every 4 weeks.

The primary outcome was PFS by blinded independent central review (BICR). The HR for PFS by BICR was 0.21 (95% CI, 0.13-0.33; p<0.001) in the ^{177}Lu-Dotatate group compared to the control group. This HR represents a very clinically meaningful improvement in PFS. The exploratory subgroup analyses performed by baseline characteristics demonstrated a consistent treatment benefit in favour of ^{177}Lu-Dotatate compared to control. Secondary endpoints included overall response rate (ORR) and overall survival (OS). ORR at the primary efficacy analysis was 15% (95% CI, 7.8-21.6) vs 4% (95% CI, 0.2-7.8) favouring the ^{177}Lu-Dotatate arm (p=0.0141). The updated, exploratory analysis of OS was performed based 71 deaths demonstrated OS was still unreached in the ^{177}Lu-Dotatate group and was 27.4 months in the control group (HR=0.54, 95% CI, 0.33-0.86). The final analysis of OS is expected after 158 deaths have accrued. While a number of limitations were identified with the trial conduct, data collection and data analysis approaches, the magnitude of benefit supersedes the limitations. These limitations were considered significant in terms of their potential to affect the internal validity of the trial and prompted reanalyses of the NETTER-1 trial data that incorporated data corrections, more rigorous approaches of analysis and multiple sensitivity analyses. However, the reanalyses performed confirmed the validity of the highly statistically significant large effect size that was obtained for the primary outcome at the primary analysis with ^{177}Lu-Dotatate relative to control therapy with octreotide LAR.

HRQoL was assessed in NETTER-1 using time to deterioration (TTD) defined as time from randomization to first deterioration ≥10 points (on a 100-point scale). For the primary analysis, TTD was significantly longer in the ^{177}Lu-Dotatate group compared to control for the following domains: global health status, physical functioning, role functioning, diarrhea, pain, body image, disease-related worries, and fatigue. There were no domains in which TTD analysis showed a benefit for the control arm.

Safety

The rate of serious adverse events was similar in both groups:26% in ^{177}Lu-Dotatate vs 24% in control. Any grade treatment-related adverse events were 86% in the ^{177}Lu-Dotatate group and 31% in the control group (p<0.001) – these included grade 1 or 2 nausea, vomiting, thrombocytopenia, lymphopenia, fatigue, decreased appetite and anorexia. No differences were observed in any grade AEs. The rates of any grade 3/4 AEs was higher in the177Lu group by 8% (41% versus 33%); and grade 3/4 lymphopenia was 9% in ^{177}Lu--Dotatate group compared to 0% in control. There was a 6% withdrawal rate due to adverse

events observed in the ^{177}Lu-Dotatate group versus 9% in control; and the withdrawal rates due to treatment-related AEs were 5% in 177Lu group compared to 0% in control. Overall, treatment with ^{177}Lu-Dotatate was generally well tolerated with manageable toxicities.

The ERASMUS study reported myelodysplastic syndrome for 17 (1.4%) of the 1,214 patients.

Additional Considerations:

- While the NETTER-1 study limited eligibility to midgut GI NETs, the CGP supports extrapolation to patients with foregut and hindgut SSR+ well-differentiated NETs who have progressed on prior therapy. ^{177}Lu- Dotatate is a directed therapy based on SSR+; extrapolation is supported by the lack of rationale that there would be a differential benefit in SSR+ disease based on anatomic site, and by the data from the ERASMUS study.
- While the NETTER-1 study limited eligibility to prior progression on octreotide LAR 30mg q4 week therapy, the CGP supports extrapolation to prior therapy with octreotide LAR at higher doses, prior therapy with lanreotide autogel, and more than one prior therapy including an SSA and everolimus.
- Therapeutic options post ^{177}Lu-Dotatate therapy will depend upon prior therapy received. Patients previously treated with SSA therapy alone would be eligible for consideration of subsequent therapy with everolimus and/or sunitinib or cytotoxic chemotherapy if pancreatic NETs.
- A maintenance dose of octreotide LAR 30mg was administered every 4 weeks in the ^{177}Lu-Dotatate arm, with a 6-week interval break prior to PRRT. In clinical practice, it is anticipated that maintenance octreotide LAR 30mg (or lanreotide 120mg autogel) would be administered during PRRT per the NETTER-1 protocol.
- The CGP agrees that the implementation of PRRT in Canada will likely include selected, high-volume academic cancer centres with the appropriate expertise and multidisciplinary support.
- The CGP recommends that SSR-positivity should be determined by either Gallium Ga-68 DOTATATE imaging or 111-In pentetreotide (OctreoScan) imaging.
- Re-treatment with lutetium may be an option depending upon the degree of response and eligibility for treatment (e.g., based on SSTR-avidity, renal and hematologic function)

1.3 Conclusions

The Clinical Guidance Panel concludes that there is a net overall clinical benefit with the use of ^{177}Lu-Dotatate (LUTATHERA™) for the treatment of unresectable or metastatic, well-differentiated, somatostatin receptor-positive GEP-NETs in adults with progressive disease compared to octreotide LAR.

• **Effectiveness:** NETTER-1 is a multicentre, international phase 3 trial demonstrating a significant and very meaningful improvement in PFS (HR 0.21, $p<0.001$) with ^{177}Lu-Dotatate in progressive, SSR+ well-differentiated GEP-NETs. The CGP concludes that this is compelling evidence of efficacy in a selected patient population based upon a predictive imaging biomarker.

It is noted that the eligible patient population includes patients with well-differentiated SSR+ disease with adequate marrow and renal reserve, ECOG PS 0-2, who have progressed

on prior SSA therapy. The CGP concludes that the eligible patient population can be extrapolated to include foregut, hindgut and midgut primaries. This is based on SSR+ and extrapolation is supported by the lack of rationale that there would be a differential benefit in SSR+ disease based on anatomic site. The CGP also concludes that this therapy may be offered beyond second-line therapy (includes patients who have progressed on an SSA and everolimus therapy).

The CGP recognize that it is difficult to interpret the efficacy and safety results from the single-arm, non-randomized study design of the ERASMUS study. However, despite the level of evidence provided in the ERASMUS study in the broader GEP-NET population, the results appear to be consistent with the results from the midgut population in the NETTER-1 study.

• **Safety:** Treatment with ^{177}Lu-Dotatate was well-tolerated and the most frequent adverse events were hematologic and expected.

• **Need**: The input from the patient advocacy group acknowledges a need for more efficacious therapies that offer prolonged disease control.

2 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Gastrointestinal Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

2.1 Description of the Condition

Neuroendocrine tumors (NETs) are an uncommon heterogeneous group of malignant neoplasms that arise from neuroendocrine cells which are distributed widely throughout the body. They most commonly arise in the gastrointestinal tract (48%), lung (25%) and pancreas (9%), but may also rarely develop in many other organs, including the breast, prostate, thymus and skin. NETs may also be classified by embryologic site of origin as follows: foregut (thymus, esophagus, lung, stomach, duodenum, pancreas), midgut (appendix, ileum, cecum, ascending colon) and hindgut (distal bowel and rectum).

In Canada, specific cancer statistics are not reported for NETs as they are most often included with the statistics based on where the primary tumour was located. Data from the Ontario Cancer Registry indicates that the incidence of NETs among adult patients increased from 2.48 to 5.86 per 100,000 per year from 1994 to 2009, with metastatic disease documented in 20.8% at presentation and developing subsequent to diagnosis in an additional 38%. Incidence was observed to increase significantly after the age of 50, peaking after the age of 70 years.[10]

NETs are characterized by generally indolent but heterogeneous biology and variable clinical behavior, as driven by tumour differentiation, mitotic count and Ki-67 proliferative index. This complexity, in combination with their relative rarity has required a multidisciplinary management approach for NETs, and attention to clinical practice guidelines based upon expert consensus opinion, and best available evidence.

2.2 Accepted Clinical Practice

An evidence-based Canadian Consensus Guideline on the management of gastrointestinal neuroendocrine tumours was published by S. Singh et al in 2016[8] and reflects the currently accepted therapeutic approaches in the management of NETs. As neuroendocrine cells can have the capability to produce biologically active hormones such as serotonin, a proportion of NETs are termed ‘functioning; based upon clinical symptoms from secreted hormones. The majority of NETs are non-functional. Over 90 percent of GastroEnteroPancreatic-NETs (GEP-NETs) have high concentrations of somatostatin receptors (SSR-positive) and can be imaged using a radiolabeled form of the somatostatin analog octreotide (111-In pentetreotide) or, more recently by PET-based Gallium Ga-68 DOTATATE with a greater sensitivity.

Locoregional therapy: cytoreductive surgery, ablative therapy and liver-directed embolotherapy may be considered in selected patients with metastatic disease with symptom control and disease control benefit.

Systemic therapy:

Somatostatin analogues (SSAs) are the mainstay of therapy for the management of secretory NETs, and also have confirmed anti-proliferative activity in well to moderately differentiated advanced NETs with randomized trial evidence of progression free survival (PFS) benefit for octreotide LAR (PROMID study) and lanreotide autogel (CLARINET study).

Targeted therapies are currently used in the management of advanced NETs either post-progression with SSAs and include everolimus (mTOR inhibitor), which has been evaluated in randomized trials with a net PFS benefit observed in the RADIANT-4 trial in patients with non-secretory lung or GI-NETs. Everolimus and sunitinib also have demonstrated PFS benefit in advanced pancreatic NETs.[11,12]

Cytotoxic chemotherapy is rarely employed for GI-NETs, but may be considered for pancreatic NETs with a fluoropyrimidine and alkylator combination, most typically administered as the CAPTEM (capecitabine and temozolomide) regimen.[13]

Peptide receptor radionuclide therapy (PRRT):

^{177}Lu-Dotatate employs ^{177}Lu-labelled high-affinity octreotate. For patients with somatostatin-receptor (SSR)-positive GI-NETs that are progressive despite standard-dose long-acting SSA, the use of 177Lu in mid-gut, SSR-positive NETS is supported by the phase III NETTER-1 trial (6). This trial compared 177Lu delivered concurrently with standard dose (30 mg) octreotide LAR every 4 weeks to high dose (60 mg) octreotide LAR for patients with disease progression on standard dose octreotide LAR. The primary end-point was PFS. At the data-cut-off date for the primary analysis, the estimated rate of PFS at month 20 was 65.2% (95% CI, 50.0 to 76.8) in the 177Lu group and 10.8% (95% CI, 3.5 to 23.0) in the control group. The objective response rate (ORR) was 18% versus 3% ($P<0.001$). In the planned interim analysis of overall survival, 14 deaths occurred in the ^{177}Lu-Dotatate group and 26 in the control group ($P = 0.004$). Grade 3 or 4 neutropenia, thrombocytopenia, and lymphopenia occurred in 1%, 2%, and 9%, respectively, of patients in the ^{177}Lu group.

Access to PRRT in Canada has been limited to a small number of treatment centres, most notably the Cross Cancer Centre in Edmonton, Alberta. In British Columbia, PRRT may be considered in well to moderately differentiated SSR-positive advanced NETs with progressive disease despite octreotide LAR therapy.[14]

2.3 Evidence-Based Considerations for a Funding Population

^{177}Lu-Dotatate is recommended for consideration for the treatment of SSR-positive, well to moderately differentiated advanced neuroendocrine tumours which have progressed or failed prior SSA therapy.

2.4 Other Patient Populations in Whom the Drug May Be Used

While NETTER-1 was limited to well-differentiated GI-NETs arising from the mid-gut, it may be clinically reasonable to consider ^{177}Lu-Dotatate for NETs arising from the foregut or hindgut as well.

3 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient group, Carcinoid Neuroendocrine Tumour Society of Canada (CNETS Canada), provided input from patients with GEPNETs. CNETS Canada used an online questionnaire using Survey Monkey and conducted telephone interviews to collect both qualitative and quantitative information on patient experience. The online survey was open from July 10, 2018 to July 30, 2018, and contained a combination of multiple choice, rating and open-ended questions; most questions were provided with the option of 'other'. Telephone interviews were conducted from July 16, 2018 to July 20, 2018. Patients who completed the telephone interviews did so either because they did not have access to a computer, or because they wanted to describe their experience with lutetium. The online survey was promoted on the CNETS Canada website, CNETS Facebook page and Facebook closed support group. Patients were also invited to participate in one-on-one telephone interviews to provide impact statements through the same methods of promotion. Some patients participated in both the online survey and a telephone interview; these patients were counted only once. Survey and interview responses were confidential and anonymous. CNETS Canada received feedback from patients with 69 GEP-NETs, including 53 patients who were treated or are currently being treated with lutetium. Demographic information on the 69 respondents is summarized below.

Demographics:

- **69** patients with GEP-NETs provided input to CNETS Canada's submission on lutetium**; 33%** of the patients had pancreatic NETs and **67%** of the patients had gastrointestinal NETs.
- **50%** were male and **50%** were female patients.
- **61** patients completed the online survey and **8** patients participated in telephone interviews.
- Age range of online survey respondents: 30-39 years (n=6), 40-49 years (n=8), 50-59 years (n=15), 60-69 years (n=21), 70-79 years (n=11) (range 33-77 years).
- Age range of telephone interview respondents: 60-69 years (n=5), 70-79years (n=3).
- **53** patients were treated or are currently being treated with lutetium.
- Respondents to the survey and interviews were from British Columbia (n=14), Saskatchewan (n=2), Alberta (n=7), Manitoba (n=1), Ontario (n=29), Quebec (n=8), Nova Scotia (n=2), New Brunswick (n=1), Newfoundland (n=1), and outside of Canada (n=4).

Respondents reported that fatigue and weakness as well as low energy levels had the most impact on their quality of life. When asked about aspects of the disease that were more important to control than others, almost all of the respondents to the online survey (96%) reported disease progression as the most important aspect to control.

Patients indicated that current treatments address symptom control, but that they were slightly or not effective at stopping disease progression, shrinking/stopping tumour growth and preventing the spread of disease to other organs. Respondents also reported that current treatments are associated with debilitating side effects and complications.

Patients who were treated with or are currently on treatment with lutetium expressed that the greatest advantages for treatment with lutetium that they did *not* get from other treatments included: slowing or stopping disease progression, tumour shrinkage, and an improved quality of life and wellbeing. The respondents who had experience with lutetium reported that the disadvantages of lutetium were related to access, travel time and costs. Overall, the core patient values included a desire for treatments that reduce or stop disease progression, treatments that provide long-term disease free survival, greater treatment options, improved quality of life or wellbeing, and fewer side effects.

Quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that are reported have also been reproduced as is according to the submission, without modification. Please see below for a summary of specific input received from CNETS Canada.

3.1 Condition and Current Therapy Information

3.1.1 Experiences Patients have with GEP-NETs

A background section about patients' experiences with the disease was provided by CNETS using the patient responses to a Global NET Patient Survey and is provided directly below. The subsequent sections reference patient responses to the CNETS online survey and telephone interviews

Background (Global NET Patient Survey)

The International Neuroendocrine Cancer Alliance (INCA) and Novartis Pharmaceuticals Corporation collaborated on the first Global Survey to gather data on the patient experience with NET. The goal of the Global NET Survey was to "increase understanding of the experiences, needs and challenges of NET patients, and to provide insights and learnings among countries and regions to advance NET care." In total, 1,928 NET patients responded to the survey worldwide. The survey found that quality of life was negatively affect in most patients with NET. The survey results showed that decreased energy levels and emotional health issues were very common among respondents. Patients also had to make necessary lifestyle changes around diet, physical activity, and spend more time and money on appointments. Their work life was also negatively affected; 80% of patients who were unemployed reported being unable to work due to their GEP-NET. Furthermore, 50% of working patients often missed work because of their disease.

The following section regarding the experiences of patients with GEP-NETs was completed using information from respondents of CNETS Canada's online survey only, and does not include any specific input from telephone respondents.

The majority of survey respondents reported a negative impact of GEP-NET on their quality of life. The 61 patients who completed the online survey were asked to rate how symptoms and the disease impacts their day-to-day life and overall quality of life on a scale of 1 (no impact) to 7 (extremely large impact). Patients rated fatigue and weakness as the symptom that had an extremely large impact on their quality of life. The weighted average ratings for "Impact of GEP-NET symptoms on quality of life" were as follows: fatigue/weakness (6.6), diarrhea (5.3), abdominal pain (4.8), flushing/rash (3.8), anxiety (4.9), and breathlessness (2.8). When evaluating the impact of the disease on their day-to-day life, patients rated decreased energy levels as having an extremely large impact on their quality of life. The weighted average ratings for "Impact of the disease on Quality of Life" were: energy (6.8), emotional (5.4), participation in leisure (5.0), social life (4.7), travel (4.3), ability to work (4.7), finances (3.9), and relationships (3.1).

Patients were also asked what aspects of the disease are more important to control than others. Most respondents (96%) indicated the most important aspect of their disease to control is disease progression, and 50% indicated fatigue as the second-most important aspect to control. Respondents also identified diarrhea (43%) and flushing (31%) as important aspects to control.

Patients indicated that they had used the following therapies and treatments: surgery (65%), somatostatin analogs (96%), liver embolization (27%), ablative techniques (10%),

chemotherapy (23%), and other treatment including biological therapies, radiation, and alternative therapies (26%).The majority of patients surveyed and interviewed described current treatments for symptom control (including bloating, diarrhea, constipation and energy levels) as being effective. The majority of patients described current treatments for the disease as slightly or not effective at stopping disease progression, shrinking/stopping tumour growth and preventing the spread to other organs.

Many patients indicated that current treatments only provided short-term benefits. Patients expressed the importance of having different treatment options. Patients also expressed anger, frustration and disappointment that Canada is so far behind Europe in approving Peptide Receptor Radionuclide Therapy (PRRT) treatment for NET cancer. Patients indicated that the biggest expectations for treatment with lutetium, that other treatments were not able to provide, were reducing/stopping disease progression, and shrinking/stopping tumour growth.

Patients were asked to describe challenges and benefits of current therapies. In terms of benefits, some patients reported that the treatments have helped temporarily slow disease progression and help control symptoms. In terms of challenges, patients indicated the treatments were associated with long recovery times, debilitating side effects, and complications (see comments below for challenges associated with specific treatments). None of the patients reported that the current therapies cured or stopped progression of their GEP-NET.

Below are quotes selected by CNETS Canada from the online survey and patient interviews related to patient experiences with currently available therapies.

"*Early in diagnosis - Sandostatin LAR reduced tumour size. Surgery to find primary but not successful in reduction of tumour around mesentery artery.*"

"Time frames for recovery from surgery were awful. Helped reduce tumour load but disease has progressed."

"Chemotherapy helped to stop the growth for a while. SA seems to help symptoms for a bit over a year."

"I have had three surgeries, bowel resection and two liver resection. The tumours reappeared and spread. I have been having Sandostatin Lar injections since 2014 which keeps carcinoid syndrome symptoms at bay."

"Surgery - most successful in removing some of the cancer but recovery can be lengthy Lanreotide - symptom control - side effects of bloating and cramping & expensive."

"Sandostatin has helped with reducing symptoms to a manageable level, but the cancer spread to my liver."

"Embolizations help, but only for a short period of time (1-3 months after treatment symptoms return)."

"I am now giving myself 6 octreotide needles every day which really impacts what I can accomplish daily. Low absorption of iron and other nutrients affects what I can do daily and how much I can socialize."

"Surgery and or Lanreotide took away the pain and bouts of diarrhea I had been experiencing before diagnosed."

"Limited long term benefits for each treatment, if any. Most recently I have had a 4th round of liver embolizations, which help with most symptoms for approx. 1-3 months after treatment, but symptoms always return. Its palliative treatment."

"Surgery for me was very important at the time of diagnosis. My bowel was in the process of obstructing. I had the tumour removed (Ileum) in Dec. 2015. It turn out to be a NETS tumour with mets to the right lobe of the liver. In March of 2016, I had a liver resection, where the right lobe of the liver was removed. Immediately after both surgeries, I felt so much better. I was put on Sandostatin, 30mg. every 28 days, then every 21 days, CT scans in the months following showed more NET tumours forming. Had I biopsy of a tumour on my ovaries. Turned out to be a NET.

3.1.2 Patients' Experiences with Current Therapy for GEP-NETs

Patients indicated that they had used the following therapies and treatments: surgery (65%), somatostatin analogs (96%), liver embolization (27%), ablative techniques (10%), chemotherapy (23%), and other treatment including biological therapies, radiation, and alternative therapies (26%).The majority of patients surveyed and interviewed described current treatments for symptom control (including bloating, diarrhea, constipation and energy levels) as being effective. The majority of patients described current treatments for the disease as slightly or not effective at stopping disease progression, shrinking/stopping tumour growth and preventing the spread to other organs.

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- "*Early in diagnosis - Sandostatin LAR reduced tumour size. Surgery to find primary but not successful in reduction of tumour around mesentery artery."*
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- *"Chemotherapy helped to stop the growth for a while. SA seems to help symptoms for a bit over a year."*
- *"I have had three surgeries, bowel resection and two liver resection. The tumours reappeared and spread. I have been having Sandostatin Lar injections since 2014 which keeps carcinoid syndrome symptoms at bay."*

- *"Surgery - most successful in removing some of the cancer but recovery can be lengthy Lanreotide - symptom control - side effects of bloating and cramping & expensive."*
- *"Sandostatin has helped with reducing symptoms to a manageable level, but the cancer spread to my liver."*
- *"Embolizations help, but only for a short period of time (1-3 months after treatment symptoms return)."*
- *"I am now giving myself 6 octreotide needles every day which really impacts what I can accomplish daily. Low absorption of iron and other nutrients affects what I can do daily and how much I can socialize."*
- *"Surgery and or Lanreotide took away the pain and bouts of diarrhea I had been experiencing before diagnosed."*
- *"Limited long term benefits for each treatment, if any. Most recently I have had a 4th round of liver embolizations, which help with most symptoms for approx. 1-3 months after treatment, but symptoms always return. Its palliative treatment."*
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3.1.3 Impact of GEP-NETs and Current Therapy on Caregivers

All respondents to CNETS Canada's online survey and telephone interviews were patients. No information was obtained from caregivers.

3.2 Information about the Drug Being Reviewed

3.2.1 Patient Expectations for and Experiences To Date with ^{177}Lu-Dotatate (Lutathera)

The 53 patients that were treated or currently being treated with lutetium were asked about what benefits they received from treatment with lutetium. Reduction in disease progression was reported by 48%, tumour shrinkage was reported by 46%, improved wellness by 43%, *"other"* by 39% and decrease in disease symptoms by 26%. There were 21 patients that chose *"other"* for benefits; 15 of these patients reported they had just started therapy and it was too early to see benefits. None of the patients reported that they did not derive any benefit from treatment with lutetium.

The same 53 patients were asked about what negative effects they experienced from treatment with lutetium. Patients reported increased diarrhea (8%), increased fatigue (57%), increased pain (9%), nausea/vomiting (23%), and other (28%). There were 15 patients that chose "other" for negative effects; 9 of these patients said they had no negative effects from the treatment, and five indicated side effects not listed: 2 (anemia), 1 (edema and weight gain), 1 (hair loss), 1 (shingles).

Patients were asked to describe the overall impact treatment with lutetium has had on their health and well-being. Many patients commented on the benefits of lutetium, and remarked on the increased amount of hope and improved quality of life they felt due to the treatment. CNETS Canada provided numerous quotes regarding the benefits of

lutetium. The following are select quotes provided to portray the optimism and positive impact patients experienced related to lutetium:

- *"Massive impact it gave me more time to live, improved quality of life, happiness and overall gratefulness."*
- *"Tremendous impact. I have a new life. I now feel like I simply live, like so many others, with a chronic condition. I adapt and enjoy each day as it comes to its fullest potential for me."*
- *"It provided a huge mental lift that finally I could get some effective treatment here in Ontario that has been commonly available elsewhere in the world. It also appears to have stunted the growth of most of my tumours."*
- *"Tumours have stayed stable. I feel blessed that I qualified for this treatment as soon as the study became available in London, ON. I am still having treatment every 6 months with no progression of disease. Enjoying good quality of life."*
- *"Positive impact due to decrease in tumours along with very few side effects compared to chemo!"*
- *"Feeling hopeful. Previously had disease progression on 2 types of chemo."*

Having experienced such positive effects due to lutetium, some patients remarked on the stress of wondering about future treatments and whether lutetium might remain an available option.

- *"Taking this treatment has given me hope and relieved anxiety that there is no hope. Due to shrinkage and no new growth there is hope. Any side effects have been worth the results. Other trials have more than 4 treatments and have ongoing or multiple "maintenance" treatments afterwards. I only received 4 but because there has been positive results I wonder how and if in the future I can receive more to keep improving and keep the cancer from growing and spreading. Obviously if this works why would I not want to continue to receive it in the future."*
- *"I am sure it has prolonged my life. I have had 10 treatments and qualify for 2 more. I am worried about what will happen when my treatments are done."*

Patients also remarked on the reduced impact of side effects, and that the results experienced due to lutetium outweighed any side effects that were experienced.

- *"The impact with Lutetium on me has been amazing. I haven't felt this good since prior to diagnosis. My symptoms of diarrhea, night sweats and flushing have diminished. The pressure from where the some of the tumours were located are gone! In fact, I know it sounds almost impossible, however, I had extreme pressure over my ovaries where 2 of the NETs tumours where located, prior to PRRT treatment, in day 2 of my first treatment, the pressure on my ovaries was gone! Continued to feel better after each treatment. I am so fortunate to be able to get into the PRRT programme, I wish everyone who needs this treatment ,would be able to have it done. Thank you."*
- *"The 6 treatment stabilized my disease. It made me feel a lot better and reduced the symptoms of the disease significantly."*
- *"Treatment one- initially loss of appetite, and diarrhea for first 2 weeks. Now less flushing, less redness, better ability to function."*
- *"Some of my pain that I used to have has now improved, and I don't seem to be getting so many fevers."*
- *"Luckily for me, I was diagnosed before I had any symptoms other than extreme fatigue and low iron. So I don't perceive any impact, for better or worse, except for the couple of days after treatment. My tumors seem to be stable, so I would say that the overall impact is progression free survival."*

- *"The most beneficial treatment I have undergone has been PRRT. With minimal side effects, primarily fatigue, I have seen a 90%+ reduction in the size of my tumours."*

One patient mentioned that despite the benefits of lutetium treatment, there was difficulty related to travel costs to receive lutetium. *"The treatment has had a positive impact on my health. The cost of the travel has had a negative impact on our finances."*

In addition, 94% of patients (50 of 53) who were treated or currently on treatment with lutetium reported that they accessed the treatment through a clinical trial. Three patients reported that they were "*forced to go out of country and pay out of pocket"* when they did not qualify for a trial.

All patients treated with or on treatment with lutetium reported that they were able to tolerate or manage the side effects of the treatment, having little or no impact on their quality of life. Patients also expressed that the treatment was far easier than the lengthy recovery from surgery (ablative, debulking, resection) or the debilitating side effects from chemotherapy.

It was reported that PRRT/lutetium treatment is not considered as a first line therapy and is generally used after surgery for ablative techniques, radiation therapy, liver directed therapies, chemotherapy, somatostatin analog therapies, and biologically targeted therapies. Many patients surveyed and interviewed also expressed disappointment that lutetium treatment was not offered earlier in their disease, but as a last resort, when the disease had progressed.

Approximately 40% of patients (21 of 53) who were treated with or are currently on treatment with lutetium reported that the biggest disadvantages were: limited access, having to travel out of province/territory, and the costs associated with travel.

Below are patient statements about the disadvantages of lutetium, which were not about the treatment itself, but around access to the treatment:

- *"Challenge: travelling for PRRT since I have a child."*
- *"Travel to obtain PRRT is a challenge and expensive."*
- *"Treatments are 2 hours away from home.*
- *"The only difficulty is I have to travel from Toronto to Quebec City to receive the treatments."*
- *"PRRT not available in BC. Have to go other state for treatment."*
- *"I travel to Edmonton so travel and hotel costs are a huge issue."*

3.3 Additional Information

<u>Information about a companion diagnostic test submitted by CNETS:</u>

CNETS stated that the companion diagnostic test to lutetium treatment is the Ga68 PET scan. Although this is a submission for lutetium, CNETS Canada has been extensively advocating for access to the Ga68 Scan as a standard of care in diagnosing GEP-NET cancer. The advantages of the Ga68 PET scan over Octreoscan include higher resolution images, detection of smaller lesions, better guidance to treatment and dosing, exposure to less radiation, greater efficiency, cost effectiveness, access and patient convenience since it involves a two to three hour procedure. Currently the only access to the Ga68 PET scan is through clinical trials. CNETS Canada produced a one page document on the Ga68 PET scan

and access in Canada: https://cnetscanada.org/wp-content/uploads/2017/05/Why-Ga68-For-NET-Patients-3.pdf

Other Additional Information submitted by CNETS Canada

CNETS Canada indicated that they have been advocates for access to peptide receptor radionuclide therapy (PRRT)/lutetium for several years. As such, many of the calls they receive (30%) from their patient support line are for GEP-NET treatment information. Of these calls, 83% of patients inquired about lutetium treatment and ways to access the treatment. CNETS indicated that progress on accessing PRRT/lutetium treatment in Canada has been slow and has resulted in delays in access to lutetium by the GEP-NET patient community.

CNETS highlighted their continued support for NET research; they indicated they have been providing research grants since 2010 made possible through private donations. Through consultations with the NET patient community and input from CNETS Canada's Scientific and Medical Advisory Board (SMAB), in 2016, CNETS determined that the highest ranking research priority was ^{177}Lutetium PRRT for NETs.

CNETS suggests that treatment with lutetium offers patients with benefits that greatly outweigh risks, and provided the following quote from a patient:

"PRRT has been a game changer for me. It has given me back my life. Prior to starting a PRRT spring 2017 in Edmonton, I felt that I was dying. Literally and figuratively. I am a realist and I did wonder whether I would make it to 2018. After my first PRRT treatment I felt the physical change. I felt stronger. This has just continued this past year and I feel in many ways better than I have felt in a decade. I still have fatigue and diarrhea sometimes but I have the emotional and physical well-being to just deal with it and move on. I am incredibly grateful for PRRT and the people and research that have brought this treatment to me. I am very concerned that it is not readily available for all Canadians. I was one of the lucky ones. I was accepted into treatment within months of the referral."

4 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website. PAG identifies factors that could affect the feasibility of implementing a funding recommendation.

Overall Summary

Input was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified the following as factors that could impact the implementation:

Clinical factors:

- Types of neuroendocrine tumours eligible for treatment, whether limited to gut NET
- Sequencing with tyrosine kinase inhibitors and somatostatin analogues
- Treatments after progression
- Use of other sources of lutetium

Economic factors:

- Resources, infrastructure and human, required to administer radiopharmaceutical
- Administration of first dose is inpatient (hospital admission), followed by outpatient administration for the remaining three doses

Please see below for more details.

4.1 Currently Funded Treatments

Sunitinib and everolimus are funded in all provinces, except for PEI, for pancreatic NET. Everolimus for NET of gastrointestinal and lung origin is funded in some provinces.

Octreotide LAR is funded in all provinces, except PEI. Lanreotide is listed on provincial drug formularies in some provinces. In most provinces, lanreotide is funded for treatment of acromegaly but not for NET.

4.2 Eligible Patient Population

PAG is seeking confirmation that lutetium would be for patients with advanced, progressive, somatostatin-receptor–positive midgut neuroendocrine tumors as in the trial. Clarity on the eligible patients and types of NET would facilitate implementation.

In the trial, eligibility was restricted to patients who progressed on octreotide LAR and patients could not have been treated with more than 30 mg of octreotide LAR at three or four week intervals within 12 weeks prior to randomization. PAG noted that some patients are being treated with octreotide LAR at 60mg.

PAG is seeking guidance on whether patients previously treated with lanreotide would be eligible or not for treatment with lutetium, noting that this may be out of scope of this review and a review of lanreotide for treatment of NET would be required for funding consideration.

PAG is seeking guidance on if and when re-treatment and re-challenge would be appropriate.

4.3 Implementation Factors

PAG noted that the oversight and funding of radiopharmaceuticals differ from province to province. In some provinces, patients may referred out of province to receive treatment with radiopharmaceuticals, where wait times and access could be issues.

PAG noted that radiopharmaceuticals would be procured by nuclear medicine programs and prepared by nuclear medicine technologists or radiopharmacists (nuclear medicine pharmacists). Radiopharmaceuticals would be administered by nuclear medicine experts in some centers and by radiation oncologists in other centres. PAG noted that administration of lutetium may be restricted to specialized centres that have the infrastructure to handle, prepare and administered lutetium in a safe manner. Additional resources and coordination of both nuclear medicine physician and medical oncologist are required for monitoring, which includes increased blood work monitoring.

Other implementation factors that need to be taken into consideration include amino acid solution and octreotide LAR that are administered with lutetium, additional imaging and inpatient hospital admission for the first dose. PAG also identified that the protocol is complex with the timing of administration of the amino acid solution and octreotide LAR.

For patients who are on more than 30mg of octreotide every three or four weeks, the doses of octreotide would likely be reduced when initiating lutetium. PAG is seeking confirmation of the maintenance dose of octreotide LAR.

4.4 Sequencing and Priority of Treatments

PAG is seeking information on the appropriate sequencing of somatostatin analogues and everolimus with lutetium. In addition, guidance on the appropriate treatments for patients who have progressed after treatment with lutetium would be helpful for implementation.

4.5 Companion Diagnostic Testing

PAG is seeking clarity on the need for a gallium-68 scan to identify the patients with the somatostatin receptors that may respond better to lutetium. It is not clear what the role of the scan would be in predicting positive outcomes with the lutetium.

4.6 Additional Information

PAG noted that there are other suppliers of lutetium, in addition to the manufacturer of the lutetium product under review at pCODR. PAG identified that a review of other lutetium products would be required for funding consideration.

5 SUMMARY OF REGISTERED CLINICIAN INPUT

pCODR did not receive input from registered clinicians.

6 SYSTEMATIC REVIEW

6.1 Objectives

The primary objective of the systematic review was to evaluate the efficacy and safety of lutetium-177 (^{177}Lu)-Dotatate (Lutathera) in adult patients with unresectable advanced or metastatic somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumours (GEP-NETs) of the foregut, midgut and hindgut.

Supplemental Questions and Comparison with Other Literature most relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined in section 7 and section 8.

- Critical Appraisal of a manufacturer-submitted mixed treatment comparison (MTC) of the relative efficacy of ^{177}Lu-Dotatate versus other comparators in patients with progressed GI-NETs
- Critical Appraisal of a manufacturer-submitted matching adjusted indirect comparison (MAIC) of the relative efficacy of ^{177}Lu-Dotatate versus other comparators in patients with progressed P-NETs
- Comparison to Other Literature: ERASMUS Study

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the CGP and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold. The literature search strategy and detailed methodology used by the pCODR Methods Team are provided in Appendix A.

Table 3: Trial Selection Criteria.

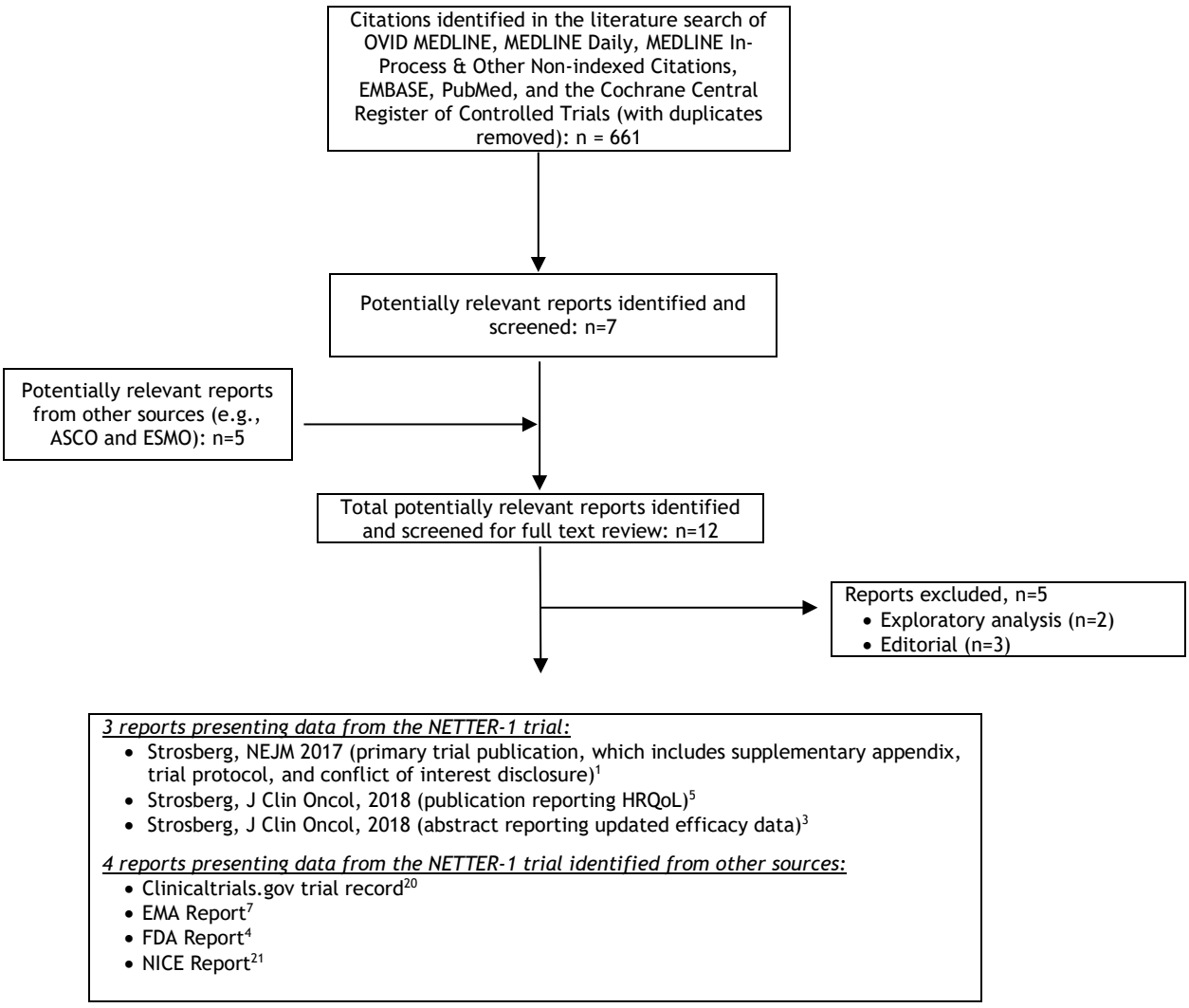
Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
• Published or unpublished RCTs	Adult patients with unresectable advanced or metastatic somatostatin receptor-positive GEP-NETs (foregut, midgut and hindgut) Subgroups of interest: • GI NETs • PNETs	• ^{177}Lu-Dotatate	• Somatostatin analogues including octreotide and lanreotide • Everolimus • Sunitinib • Capecitabine + temozolamide[a]	Primary: • PFS Secondary: • OS • ORR • HRQoL Safety: • AEs • SAE • WDAE • AEs of interest o Myelotoxicity o Renal toxicity o Transformation to leukemia, MDS o Nausea/vomiting
Abbreviations: AE(s) - adverse event(s); **GEP-NETs** - gastroenteropancreatic neuroendocrine tumours; **GI-NETs**- gastrointestinal neuroendocrine tumours; **HRQoL** - health-related quality of life; **MDS** - myelodisplastic syndrome; **ORR** - objective response rate; **OS** - overall survival; **PNETs** - pancreatic neuroendocrine tumours; **PFS** - progression-free survival; RCTs - randomized controlled trials; **SAE(s)** - serious adverse event(s); **WDAE** - withdrawals due to adverse event(s).				
Notes: * Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions). [a] For the treatment of PNETs.				

6.3 Results

6.3.1 Literature Search Results

Of the 661 potentially relevant reports identified, one clinical trial (NETTER-1) published in three separate reports,[1,3,5] was included in the pCODR systematic review (Figure 1). A total of five reports were excluded upon full-text review because they were exploratory analyses of the NETTER-1 trial not of interest to this review,[15,16] or were editorial in nature.[17-19] Four additional reports presenting data on the NETTER-1 trial were obtained from other sources.[4,7,20,21]

Figure 1: QUOROM Flow Diagram for Inclusion and Exclusion of Reports



Note: Additional data related to the NETTER-1 trial were also obtained from documents provided in the pCODR submission,[22] and through requests to the Submitter by pCODR [Checkpoint Meeting Responses,[6] Clinical Study Report,[2] Statistical Analysis Plan[23]]

6.3.2 Summary of Included Studies

One clinical trial was identified that met the eligibility criteria of the pCODR systematic review (Table 4); NETTER-1 is an ongoing, randomized, international, multicentre phase 3 trial that evaluates the efficacy and safety of ^{177}Lu-Dotatate compared to high-dose octreotide long-acting repeatable (LAR) in patients with advanced, progressive, somatostatin-receptor positive GEP-NETs of the midgut.[1] Details of the included NETTER-1 trial are summarized in Table 4.

6.3.2.1 Detailed Trial Characteristics

Table 4: Trial Characteristics of the Included NETTER-1 Trial.[1,5]

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
NETTER-1 Trial NCT01578239 2011-005049-11 Phase 3, open-label, central and stratified randomization, 1:1 ratio N randomized=229; N treated=221 41 centres (27 in Europe; 14 in US) in 8 countries including Belgium, France, Germany, Italy, Portugal, Spain, UK and US[7] Patient Enrolment Dates: September 2012 to January 2016 Data cut-off date for primary analysis: July 24, 2015 Final Analysis Date: February 2021[20] Funded by Advanced Accelerator Applications	<u>Key Inclusion Criteria:</u> • Locally advanced or metastatic, histologically confirmed and centrally verified, inoperable NETs of the midgut • Documented disease progression (RECIST version 1.1) on CT or MRI over the course of a 3-year period[7] while receiving an uninterrupted dose of octreotide LAR (20-30 mg every 3-4 weeks for at least 12 weeks before randomization) • Presence of somatostatin receptors on all target lesions documented by CT/MRI and confirmed by BICR[a] • Karnofsky PS score ≥60 • Well-differentiated tumours, defined as a Ki67 index of ≤20%[b] <u>Key Exclusion Criteria:</u> • Serum creatinine level of >150 µmol per liter (1.7 mg per deciliter) or a creatinine clearance <50 ml per minute[e] • Hemoglobin level <8.0 g per deciliter[e] • White-cell count <2000 per cubic millimeter[e] • Platelet count <75,000 per cubic millimeter[e] • Total bilirubin >3 times ULN[e] • Serum albumin level >3.0 g per deciliter, unless the prothrombin time is within the normal range[e] • Uncontrolled diabetes mellitus as defined by a fasting blood glucose >2 ULN[e] • Treatment with >30 mg of octreotide LAR within 12 weeks before randomization • Peptide receptor radionuclide therapy at any time before randomization	<u>Intervention:</u> • ^{177}Lu-Dotatate 7.4 GBq (200 mCi) IV infused over 30 minutes; four infusions every 8 weeks for a total cumulative radioactivity of 29.6 GBq (800 mCi); combined with BSC consisting of octreotide LAR IM 30 mg, 24 hours after each infusion of ^{177}Lu-Dotatate, then monthly after completion of the four infusions[c,d] <u>Control</u>: • Octreotide LAR IM 60 mg every 4 weeks[d] <u>Treatment Duration:</u> • In both groups, assigned octreotide treatment continued until disease progression, unacceptable toxicity, patient was unable/unwilling to comply with procedures, withdrawal of consent, or death.	<u>Primary:</u> • PFS by BICR <u>Secondary:</u> • ORR • DOR • TTP • OS • HRQoL (EORTC QLQ-30 and GI NET-21 module) • Safety

Trial Design	Inclusion Criteria	Intervention and Comparator	Trial Outcomes
	• Surgery, liver directed transarterial therapy, or chemotherapy within 12 weeks before randomization • Known brain metastases; unless treated and stabilized for at least 24 weeks prior to randomization[7]		

Abbreviations: **BICR** - blinded independent central review; **CT** - computed tomography; **EORTC QLQ** - European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; **HRQoL** - health-related quality of life; **IM** - intramuscular; **IV** - intravenous; **LAR** - long acting repeatable; **MRI** - magnetic resonance imaging; **NETs** - neuroendocrine tumours; **ORR** - objective response rate; **OS** - overall survival; **PFS** - progression-free survival; **PS** - performance status; **TTP** - time-to-progression; **ULN** - upper limit of the normal range.

Notes:
[a] - The degree of somatostatin receptor expression was determined on the basis of the lesion that had the highest update of radiotracer observed on planar somatostatin receptor scintigraphy (OctreoScan) within 24 weeks before randomization.
[b] - Ki67 index refers to the percentage of cells that are positive for Ki67 as determined by immunostaining of the primary tumour. Tumours were assessed as low-grade (lower rate of cell proliferation activity) if the Ki67 index was between 0-2%, intermediate grade the index was between 3-20% or high-grade if <20%.
[C] - For renal protection, IV amino acid solution (Aminosyn II 10% [21.0 g of lysine and 20.4 g of arginine in 2 liters of solution] or VAMIN-18 [18 g of lysine and 22.6 g of arginine in 2 liters of solution]) was administered concomitantly for at least 4 hours, starting 30 minutes before infusions of the radiopharmaceutical.
[d] - In both groups patients were permitted to receive subcutaneous rescue injections of octreotide in the event of hormonal symptoms (diarrhea, flushing) associated with carcinoid syndrome.
[e] - Exclusion criterion was applicable to all subsequent treatments, when the corresponding toxicity was not resolved and a relationship could not be excluded with either of the study drugs. In relation to renal function: patients were also excluded from further treatment in the case of >40% increase of serum creatinine over the baseline and a concomitant decrease of >40% in creatinine clearance (as calculated according to the Cockroft Gault method eventually confirmed by measured creatinine clearance or Glomerular Filtration Rate), if the corresponding toxicity had not resolved and a relationship could not be excluded with either of the study drugs. Criteria for dose modifying toxicity had to be verified, when applicable. All other exclusion criteria for enrollment eligibility were applicable to all subsequent treatments with no further restrictions.

a) Trial

NETTER-1 is an open label, multicentre, international phase 3 trial[1] conducted at 41 centres (27 in Europe; 14 in the United States [US]) in eight countries including the US, United Kingdom, Belgium, France, Germany, Italy, Portugal, and Spain.[7] Patients included in the trial were adult patients who had inoperable, locally advanced or metastatic GEP-NETs of the midgut (defined as the jejunoileum and the proximal colon), who met the following key eligibility criteria:

- Disease progression (RECIST version 1.1) on either computed tomography (CT) or magnetic resonance imaging (MRI) over a maximum period of three-years while receiving an uninterrupted dose of octreotide LAR (20 to 30 mg every three to four weeks) for at least 12 weeks before randomization;
- Karnofsky performance status of at least 60;
- Well-differentiated histologic tumour features, defined as a Ki67 index of 20% or less;
- Somatostatin receptors present on all target lesions (as confirmed by blinded independent central review [BICR]); degree of expression was determined by the lesion that had the highest uptake of radiotracer

observed on planar somatostatin receptor scintigraphy (OctreoScan) within 24 weeks before randomization.

- Patients treated with >30 mg of octreotide LAR within 12 weeks before randomization, or who had received peptide receptor radionuclide therapy at any time, were excluded.

For a more detailed list of the key eligibility criteria used in the trial, refer to Table 4.

Funding

The trial was funded by the manufacturer, Advanced Accelerator Applications (AAA), who also designed the trial in collaboration with two of the trial authors. Trial oversight, including monitoring, data collection and analyses, were performed by a clinical research organization. The trial manuscript was prepared by the trial authors and a medical writer hired by AAA.

Some trial authors disclosed potential conflicts of interest related to the study drug in the form of employment, shareholder status, or advisory board membership with the drug manufacturer AAA, or having received compensation in the form of grant funding, honoraria, consultancy fees, and possible royalties from patents.[1]

Outcomes and Disease Assessment

The primary endpoint of the NETTER-1 trial was progression-free survival (PFS) by blinded independent central review (BICR). Key secondary outcomes included objective response rate (ORR), time-to-progression (TTP), duration of response (DOR), overall survival (OS), health-related quality of life (HRQoL) and safety.

Disease assessment was performed every 12 weeks from the date of randomization until the primary endpoint was reached, or up to 76 weeks from randomization after the required number of PFS events in the trial was reached. After progression or week 76, patients proceeded to long-term follow-up with assessments performed every six months until the last randomized patient had completed five years of study from the date of randomization. Progressive disease (PD) was determined on CT or MRI imaging by BICR (RECIST).

Randomization, Sample Size and Statistical Analyses

Information on randomization, required sample size, statistical assumptions, and other indicators of trial quality are detailed in Table 5.

Randomization was implemented via an interactive web-based response system. Patients were randomized in a 1:1 ratio to receive ^{177}Lu-Dotatate or high-dose octreotide LAR using a centralized permuted block (block size of 4) randomization scheme that was stratified by somatostatin receptor scintigraphy (OctreoScan) tumour uptake score (grade 2, 3 and 4, on a scale where grade 0 is no uptake by tumour, and grade 4 is intense uptake by tumour) and by length of time patients had been on a constant dose of octreotide (≤ 6 months versus > 6 months).

The trial was originally designed to enroll 124 patients (74 PFS events) over a period of 18 months based on a median PFS of 30 months in the ^{177}Lu-Dotatate group and 14 months in the control group (Table 5). However, the protocol was amended to increase the sample size to 230 patients in order to enable sufficient power to formally test for a statistically significant difference in OS between the treatment groups (Table 5). A pre-specified interim analysis of OS was performed at the primary analysis of PFS, which utilized an O'Brien-Fleming α-spending function to control the type 1 error rate. The boundary set for statistical

significance of OS at the interim analysis was p=0.0085% (p=0.000085). As the NETTER-1 trial is ongoing, the final analysis of OS is planned after 158 deaths have been observed, or five years after the last patient was randomized, whichever occurs first.

A fixed sequence testing procedure was used in the trial to account for multiple testing of outcomes that included the primary outcome of PFS by BICR and secondary outcomes ORR and OS. The secondary outcomes were tested in a pre-determined order (ORR then OS) and only if the preceding outcome was statistically significant. No adjustments were made for all other outcomes analyzed in the trial, and therefore they should be interpreted as exploratory outcomes.

For all time-to-event outcomes median point estimates and 95% confidence intervals (CI) were estimated using Kaplan-Meier (KM) methodology and survival curves were compared using unstratified log-rank tests. Hazard ratios (HR) were estimated using an unstratified Cox proportional hazards model. ORR and corresponding 95% CI were calculated and compared between groups using Fisher's exact test. Subgroup analyses of the primary outcome were performed by stratification, patient and disease-related factors to examine the internal consistency of the treatment effect; these analyses were exploratory and uncontrolled for multiple testing. Sensitivity analyses were also conducted to assess the robustness of the trial results to different sources of bias (e.g., investigator assessment, PFS time calculated from baseline scan versus date of first drug administration, subsequent anti-tumour treatments).[23] The primary efficacy analysis was performed by intention-to-treat (ITT) and was based on a data cut-off date of July 24, 2015.

After the first marketing authorization application (MAA) and new drug application (NDA) were submitted by AAA in April of 2016, the European Medicines Agency (EMA) and United States Food and Drug Administration (FDA) requested additional (unplanned) efficacy analyses be performed to support the applications.[6] The statistical analysis plan (SAP) of the trial was amended to include post-hoc analyses that included an updated efficacy analysis of OS, subgroup analyses of OS, additional subgroup analyses of PFS, and a covariate regression analysis to examine the impact of selected covariates on PFS. The amended SAP was finalized after the trial was published (SAP version 3.0).[23] Of note, the additional efficacy analysis of OS was considered an administrative look at the trial data for regulatory purposes, and was not considered one of the pre-specified analyses of OS detailed in the SAP.[6] The aforementioned updated efficacy analyses were based on a data cut-off date of June 30, 2016.

HRQoL was considered a key secondary outcome of the trial[5] and assessed using the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ-C30), which is a non-specific cancer survey that includes a global health status scale, functional scale domains (physical, role, emotional, cognitive, and social) and symptom scale domains (fatigue, nausea, vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Additionally, the trial also administered the Gastrointestinal (GI)-NET-21, which is a module specific to NET-related symptoms and includes 21 questions related to the following scale domains: endocrine (flushing, sweats), GI (bloating, flatulence), treatment, social functioning, disease-related worries, muscle/bone pain, sexual function, information/communication function, and body image. Higher scores equate to increased/worse symptoms. The QLQ-C30 global health and function scales are positive scales where higher scores correspond to better QoL; while the

symptom scales of the QLQ-C30 and GI-NET-21 are negative scales where higher scores correspond to increased symptoms or problems. Trial patients completed HRQoL questionnaires at baseline and every 12 weeks until centrally confirmed progression or until a maximum of 72 weeks from randomization had elapsed. For domains with multiple questions, if ≥ 50% but < 100% of questions were completed at a visit, then the visit was deemed evaluable for the domain and the average of the remaining assessed questions was used in analyses. Visits with > 50% of questions missing for a particular domain were excluded from analyses. Questionnaire results were converted to a 100-point scale and a 10-point change in a scale score was considered the minimal clinically important difference (MCID).

The primary objective of the HRQoL analysis was to compare between treatment groups the time-to-deterioration (TTD) in a particular domain scale, which was defined as the time from randomization to the first deterioration of ≥ 10 points compared with the baseline score for the domain.[5] TTD was assessed using the same statistical methods as described above for efficacy (KM methods and Cox proportional hazards regression model using p=0.05 for statistical significance) but with no adjustments for multiple testing. Patients with no deterioration or no baseline/follow-up data were censored at the last assessment date and date of randomization, respectively. For domains where a univariate regression model showed a statistically significant effect of treatment, the Cox proportional model was used to assess the impact of multiple covariates on the HRs obtained. The full regression model included randomized treatment, stratification factors, disease stage, tumour burden, Ki67 index, sex, body mass index, age, creatinine clearance, and relative QoL domain score. The final model was determined using a backward selection process that removed covariates that did not reach statistical significance with the exception of randomized treatment, which was retained in the model. Sensitivity analyses were performed by stratification factors, and by censoring patients with worst possible score at baseline. Several alternate definitions of TTD were also explored to compensate for potential shifts in patient responses over time. The HRQoL analysis included all randomized patients (ITT; n=231) and was based on the data cut-off date of June 30, 2016.

Table 5: Select quality characteristics of the included NETTER-1 trial.[1]

Trial Quality Characteristics	NETTER-1 Trial
Treatment vs. Control	• ^{177}Lu-Dotatate + BSC (octreotide LAR 30 mg) *vs.* • Octreotide LAR 60 mg (high-dose)
Primary outcome	• PFS by BICR
Required sample size	• Original: 124 patients, based on the following assumptions:[23] o Median PFS of 30 months in the ^{177}Lu-Dotatate group o Median PFS of 14 months in the control group o 90% power at an alpha level of 5% o Enrollment and follow-up period of 18 months o 74 PFS events (at primary analysis) • Amended: increased to 230 patients, in order to detect a statistically and clinically relevant difference in OS, based on the following assumptions:[23] o Median OS of 50 months in ^{177}Lu-Dotatate group o Median OS of 32 months in the control group o 80% power at an alpha level of 5% o Long-term follow-up period of 60 months
Randomization method	• Central randomization (permuted block)[a] by interactive web-based response system[7] stratified by somatostatin receptor scintigraphy tumour uptake score[b] and length of time on most recent constant dose of octreotide prior to randomization (≤6 months vs. >6 months)
Allocation concealment (yes/no)	• Yes
Blinding	• Open label • BIRC primary outcome assessment
ITT analysis (yes/no)	• Yes
Interim analyses	• Pre-specified interim analysis of OS at the time of primary analysis (PFS), with O'Brien-Fleming α-spending function o Significance level of 0.0085% (p=0.000085) at interim analysis[23]
Final analysis (yes/no)	• No • Final analysis (OS) expected after 158 deaths or five years from date of randomization of the last randomized patient, whichever occurs first
Early termination (yes/no)	• No
Ethics approval (yes/no)	• Yes

Abbreviations: BICR - blinded independent central review; CR - complete response; HR - hazard ratio; IDMC - Independent Data Monitoring Committee; INV - investigator assessment; IRC - independent review committee; ITT - intent-to-treat; PFS - progression-free survival; vs. versus.

Notes:
[a] - The randomization scheme used in the trial was changed following FDA advice in July 2013; 28 patients were randomized into the trial using a coin toss method before the switch to a permutated block randomization scheme.[2]
[b] - The highest uptake score (grade 2, 3 or 4) measured on somatostatin receptor scintigraphy among all target lesions was used for stratification.

b) Populations

A total of 229 patients were randomized into the NETTER-1 trial between September 2012 and January 2016. The demographic and clinical characteristics of randomized patients at baseline are summarized in Table 6, and were reported to be well-balanced between the treatment groups. The median age of patients was approximately 64 years and most trial patients were treated in US centres (59%),[7] were white (82%),[7] had a mean Karnofsky performance status score of approximately 88%, primary tumours located in the ileum (73%), and presented with metastases in the liver (83%), lymph nodes (62%), or both (typically in the mesentery or retroperitoneum). The majority of patients in both treatment groups had tumours considered low grade by the Ki67 proliferation index (66% in the ^{177}Lu-Dotatate group, and 72% in the control group) and highest grade in terms of uptake of tumour somatostatin radiotracer (grade 4: 61% in the ^{177}Lu-Dotatate group, and 59% in the control group). Serum chromogranin A, 5-hydroxyindoleacetic acid and alkaline phosphatase levels were also similar at baseline. The median time since first progression of disease was 20.2 months in ^{177}Lu-Dotatate group and 23.4 months in the control group.[7] Most patients had undergone prior surgical resection (80% in ^{177}Lu-Dotatate group, 82% in control group); and a significant proportion of patients had received systemic therapy other than somatostatin analogue therapy (41% in ^{177}Lu-Dotatate group, 45% in control group). In the last 12 weeks prior to trial enrolment, the most recent constant dose of octreotide LAR received by patients was 30 mg (3-4 week intervals) in both treatment groups (94% of patients in each group).[2]

Table 6: Demographic and baseline clinical characteristics of patients in the NETTER-1 trial.[1]

Characteristic n (%)* unless otherwise noted	Netter-1 Treatment Groups	
	^{177}Lu-Dotatate (n=116)	Control (n=113)
Age, mean (±SD)	63 (±9)	64 (±10)
Sex		
Male	63 (54)	53 (47)
Female	53 (46)	60 (53)
Race		
Caucasion/White	92 (79)[7]	96 (85)[7]
Black or African American	5 (4)	5 (4)
Asian	1 (1)	0
Hispanic	6 (5)	2 (2)
Other	0	1 (1)
NA	12 (10)	9 (8)
Continent of Origin		
USA	66 (57)	69 (61)
EU	50 (43)	44 (39)
BMI, mean (±SD)	25 (±5)	26 (±7)
Time since diagnosis, median (years)	3.8	4.8
KPS, mean (±SD)	88.6 (±9.32)	88.0 (±9.56)
Primary tumour site		
Ileum	86 (74)	82 (73)
Small intestine NOS	11 (9)	12 (11)
Midgut NOS	9 (8)	7 (6)
Jejunum	6 (5)	9 (8)
Right colon	3 (3)	1 (1)
Appendix	1 (1)	2 (2)
Ki67 index - grade		
Grade 1	76 (66)	81 (72)
Grade 2	40 (35)	32 (28)
SRS Krenning Scale[a]		
Grade 2	11 (10)	12 (11)
Grade 3	34 (29)	34 (30)
Grade 4	71 (61)	67 (59)
Median CgA (quartiles) - µg/l[d]	604 (247-2626)	648 (290-2674)
Median 5-HIAA (quartiles) - mg/24 hr[d]	36 (17-126)	44 (21-92)
Median serum AP (quartiles) - U/l[d]	99 (74-160)	106 (75-152)
Time since first progression of disease, median (months)	20.2[7]	23.4[7]
Time since first diagnosis of metastases, median (months)	42.6[7]	38.3[7]
Site of metastases		
Liver	97 (84)	94 (83)
Lymph nodes	77 (66)	65 (58)
Mesentery	17 (15)	8 (7)
Bone	13 (11)	12 (11)
Other	15 (13)	10 (9)
Peritoneum	7 (6)	10 (9)
Lungs	11 (9)	5 (4)
Ovaries	1 (1)	9 (8)
Previous treatments		
Surgery	93 (80)	93 (82)
Tumour resection	90 (78)	93 (82)
Tumour ablation	6 (5)	11 (10)
Targeted therapy[b]	19 (16)	17 (15)
Embolization[c]	18 (16)	13 (12)
Chemotherapy	11 (9)	14 (12)
Interferon	8 (7)	7 (6)

Characteristic n (%)* unless otherwise noted	Netter-1 Treatment Groups	
	^{177}Lu-Dotatate (n=116)	Control (n=113)
Angiogenesis inhibitor	6 (5)	2 (2)
Radiotherapy (external beam)	4 (3)	6 (5)
PRRT	1 (1)	0
Investigational drug	1 (1)	1 (1)
^{131}I MIBG	0	2 (2)
Abbreviations: AP - alkaline phosphatase; BMI - body mass index; CgA - chromagranin A; EU - European Union; KPS - Karnofsky performance status; NA - not available; NOS - not otherwise specified; PRRT - peptide receptor radionuclide therapy; SD - standard deviation; SRS - somatostatin receptor scintigraphy; ^{131}I MIBG - metaiodobenzylguanidine		
Notes: * - Percentages may not sum to 100 due to rounding. [a] - Highest grade. [b] - Includes everolimus, temsirolimus, sunitinib, imatinib, sorafenib, pazopanib, axitinib, and gefitinib. [c] - Includes chemo-embolization, radioembolization, and trans-arterial embolization. [d] - Normal range values: CgAL, 19.4 to 98.1 µg/l; 5HIAA, 0 to 15 mg/24 hrs; AP, 0 to 150 U/l.		

c) Interventions

In the experimental group, treatment with ^{177}Lu-Dotatate consisted of four administrations at a dose of 7.4 GBq (200 mCi) infused intravenously over a 30 minute period every eight weeks, equating to a cumulative radioactivity of 29.6 GBq [800 mCi] unless unacceptable toxicities occurred, centrally confirmed progression was present on imaging, or the patient was unable or unwilling to adhere to trial procedures, withdrawal of consent or patient death. The time interval for administration of ^{177}Lu-Dotatate could be extended up to 16 weeks to accommodate resolution of acute toxicity. After resolution of a dose-limiting toxicity (DLT), subsequent planned infusions could be administered at 50% of the standard treatment dose. In the event the same DLT did not resolve within 16 weeks or reoccurred after a reduced dose, ^{177}Lu-Dotatate was discontinued. The majority of patients (77%; n=77) completing the treatment phase of the trial received all four administrations of ^{177}Lu-Dotatate (Table 7), and eight patients (n=7%) experienced a DLT. The DLT experienced by patients included thrombocytopenia (n=4), neutropenia (n=1), renal impairment (n=1), and increased hepatic enzymes and slight increase in bilirubin (both occurring in 1 patient requiring two dose reductions).[2] In addition to ^{177}Lu-Dotatate, patients received best supportive care with octreotide LAR, which was administered intramuscularly 24 hours (30 mg) after each ^{177}Lu-Dotatate infusion and then monthly after completion of all four infusions.

In the control group, patients received high-dose (60 mg) octreotide LAR intramuscularly every four weeks (± 3 days).

In both treatment groups, patients continued the four-week interval administrations of octreotide LAR until the primary outcome (PFS) was reached or until 72 weeks from randomization after the primary outcome was reached, unless patients progressed or died.

Patient crossover was not permitted in the NETTER-1 trial per protocol; however, for ethical reasons patients who had progressed were free to receive other available treatments outside of the trial, which included ^{177}Lu-Dotatate. A total of 26 (22.8%) control patients received ^{177}Lu-Dotatate after disease progression.[21] These patients were censored in the analysis of OS. Information on other

subsequent treatments received by patients in each treatment group has not been reported.

Table 7: Exposure to ^{177}Lu-Dotatate in the NETTER-1 trial.

Patients who completed treatment phase (N=103†)	no. (%)
Number of administrations	
4	79 (77)
3	6 (6)
2	12 (12)
1	5 (5)
0	1 (1)
All treated patients (N=111)	
No DMT	103 (93)
DMT	8 (7)

* DMT denotes dose-modifying toxicity.

† Excluding patients still under treatment (n=8) or no treatment (n = 5).

From New England Journal of Medicine, Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 trial of 177lu-dotatate for midgut neuroendocrine tumors, volume 376 no: 2, page:125-135. Copyright © 2017 from Massachusetts Medical Society.

At the June 30, 2016 data cut-off date, which included 111 patients who had completed the treatment phase of the trial, 76% (n=84) of patients received all four administrations of ^{177}Lu-Dotatate and received a mean cumulative radioactivity of 29.1 GBq. Considering all patients in the ^{177}Lu-Dotatate group, a majority (79.3%; n=88) received >22.2 GBq (>600 mCi) of drug exposure.[2]

Concomitant Medications

The trial protocol specified that patients treated with ^{177}Lu-Dotatate also receive intravenous amino acid solution (Aminosyn II 10% [21.0g of lysine and 20.4 g of arginine in 2 litres of solution] or VAMIN-18 [18 g of lysine and 22.6 g or arginine in 2 litres of solution] administered concomitantly for renal protection for a duration of at least four hours starting 30 minutes prior to ^{177}Lu-Dotatate infusions. Further, the protocol also specified that patients in both treatment groups were permitted to receive rescue injections of subcutaneous octreotide for hormonal symptoms (i.e., diarrhea or flushing) associated with carcinoid syndrome.

Other concomitant medications frequently used by patients in the trial included antiemetics and antinauseants, which were received by more patients in the ^{177}Lu-Dotatate group (88%) compared to the control group (20%).[2] This was expected considering antiemetic prophylaxis was recommended to prevent nausea and vomiting associated with renal protectant amino acids. Notable other medications used in a higher frequency in the ^{177}Lu-Dotatate group included drugs for functional gastrointestinal disorders (27% versus 18%), psycholeptics (59% versus 28%), blood substitutes and perfusion solutions (14% versus 4%), and corticosteroids for systemic use (26% versus 2%).[2] Conversely, the most frequent concomitant medication used among patients in the control group was analgesics (58%; versus 60% in the ^{177}Lu-Dotatate group) and laxatives were used in greater frequency amongst control patients (20%) compared to patients in the ^{177}Lu-Dotatate group (10%).[2]

d) Patient Disposition

The disposition of patients through the NETTER-1 trial, by data cut-off date, is summarized in Table 8. Of note, randomization and treatment were still ongoing at the time of the primary efficacy analysis; therefore, the updated efficacy analysis includes two additional patients who were randomized after the primary efficacy analysis data cut-off date and is based on a trial sample size of 231 patients (n=117 in the ^{177}Lu-Dotatate group and n=114 in the control group).[7]

In total, 360 patients were screened for the trial (316 at the time of the primary efficacy analysis, and 44 at the time of the updated analysis). A total of 129 patients were excluded, which included 107 screen failures (failure to meet eligibility criteria, n=96; physician decision, n=1; withdrawal by subject, n=6; other, n=4) and 22 non-randomized patients who were enrolled in a separate dosimetry and pharmacokinetics sub-study.[6] There were eight patients who did not receive assigned study medication (Table 8).[4]

At the updated analysis (June 30, 2016), almost all patients had discontinued treatment (97% and 98% of patients in the^{177}Lu-Dotatate and control groups, respectively). The primary reason for treatment discontinuation in the^{177}Lu-Dotatate group was completion of treatment (39%) compared to disease progression in the control group (56%). The majority of patients entered into long-term follow-up; 84% in the ^{177}Lu-Dotatate group and 87% in the control group. A higher percentage of patients discontinued long-term follow-up in the control group (45%, versus 27%); discontinuations were primarily due to death in both groups (39% and 25%, respectively).[4]

Fifty-nine major protocol deviations occurred in 48 patients; 33 deviations (26%) were in the ^{177}Lu-Dotatate group and 29 (27%) were in the control group.[7] Although the frequency of deviations was balanced between groups, there was a higher frequency of deviations related to assessments performed outside of the permitted time window in the ^{177}Lu-Dotatate group (12% versus 7% in control); and a higher frequency of deviations related to incorrect procedures in the control group (12% versus 6% in the ^{177}Lu-Dotatate group).

Although not considered protocol deviations, the FDA noted that a discrepancy between the treatment groups in the number of patients with a delay between the baseline tumor assessment and the first study treatment was a cause for concern in terms of potential influence on the efficacy analysis.[4] While the trial protocol permitted up to 12 weeks between baseline screening and the date of first treatment, 14% of patients in the ^{177}Lu-Dotatate group and only 1% of patients in the control group had a delay of 30 days or more between the baseline screen and the date of first treatment.[4] The potential impact of the delay in initial treatment on the efficacy analysis is further discussed in the summary of efficacy results for PFS (sensitivity analyses).

Table 8: Patient disposition in the NETTER-1 trial (ITT population).

Patient Disposition, n (%)	Netter-1 Treatment Groups	
	^{177}Lu-Dotatate	Control
Primary analysis data cut-off date	**July 24, 2015**	
Screened	316	
Randomized total	229	
Randomized per group	116	113
Received allocated treatment	111 (96)	110
Did not receive allocated induction treatment[22]	5 (4)	3 (3)
Reasons:[2,6]		
Withdrawal by subject	1 (<1)	2 (2)
Physician decision	1 (<1)	1 (<1)
AEs	3 (3)	NA
Other	NA	1 (<1)
Discontinued treatment[6,22]	52 (45)	87 (77)
Reasons		
PD	19 (16)	58 (51)
Physician decision	10 (9)	9 (8)
Consent withdrawal	9 (8)	9 (8)
AEs	7 (6)	7 (6)
Other	7 (6)	4 (4)
Entered long-term follow-up[22]	107 (92)	97 (86)
Did not enter long-term follow-up[22]	9 (8)	16 (14)
Reasons[6]		
Consent withdrawal	4 (3)	9 (8)
Lost to follow-up	1 (<1)	2 (2)
Other	4 (3)	5 (4)
Included in primary analysis	116	113
Included in safety analysis	111	110
Updated analysis data cut-off date	**June 30, 2016**	
Additional patients screened	44	
Additional patients randomized[6]	2[a]	
Randomized per group	117	114
Discontinued treatment	113 (97)	112 (98)
Reasons:[2]		
PD	19 (16)	64 (56)
Completed treatment	46 (39)	11 (10)
Physician decision	17 (15)	17 (15)
Withdrawal by patients	10 (9)	10 (9)
AEs	13 (11)	10 (9)
Non-compliance	2 (2)	0
Other	6 (5)	0
Entered follow-up[2]	95 (84)	97 (87)
Did not enter follow-up[2]	18 (16)	15 (13)
Stopped follow-up[2]	26 (27)	44 (45)
Reasons[2]		
Death	24 (25)	38 (39)
Consent withdrawal	0	2 (2)
Lost to follow-up	2 (2)	4 (4)
Included in updated analysis[6]	117	114
Included in safety analysis[4]	111	112
Protocol Deviations[7]		
Major protocol deviations	30 (26)	29 (27)
Inclusion/exclusion criteria	9 (8)	8 (7)
Incorrect procedure	7 (6)	13 (12)
Out of window	14 (12)	8 (7)

Patient Disposition, n (%)	Netter-1 Treatment Groups	
	^{177}Lu-Dotatate	Control
Primary analysis data cut-off date	July 24, 2015	
Abbreviations: AE(s) - adverse event(s); NA - not applicable; PD - progressive disease; SAE - serious adverse event; SD - stable disease.		
Notes: [a] - Two patients screened were randomized after the primary efficacy endpoint cut-off date; the data from these two patients were included in the safety analysis.		

e) Limitations/Sources of Bias

The NETTER-1 trial[1] had several limitations identified by the FDA and EMA as part of the MAA and NDA processes, which stemmed from sub-optimal design features, issues with trial conduct and data collection, and inappropriate data analysis approaches. These limitations were considered significant by the FDA and EMA in terms of their potential to affect the internal validity of the trial and prompted reanalyses of the NETTER-1 trial data that incorporated data corrections, more rigorous approaches of analysis and multiple sensitivity analyses. The reanalyses performed of the trial data (HR for PFS by BICR=0.18 [95% CI, 0.11-0.29]; p<0.0001),[2] however, confirmed the validity of the highly statistically significant large effect size that was obtained for the primary outcome at the primary analysis with ^{177}Lu-Dotatate relative to control therapy with octreotide LAR (HR for PFS by BICR=0.21 [95% CI, 0.13-0.33]; p<0.001).[1] The magnitude of treatment benefit in the ITT population was observed across all patient subgroups examined. Further, the results obtained for the secondary efficacy outcomes examined in the trial (ORR, time-to-progression) also demonstrated the superiority of ^{177}Lu-Dotatate compared with control therapy, which offers further evidence of clinical benefit. At the interim analysis for OS, the difference in survival estimates between the treatment groups did not reach the predefined threshold for statistical significance (p=0.0085%); median OS was not reached in the ^{177}Lu-Dotatate group and was 27.4 months in the control group (95% CI, 20.1-not estimable). The final analysis is expected after 158 deaths have occurred. The most recent OS analysis comes from an unplanned administrative look at the trial data based on 71 deaths (45% information fraction), [2] which showed a trend toward improved OS with ^{177}Lu-Dotatate relative to control therapy (HR for death=0.54; 95% CI, 0.33-0.86).[3,4]The results of the HRQoL assessment demonstrated that depending on the domain scale, TTD was either significantly prolonged in patients treated with ^{177}Lu-Dotatate compared to control therapy, or there were no differences in TTD that suggested ^{177}Lu-Dotatate was associated with no detriment on HRQoL.[5] These findings were observed despite a much higher frequency of toxicity in the ^{177}Lu-Dotatate treatment group.

Notwithstanding the magnitude of treatment benefit observed with ^{177}Lu-Dotatate in the NETTER-1 trial, consideration should be given to the following factors when interpreting the results of the trial:

- It should be highlighted that the trial limited enrollment to patients with GEP-NETS of the midgut and did not evaluate the efficacy of ^{177}Lu-Dotatate in patients with other GI-NET tumours (foregut, hindgut) and other GEP-NET tumour locations (pancreas, lung). Refer to Sections 7 and 8 of this report for a summary of the evidence on the use of ^{177}Lu-Dotatate in other tumour locations.

- The dose of octreotide LAR used in the control group of the NETTER-1 trial (60 mg) is not consistent with the approved dose in Canada, which is 30 mg. Whether the dose of octreotide control therapy affects the relative magnitude of the treatment benefit observed with ^{177}Lu-Dotatate is unclear.
- It's possible that the use of an open-label trial design, where patients were aware of their treatment assignment, influenced the reporting of HRQoL outcomes in the trial in favour of the experimental treatment group. Additional limitations of the HRQoL analysis were also identified and include the following:
    - A lack of adjustment for multiple testing raises the possibility of type 1 error for the HRQoL outcomes assessed in the trial (that is, claiming a statistically significant difference when one does not exist; the false positive result is a product of chance, where the risk of type 1 error increases as the number of tests performed increases).
    - For some of the statistically significant results obtained, it's unclear whether the differences in TTD would be considered clinically meaningful (fatigue for example, where the difference between groups in TTD was 0.9 months; and potentially other domains where the medians were not reached in either treatment group).
    - The small numbers of patients at risk in both treatment groups for the majority of time points (across domain scales) raises concern about the reliability of the results obtained.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

After the first MAA and NDA were submitted by AAA in April of 2016, the EMA and FDA requested changes and updates to the original trial data set, which included applying practice standards related to data tabulation and analysis as well as additional data cleaning activities.[6] Further, after the EMA and FDA inspection of NETTER-1 trial sites, AAA identified the need to correct the scans used in the analysis of PFS for 15 patients for whom post-randomization scans (BICR and investigator assessments) were used instead of baseline scans.[2] In these 15 patients, post-randomization scans were taken due to an unexpected delay in the start of treatment and were inappropriately used in place of the original baseline scans[2]. Once the scan errors were identified, the original baseline scans were centrally re-evaluated and all subsequent scans for these patients were also chronologically re-evaluated.[2] The aforementioned corrections to the trial data occurred after the trial was submitted for publication; therefore, the published results of the trial do not incorporate data corrections.[6] AAA supplied the final version of the CSR (version 2.0) to pCODR, which reports the trial results using corrected data. These results, in addition to the trial publication results have been summarized in the presentation of efficacy results in this report.

Efficacy Outcomes

The efficacy outcomes in the NETTER-1 trial are summarized in Tables 9 and 10. The median duration of patient follow-up at the primary/updated efficacy analyses for the ^{177}Lu-Dotatate group and control groups was 9.2/5.5 months and 14.4/6.0 months, respectively.[6]

Primary Outcome – Progression-free survival

PFS was defined as the time from randomization to documented disease progression (BICR) or death from any cause.

Based on the trial publication,[1] at the time of the primary efficacy analysis a total of 91 PFS events had occurred in the trial; 23 in the ^{177}Lu-Dotatate group and 68 in the control group. Median PFS had not been reached in the ^{177}Lu-Dotatate group and was 8.4 months (95% CI, 50.0-76.8) in the control group. The HR for PFS by BICR was 0.21 (95% CI, 0.13-0.33; p<0.001), which indicated a statistically significant improvement in PFS (or a 79% reduction in the risk of a PFS event) in the ^{177}Lu-Dotatate group compared to the control group. The KM curve for PFS by BICR is presented in Figure 2 A. Correcting for scan errors (explained above) had a limited impact on the HR (HR=0.18, 95% CI, 0.11-0.29; p; <0.0001),[2] and the results remained statistically significant in favour of treatment with ^{177}Lu-Dotatate compared to control therapy. Similar results were obtained for PFS by investigator assessment (sensitivity analysis), which are available in Table 9.

The results of exploratory subgroup analyses performed by baseline characteristics are available in Figure 2 C, and demonstrate a consistent treatment benefit in favour of ^{177}Lu-Dotatate compared to control therapy. The magnitude of HRs (treatment effect) ranged from 0.14-0.24,[1] with no upper bounds of associated CIs crossing unity. The results of subgroup analyses using corrected PFS data were consistent with the results reported in Figure 2C.[6]

Several sensitivity analyses were performed to evaluate the robustness of the primary outcome results to changes in various parameters, including the observed difference between the treatment groups in the time delay between the baseline

tumour assessment and the first study treatment.[2] All sensitivity analyses performed clearly supported the primary outcome results.[2]

Secondary Outcomes

Based on the primary outcome obtaining statistical significance at the primary analysis, the secondary outcomes ORR and OS were formally and sequentially tested. The remaining secondary outcomes (DOR, TTP) were analyzed descriptively (Table 9) and should be considered exploratory in nature.

Objective Response Rate

ORR by BICR was calculated as the sum of partial responses (PR) and complete responses (CR); DOR was calculated from the time of initial response until documented tumour progression.

The ORR obtained at the primary efficacy analysis was 15% (95% CI, 7.8-21.6) in the ^{177}Lu-Dotatate group and 4% (95% CI, 0.2-7.8) in the control group.[7] The difference in ORR between the treatment groups was statistically significant (p=0.014).

Overall Survival

As mentioned previously, since the publication of the NETTER-1 trial, changes to the original trial data set were made at the request of the EMA and FDA. At the primary efficacy analysis (interim OS analysis), and prior to data corrections, an HR of 0.40 (95% CI, 0.21-0.77; p=0.004)[4] was obtained that did not reach the level of statistical significance pre-specified by the O'Brien-Fleming alpha spending boundary (p=0.0085%).[1] A corrected interim analysis of OS (based on CSR version 2.0) produced an HR of 0.46 (0.25-0.83; p<0.0083) based on 48 deaths; 17 and 31 in the ^{177}Lu-Dotatate and control groups, respectively.[2]

The updated exploratory analysis of OS was performed based on 71 deaths; 28 in the ^{177}Lu-Dotatate group and 43 in the control group.[2] Median OS was still unreached in the ^{177}Lu-Dotatate group and was 27. 4 months in the control group (HR=0.54, 95% CI, 0.33-0.86).[3,4] The final analysis of OS is expected after 158 deaths have accrued.

In response to the pERC Initial Recommendation, the Submitter provided feedback noting that, while the OS data remains immature, a statistically significant OS benefit has been shown in a corrected interim analysis (HR = 0.46, 95% CI, 0.25 to 0.83; P < 0.0083).

The pCODR Methods Team confirmed that during the review, the pCODR Methods team requested that the Submitter clarify whether the p-value was considered statistically significant for the corrected interim analysis of OS. The Submitter provided a response confirming that the p-value at the corrected interim analysis was p=0.0083 (unstratified log-rank test) and that the pre-defined threshold was 0.0085%=0.000085. Since the p-value exceeded the threshold the test was not significant.[24]

Table 9: Efficacy outcomes in the NETTER-1 trial.

Efficacy Outcomes	NETTER-1 Treatment Groups			
	^{177}Lu-Dotatate n=116	Control n=113	^{177}Lu-Dotatate n=116	Control n=113
	Primary Trial Publication[1]		CSR version 2.0[2]	
Analysis data cut-off date	July 24, 2015		July 24, 2015	
Median follow-up, months	9.2	5.5	9.2	5.5
Primary outcome				
PFS by BICR				
No. events (%)	23 (20)	68 (60)	21 (18)	70 (62)
Median in months (95% CI)	Not reached	8.4 (5.8-9.1)	Not reached	8.5 (5.8-9.1)
20-month PFS rate, % (95% CI)	65.2 (50.0-76.8)	10.8 (3.5-23.0)	NR	NR
HR (95% CI); p-value	0.21 (0.13-0.33); 0.001		0.18 (0.11-0.29); <0.0001	
PFS by Investigator				
No. events (%)	NR		31 (27)	62 (55)
Median in months (95% CI)			26.0 (18.4-NE)	8.4 (6.0-11.01)
HR (95% CI); p-value			0.26 (0.17-0.41); <0.0001	
Secondary outcomes				
ORR by BICR	n=101[a]	n=100[a]	NR	
n	18	3		
% (95% CI)	18 (10-25)	3 (0-6)		
p-value	0.001			
CR, n (%)	1 (1)	0		
PR, n (%)	17 (17)	3 (3)		
ORR by BICR - ITT				
n	NR		15	4
% (95% CI)			15 (7.8-21.6)	4 (0.2-7.8)
p-value			0.0141	
CR, n (%)			1 (0.09)	0
PR, n (%)			14 (12.1)	4 (3.5)
DOR				
Median, months (95% CI)	Not reached	1.9 (1.9-NE)	Not reached	1.9 (1.9-NE)
Time-to-progression by BICR				
No. of events (%)	NR		15 (13)	61 (54)
Median, months (95% CI)			Not reached	8.7 (6.0-11.1)
HR (95% CI)			0.14 (0.08-0.24)	
OS				
Medium follow-up, months	9.2	5.5	9.2	5.5
No. of events (%)	14 (12)	26 (23)	17 (15)	31 (27)
Median, months (95% CI)	NR	NR	Not reached	27.4 (20.1-NE)
HR (95% CI); p-value	0.40 (0.21-0.77); 0.004[4]		0.46 (0.25-0.83); 0.0083	
Updated OS analysis data cut-off date	NA		July 30, 2016[2,3]	
Medium follow-up, months[6]			14.4	6.0
No. of events (%)			28 (24)	43 (38)
Median, months (95% CI			Not reached	27.4 (23.1-NE)
HR (95% CI)			0.54 (0.33-0.86)[4]	

Abbreviations: BICR - blinded independent central review; CI confidence interval; CR - complete response; DOR - duration of response; HR - hazard ratio; ITT - intent-to-treat; NA - not applicable; NE - not estimable; NR - not reported; OS - overall survival; PFS - disease-free survival; PR - partial response.

Notes:
[a] - The ORR was defined as the percentage of patients who had a response according to RECIST (sum of CR and PR). Patients for whom no post-baseline CT or MRI or central response data were available (n=15 in ^{177}Lu-Dotatate groups and 13 patients in the control group) were excluded from the analysis of ORR (trial is still ongoing).
* Unstratified HR < 1.00 favour treatment with ^{177}Lu Dotatate.

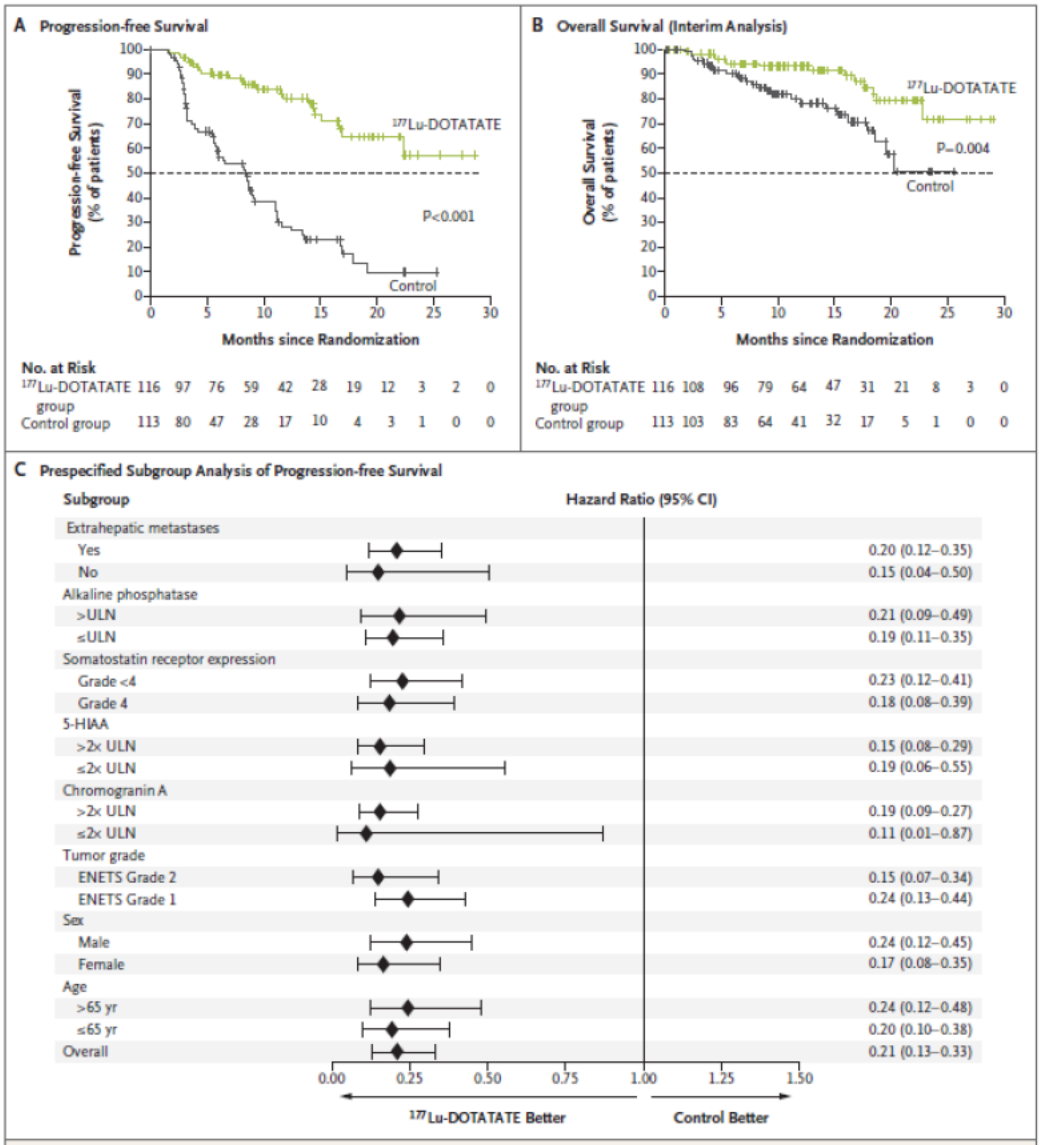


Figure 1. Progression-free Survival and Overall Survival.
Panel A shows the results of the Kaplan–Meier analysis of progression-free survival as assessed by independent central reviewers who were unaware of the treatment assignments, and Panel B the results of the planned interim analysis of overall survival. Tick marks in Panel A represent data censored at the last time the patient was known to be alive and without disease progression and tick marks in Panel B represent data censored at the last time the patient was known to be alive. Panel C shows the effect of trial treatment on progression-free survival in prespecified subgroups. European Neuroendocrine Tumor Society (ENETS) grade 1 indicates a low-grade tumor, and ENETS grade 2 indicates an intermediate-grade tumor. The ^{177}Lu-Dotatate group received ^{177}Lu-Dotatate at a dose of 7.4 GBq every 8 weeks (four intravenous infusions, plus best supportive care including octreotide long-acting repeatable [LAR] administered intramuscularly at a dose of 30 mg). The control group received octreotide LAR alone administered intramuscularly at a dose of 60 mg every 4 weeks. 5-HIAA denotes 5-hydroxyindoleacetic acid, CI confidence interval, and ULN upper limit of the normal range.

Figure 2: PFS and OS in the NETTER-1 trial at the primary analysis data cut-off date - July 24, 2015.

From New England Journal of Medicine, Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 trial of 177lu-dotatate for midgut neuroendocrine tumors, volume 376 no: 2, page:125-135. Copyright © 2017 from Massachusetts Medical Society.

Health-related Quality of Life[5]

Compliance rates for patients completing questionnaires were reported as high (>80%) in both treatment groups for all assessment visits, and baseline domain scores appeared balanced between the treatment groups (Table 10).

Table 10: Baseline HRQoL scores by treatment group in the NETTER-1 trial.

Table 1. Baseline HRQoL Scores by Randomly Assigned Group

	^{177}Lu-Dotatate (n = 117)				Octreotide LAR (n = 114)				
HRQoL Domain	No.	Mean (SD)	Median	Q1-Q3	No.	Mean (SD)	Median	Q1-Q3	*P**
Global health status/QoL	100	67.0 (22.3)	66.7	50.0-83.3	104	64.6 (23.3)	66.7	50.0-83.3	.577
Physical functioning	101	82.7 (19.5)	86.7	73.3,100.0	103	80.1 (19.3)	86.7	66.7-93.3	.178
Role functioning	101	75.4 (30.0)	83.3	66.7-100.0	103	75.4 (30.5)	83.3	66.7-100.0	.881
Emotional functioning	100	75.3 (23.7)	83.3	58.3-91.7	104	74.8 (24.9)	83.3	58.3-91.7	.721
Cognitive functioning	100	83.1 (22.4)	83.3	66.7.0-100.0	104	81.7 (22.5)	83.3	66.7-100.0	.433
Social functioning	100	76.5 (30.5)	91.7	66.7-100.0	104	76.6 (27.2)	83.3	66.7-100.0	.537
Fatigue	101	33.0 (26.4)	33.3	11.1-55.6	103	35.5 (27.7)	33.3	11.1-55.6	.437
Nausea and vomiting	101	8.9 (14.8)	0	0.0-16.7	103	8.9 (17.8)	0	0.0-16.7	.436
Pain	101	28.4 (29.9)	16.7	0.0-33.3	104	28.4 (28.7)	16.7	0.0-50.0	.900
Dyspnea	100	18.3 (26.5)	0	0.0-33.3	103	18.8 (26.7)	0	0.0-33.3	.843
Insomnia	100	27.7 (31.8)	33.3	0.0-33.3	103	31.1 (33.7)	33.3	0.0-66.7	.424
Appetite loss	101	15.2 (23.3)	0	0.0-33.3	103	19.1 (27.1)	0	0.0-33.3	.310
Constipation	100	5.7 (15.8)	0	0.0-0.0	102	9.8 (21.3)	0	0.0-0.0	.160
Diarrhea	100	43.3 (33.3)	33.3	33.3-66.7	104	41.7 (37.1)	33.3	0.0-66.7	.428
Financial difficulties	100	23.3 (33.0)	0	0.0-33.3	104	17.3 (29.4)	0	0.0-33.3	.120
Endocrine scale	101	22.0 (20.8)	22.2	0.0-33.3	104	20.9 (21.9)	11.1	0.0-33.3	.583
GI scale	101	22.8 (20.1)	20	6.7-33.3	104	23.8 (19.9)	20	6.7-33.3	.702
Treatment scale	68	11.6 (14.1)	11.1	0.0-19.4	62	11.9 (20.2)	0	0.0-11.1	.361
Social functioning scale	100	33.4 (25.5)	33.3	11.1-44.4	103	37.1 (27.4)	33.3	11.1-55.6	.440
Disease related worries scale	100	43.7 (27.7)	33.3	22.2-55.6	103	43.8 (30.5)	33.3	22.2-66.7	.861
Muscle/bone pain symptom	100	29.0 (30.6)	33.3	0.0-33.3	102	34.6 (31.8)	33.3	0.0-66.7	.164
Sexual function	74	30.6 (38.5)	0	0.0-66.7	72	28.2 (37.0)	0	0.0-66.7	.712
Information/communication function	99	5.4 (14.0)	0	0.0-0.0	103	12.3 (24.2)	0	0.0-33.3	.030
Body image	100	20.0 (32.1)	0	0.0-33.3	102	20.3 (30.8)	0	0.0-33.3	.774

Abbreviations: HRQoL, health-related quality of life; LAR, long-acting repeatable; Q, quartile; QoL, quality of life; SD, standard deviation.
*Wilcoxon rank sum test.

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At the June 30, 2016 data cut-off date, TTD (≥ 10 points change compared with baseline score) was significantly longer in the ^{177}Lu-Dotatate treatment group compared to control for domain scales (Table 11) including global health status, physical functioning, role functioning, diarrhea, pain, body image, disease-related worries, and fatigue (Figure 3); the statistically significant differences in median TTD between the treatment groups were as follows:[6]

- Global health status scale – 22.7 months (HR=0.41, 95% CI, 0.24-0.69; p<0.001)
- Physical functioning – 13.7 months (HR=0.52, 95% CI, 0.30-0.89; p=0.015)
- Role functioning – not estimable due to median not reached in the ^{177}Lu-Dotatate group (HR=0.58, 95% CI, 0.35-0.96; p=0.03)
- Diarrhea - not estimable due to median not reached in either treatment group (HR=0.47, 95% CI, 0.26-0.85; p=0.011)
- Pain - 3.7 months (HR=0.57, 95% CI, 0.34-0.94; p=0.025)
- Body image - not estimable due to median not reached in control group (HR=0.43, 95% CI, 0.23-0.80; p=0.006)
- Disease-related worries – 5.8 months (HR=0.57, 95% CI, 0.36-0.91; p=0.018)

- Fatigue – 0.9 months (HR=0.62, 95% CI, 0.42-0.96; p=0.030)

There remaining scales showed no significant differences between the treatment groups; and there were no domains in which the TTD analysis showed a statistically significant benefit for the control group.

After adjustment for the influence of other important baseline factors in the covariate analysis, the impact of treatment remained statistically significant for the following scales: global health status, physical functioning, diarrhea, and body image. Moreover, all the domains deemed statistically significant by the primary analysis definition were confirmed using at least one of the other two definitions of TTD. All three definitions demonstrated a significant improvement in global health status, diarrhea, pain, body image, and disease-related worries (Table 11).

Table 11: Hazard ratio estimates for TTD (primary analysis and two alternate definitions) in the NETTER-1 trial.

Table 2. HR for Time to Deterioration, Time to Deterioration From Highest Score, and Time Until Definitive Deterioration: Comparison of Treatment Arms

	Time to Deterioration From Baseline (primary analysis)		Time to Deterioration From Highest Score		Time Until Definitive Deterioration (or death)	
Domain	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Global health scale	0.41 (0.24 to 0.69)	< .001	0.41 (0.26 to 0.64)	< .001	0.39 (0.24 to 0.63)	< .001
Body image	0.43 (0.23 to 0.80)	.006	0.44 (0.25 to 0.78)	.004	0.44 (0.26 to 0.74)	.002
Diarrhea	0.47 (0.26 to 0.85)	.011	0.40 (0.25 to 0.64)	< .001	0.42 (0.25 to 0.70)	.001
Physical functioning	0.52 (0.30 to 0.89)	.015	0.69 (0.43 to 1.10)	.118	0.47 (0.29 to 0.78)	.002
Disease-related worries	0.57 (0.36 to 0.91)	.018	0.53 (0.35 to 0.80)	.002	0.46 (0.28 to 0.75)	.001
Pain	0.57 (0.34 to 0.94)	.025	0.62 (0.40 to 0.98)	.036	0.47 (0.28 to 0.77)	.002
Role functioning	0.58 (0.35 to 0.96)	.030	0.68 (0.43 to 1.08)	.100	0.41 (0.25 to 0.68)	< .001
Fatigue	0.62 (0.40 to 0.96)	.030	0.63 (0.43 to 0.93)	.017	0.70 (0.45 to 1.09)	.108
Constipation	0.55 (0.27 to 1.12)	.094	0.57 (0.30 to 1.11)	.092	0.56 (0.32 to 0.99)	.042
Social functioning	0.67 (0.41 to 1.09)	.100	0.63 (0.41 to 0.97)	.034	0.48 (0.30 to 0.76)	.001
GI scale	0.68 (0.40 to 1.15)	.147	0.65 (0.42 to 1.00)	.045	0.51 (0.31 to 0.82)	.005
Insomnia	0.70 (0.42 to 1.18)	.175	0.62 (0.39 to 1.00)	.042	0.59 (0.37 to 0.95)	.026
Treatment scale	0.70 (0.39 to 1.27)	.237	0.75 (0.43 to 1.30)	.297	0.42 (0.24 to 0.73)	.002
Muscle/bone pain symptoms	0.74 (0.42 to 1.28)	.276	0.61 (0.38 to 0.95)	.028	0.63 (0.38 to 1.04)	.067
Appetite loss	0.72 (0.38 to 1.35)	.300	0.67 (0.38 to 1.18)	.157	0.49 (0.28 to 0.85)	.009
Emotional functioning	0.73 (0.40 to 1.36)	.320	0.59 (0.37 to 0.95)	.027	0.52 (0.30 to 0.91)	.020
Social function scale	0.84 (0.51 to 1.39)	.494	0.68 (0.45 to 1.02)	.060	0.53 (0.32 to 0.87)	.011
Sexual function	0.79 (0.40 to 1.58)	.507	0.79 (0.41 to 1.50)	.470	0.63 (0.35 to 1.15)	.129
Nausea and vomiting	1.16 (0.66 to 2.04)	.613	1.28 (0.75 to 2.18)	.359	0.86 (0.51 to 1.44)	.560
Cognitive functioning	0.89 (0.53 to 1.49)	.649	0.71 (0.46 to 1.11)	.132	0.76 (0.46 to 1.26)	.284
Endocrine scale	0.89 (0.52 to 1.55)	.686	0.82 (0.52 to 1.27)	.366	0.78 (0.46 to 1.31)	.347
Financial difficulties	0.89 (0.46 to 1.72)	.737	0.75 (0.43 to 1.31)	.312	0.63 (0.37 to 1.10)	.099
Information/communication function	1.13 (0.47 to 2.74)	.780	0.98 (0.42 to 2.29)	.954	0.57 (0.30 to 1.08)	.079
Dyspnea	1.06 (0.59 to 1.91)	.844	1.06 (0.64 to 1.75)	.821	0.70 (0.41 to 1.19)	.188

Abbreviation: HR, hazard ratio.

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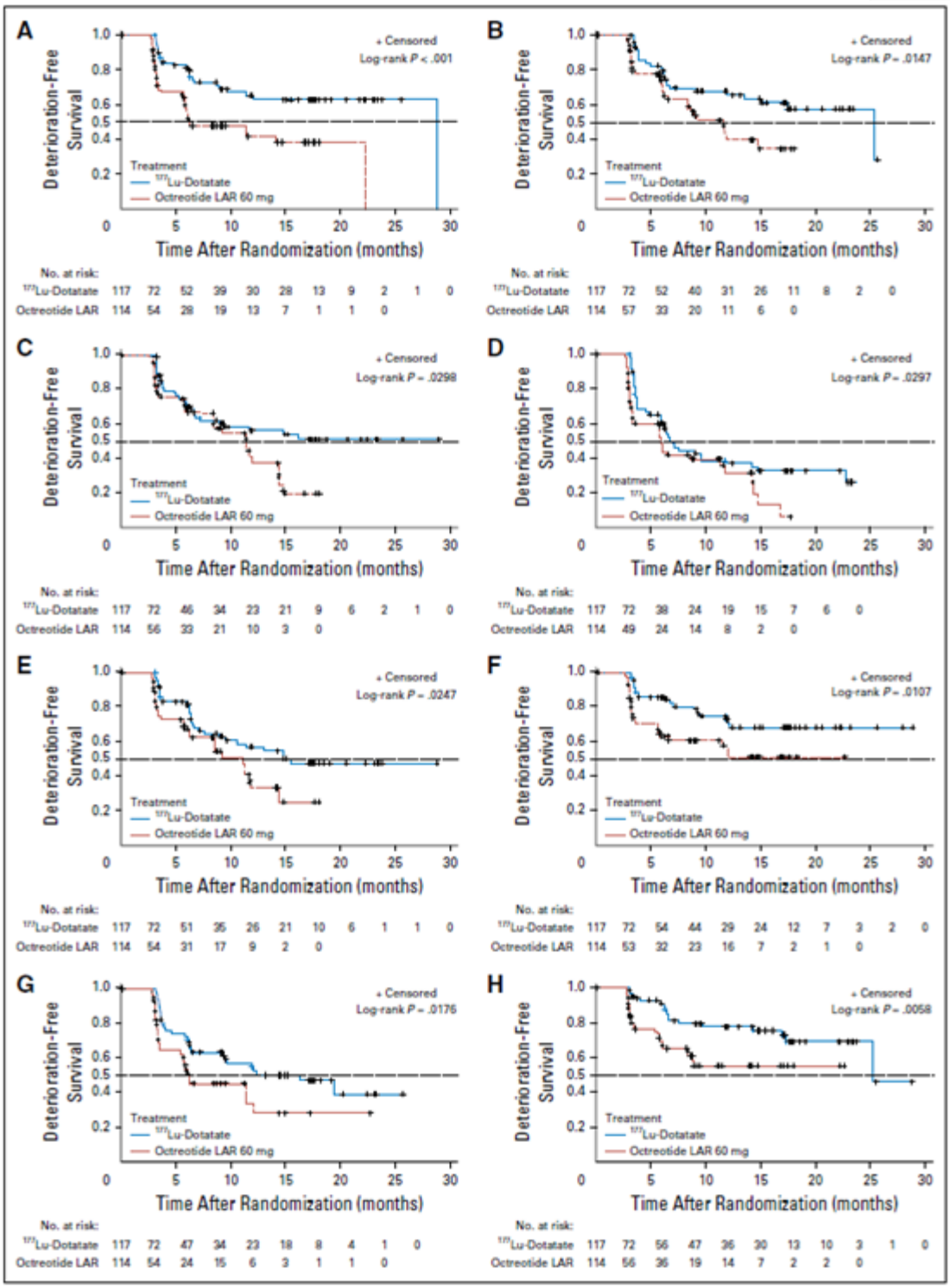

Figure 3: KM curves showing TTD in HRQoL for select domains: (A) Global health status; (B) physical functioning; (C) role functioning, (D) fatigue, (E) pain; (F) diarrhea; (G) disease-related worries; and (H) body image.

Strosberg J, Wolin E, Chasen B, et al. J Clin Oncol. Vol. 36 issue 25, 2018: 2578-2584.

Harms

All patients were assessed for safety every 12 weeks from the signing of informed consent to last study-related visit, with additional safety visits performed in the ^{177}Lu-Dotatate group every two to four weeks during the treatment phase of the trial.[1] During long-term follow-up only data on SAEs related to ^{177}Lu-Dotatate were reported as per protocol. The safety analysis included all patients who received at least one dose of study medication and adverse events (AEs) were graded according to NCIC common terminology criteria for AEs version 4.03.

Table 12 provides an overview of the AEs occurring in patients enrolled in the NETTER-1 trial based on the primary analysis data cut-off date of July 24, 2015. AEs of any grade occurred in 95% of patients in the ^{177}Lu-Dotatate and 86% of patients in the control group. AEs judged by investigators to be related to study treatment occurred in higher frequency in the ^{177}Lu-Dotatate group at 86% versus 31% in the control group. Treatment-related SAEs were also higher in the ^{177}Lu-Dotatate group at 9% compared with 1% in the control group. Treatment discontinuation due to treatment-related AEs occurred in 5% of patients in the ^{177}Lu-Dotatate group compared to 0% in the control group.

Table 12: Overview of AEs in the NETTER-1 trial - July 24, 2015 data cut-off date (primary analysis).

Event	^{177}Lu-Dotatate Group (N=111)	Control Group (N=110)	P Value†
	number of patients (percent)		
Adverse event			
Any	106 (95)	95 (86)	0.02
Related to treatment	95 (86)	34 (31)	<0.001
Serious adverse event			
Any	29 (26)	26 (24)	0.76
Related to treatment	10 (9)	1 (1)	0.01
Withdrawal from trial because of adverse event			
Because of any adverse event	7 (6)	10 (9)	0.46
Because of adverse event related to treatment	5 (5)	0	0.06

* The safety population included all patients who underwent randomization and received at least one dose of trial treatment.
† P values were calculated with the use of Fisher's exact text.

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Table 13 provides a similar overview of AEs based on the updated data cut-off date of June 30, 2016. The incidence of AEs increased slightly for all categories of AEs captured in the Table and demonstrates a sustained significantly higher frequency of treatment-related AEs and treatment-related SAEs in the ^{177}Lu-Dotatate group when compared to control therapy. A total of 16 patients (7%) in the trial experienced a treatment-emergent AE leading to death; 7 (6%) occurred in the ^{177}Lu-Dotatate group and 9 (8%) in the control group; however, none of the deaths in either group were deemed related to study drug.[2]

Table 13: Overview of adverse events in the NETTER-1 trial – June 30, 2016 data cut-off date (updated analysis).[7]

Event	^{177}Lu-Dotatate Group (n=112)	Control (n=111)
Adverse event		
Any	111 (99)	105 (95)
Related to treatment	102 (91)	45 (41)
Serious adverse event		
Any	37 (33)*	30 (27)*
Related to treatment	13 (12)**	3 (3)**
Withdrawal from trial because of AE		
Because of any adverse event	14 (13)*	12 (11)*
Because of adverse event related to treatment	8 (7)**	1 (1)**
*Difference observed between treatment groups was not statistically significant (p >0.05). **Difference observed between treatment groups was statistically significant (p<0.05).		

Table 14 summarizes the AEs occurring in the NETTER-1 trial by organ class and preferred term based on the primary analysis data cut-off date of July 24, 2015; the rates of specific AEs were very similar at the updated analysis (June 30, 2016), and therefore have not been reproduced here. The most common class of AEs observed in both treatment groups was gastrointestinal disorders (GI); however, the incidence of nausea and vomiting were significantly higher in patients treated with ^{177}Lu-Dotatate occurring in 59% and 47% of patients, respectively, versus 12% and 10% in control patients. The majority of these events were low grade in severity and were attributed by the trial authors to amino acid infusions administered concomitantly with ^{177}Lu-Dotatate; it was reported that these AEs resolved after infusions were completed. Other GI AEs including diarrhea (29%), abdominal pain (26%) and distension (13%) occurred with less frequency in the ^{177}Lu-Dotatate group and were not significantly different from the rates observed in the control group (Table 14). Abdominal pain was the most frequent AE observed in the control group (26% of patients).

Other common AEs in the ^{177}Lu-Dotatate group included fatigue/asthenia (40%), musculoskeletal pain (29%), thrombocytopenia (25%), lymphopenia (18%), decreased appetite (18%), headache (16%) and anemia (14%). With the exception of musculoskeletal pain, the frequency of these AEs was significantly higher in the ^{177}Lu-Dotatate group compared to the control group (Table 14). Similarly, the incidence of grade 3-4 AEs was also higher in patients treated with ^{177}Lu-Dotatate (41%) compared with patients in the control group (33%). Of note, grade 3-4 hematologic events were only observed in the ^{177}Lu-Dotatate group and included lymphopenia (9%), thrombocytopenia (2%), and neutropenia (1%). It was reported by the trial authors that no renal toxic effects were observed in patients treated with ^{177}Lu-Dotatate; and myelodysplastic syndrome (MDS), an AE of special interest, was suspected in one patient with a history of monoclonal gammopathy who underwent bone marrow biopsy and had significant cytopenias consistent with MDS.

Table 14: Adverse events by system organ class in the NETTER-1 trial – July 24, 2015 data cut-off date (primary analysis).

Event	^{177}Lu-Dotatate Group (N=111)		Control Group (N=110)		P Value†
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade
	number of patients (percent)				
Any adverse event	105 (95)	46 (41)	92 (84)	36 (33)	0.01
Gastrointestinal disorders					
Nausea	65 (59)	4 (4)	13 (12)	2 (2)	<0.001
Vomiting	52 (47)	8 (7)	11 (10)	1 (1)	<0.001
Abdominal pain	29 (26)	3 (3)	29 (26)	6 (5)	1.00
Diarrhea	32 (29)	3 (3)	21 (19)	2 (2)	0.11
Distension	14 (13)	0	15 (14)	0	0.84
General disorders					
Fatigue or asthenia	44 (40)	2 (2)	28 (25)	2 (2)	0.03
Edema peripheral	16 (14)	0	8 (7)	0	0.13
Blood disorders					
Thrombocytopenia	28 (25)	2 (2)	1 (1)	0	<0.001
Anemia	16 (14)	0	6 (5)	0	0.04
Lymphopenia	20 (18)	10 (9)	2 (2)	0	<0.001
Leukopenia	11 (10)	1 (1)	1 (1)	0	0.005
Neutropenia	6 (5)	1 (1)	1 (1)	0	0.12
Musculoskeletal disorders					
Musculoskeletal pain	32 (29)	2 (2)	22 (20)	1 (1)	0.16
Nutrition disorders					
Decreased appetite	20 (18)	0	9 (8)	3 (3)	0.04
Nervous system disorders					
Headache	18 (16)	0	5 (5)	0	0.007
Dizziness	12 (11)	0	6 (5)	0	0.22
Vascular disorders					
Flushing	14 (13)	1 (1)	10 (9)	0	0.52
Skin disorders					
Alopecia	12 (11)	0	2 (2)	0	0.01
Respiratory disorders					
Cough	12 (11)	0	6 (5)	0	0.22

* Shown are all adverse events that were reported in at least 10% of the patients in the ^{177}Lu-Dotatate group, with the exception of neutropenia, which was reported in less than 10% of the patients in the ^{177}Lu-Dotatate group. For the individual events, the system organ classes in the *Medical Dictionary for Regulatory Activities* (MedDRA) hierarchy are shown in bold and are followed by the MedDRA preferred terms (not bold). The safety population included all patients who underwent randomization and received at least one dose of trial treatment.
† P values were calculated with the use of Fisher's exact text.

From New England Journal of Medicine, Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 trial of 177lu-dotatate for midgut neuroendocrine tumors, volume 376 no: 2, page:125-135. Copyright © 2017 from Massachusetts Medical Society.

6.4 Ongoing Trials

Two ongoing trials were identified that evaluate the efficacy of ^{177}Lu-Dotatate in adult patients with unresectable advanced or metastatic somatostatin receptor-positive GEP-NETs (Table 15).

Table 15: Ongoing trials of ^{177}Lu-Dotatate in adult patients with unresectable advanced or metastatic somatostatin receptor-positive GEP-NETs.

Trial Design	Eligibility Criteria	Intervention and Comparator	Trial Outcomes
NCT03049189 [20] Phase 3, open-label, multicentre randomized clinical trial Estimated enrollment: n=300 Centres in 10 countries (Australia, Austria, France, Germany, Italy, Netherlands, Poland, South Africa, Switzerland, and United Kingdom) Study start date: February 2, 2017 Estimated completion date: December 2020 Funding: ITM Solucin GmbH	<u>Key Inclusion Criteria:</u> • Age 18 years or older • Histologically and clinically confirmed diagnosis of well-differentiated non-functional gastroenteric origin (GE-NET) or both functional or non-functional pancreatic origin (P-NET) • Measurable disease per RECIST 1.1 • Somatostatin receptor positive (SSTR+) disease • Radiological disease progression, defined as progressive disease per RECIST 1.1. criteria <u>Key Exclusion Criteria:</u> • Known hypersensitivity to edotreotide or everolimus • Known hypersensitivity to DOTA, lutetium-177, or any excipient of edotreotide or everolimus or any other Rapamycin derivative • Prior exposure to any peptide receptor radionuclide therapy (PRRT) • Prior therapy with mTor inhibitors • Prior EFR (external field radiation) to GEP-NET lesions or radioembolisation therapy • Therapy with an investigational compound and/or medical device within 30 days prior to randomisation • Indication for surgical lesion removal with curative potential • Planned alternative therapy (for the period of study participation)	<u>Intervention:</u> ^{177}Lu-edotreotide (^{177}Lu-DOTATOC) A maximum of four cycles of 7.5 ± 0.7 GBq ^{177}Lu-edotreotide Slow intravenous infusion/injection (i.v.) Duration of treatment: 4 cycles, 90 days apart (total duration: 270 days/9 months) <u>Comparator:</u> Everolimus orally 10 mg/day Duration of treatment: Continuous daily treatment until diagnosis of progression or End of Study (EOS)	<u>Primary:</u> • Progression-free survival (PFS) <u>Secondary:</u> • Overall survival (OS)

Trial Design	Eligibility Criteria	Intervention and Comparator	Trial Outcomes
	• Serious non-malignant disease • Renal, hepatic, cardiovascular, or haematological organ dysfunction, potentially interfering with the safety of the study treatments		
NCT02230176[25] Phase 2, open-label, multicentre randomized clinical trial Estimated enrollment: n=80 Centres in France Study start date: February 2015 Estimated completion date: December 2023 Funding: Gustave Roussy, Cancer Campus, Grand Paris	<u>Key Inclusion Criteria:</u> • Age 18 years or older • Histologically proven well differentiated malignant pancreatic sporadic NET, metastatic disease not amenable to surgical resection • All target lesions (lesions measurable and non-measurable according to the RECIST 1.1 criteria), of a size ≥ 15 mm, twice the spatial resolution of the somatostatin receptor scintigraphy (SRS), should be positive (grade of uptake at SRS≥ 2, equal to the physiologic liver uptake) within 24 weeks prior to enrollment. Negative target lesions acceptable if below 15mm • Post first-line, only one line of cytotoxic chemotherapy is authorized: cytotoxic chemotherapy or everolimus or somatostatin analogs • Progressing disease within 12 months prior to randomization according to RECIST 1.1 criteria. • ECOG performance status 0-2 • Life expectancy ≥ 6 months • Adequate bone marrow reserve <u>Key Exclusion Criteria:</u> • Large or small cell-poorly differentiated pancreatic neuroendocrine tumor according to WHO 2010 classification • Any patient receiving treatment with short-acting Octreotide, which cannot be interrupted for 24 h before	<u>Intervention:</u> ^{177}Lu-DOTA0-Tyr3-Octreotate 7.4 GBq per injection Maximum of 4 injections <u>Comparator:</u> Sunitinib 37.5 mg/day	<u>Primary:</u> • 12-month progression-free survival (PFS) <u>Secondary:</u> • Overall survival (OS) • Best response

Trial Design	Eligibility Criteria	Intervention and Comparator	Trial Outcomes
	and 24 h after the administration of ^{177}Lu-DOTA0-Tyr3-Octreotate, or any patient receiving treatment with Octreotide LAR, which cannot be interrupted for at least 6 weeks before the administration of 177Lu-DOTA0-Tyr3-Octreotate, unless OctreoScan® imaging during continued Octreotide treatment is in accordance with the inclusion criteria. • More than one line of cytotoxic chemotherapy • Prior external beam radiation therapy to more than 25% of the bone marrow • Severe renal or hepatic insufficiency • Abnormal cardiac function • Serious non-malignant disease • Brain metastases (unless these metastases have been treated and stabilized for at least 24 weeks, prior to enrolment in the study. • Previous treatment with the drugs under study. • Current treatment with another investigational drug. • Treatment with potent CYP3A4 inhibitors and inducers within 7 and 12 days, respectively prior to study drug administration. • Prior treatments with chemotherapy or immunotherapy or somatostatine analog therapy drug (except in case of functioning syndrome for somatostatine analogue therapy) or thoracic radiotherapy within 4 weeks prior to start of treatment		

7 SUPPLEMENTAL QUESTIONS

The following supplemental questions were identified during development of the review protocol as relevant to the pCODR review of lutetium GEP-NETs.

- Matched-treatment comparison (MTC) comparing the efficacy of lutetium to relevant comparators, everolimus, sunitinib and best supportive care 26
- Critical appraisal of the Manufacturer's submitted matching adjusted indirect comparisons (MAIC) of lutetium compared to everolimus, sunitinib and placebo or BSC in patients with P-NETs27
- Critical appraisal of a published MAIC by Signorovitch et al.28 comparing everolimus to sunitinib among patients with advanced P-NETs.

Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

7.1 Matched-treatment comparison comparing the efficacy of lutetium to relevant comparators, everolimus, sunitinib and best supportive care

7.2 Objective

In the absence of RCTs comparing lutetium to relevant comparators, the Submitter performed an ITC in the form of an MTC to evaluate the relative efficacy between lutetium and relevant comparators for the GI-NET subgroup. The results of the MTC were incorporated into the economic analysis to inform the cost-effectiveness estimates for lutetium for GI-NETs. The manufacturer conducted several scenarios assessing the comparative effectiveness of lutetium compared to everolimus, Octreotide LAR, lanreotide, and sunitinib and placebo for patients with both GI-NETs and P-NETs. The economic analysis for the GI-NET subgroup was informed by the MTC. Therefore, this section will report only on scenarios that are relevant to patients with GI-NETs.

The Manufacturer provided an addendum to their MTC report with additional scenarios that included indirect comparisons for the progressive networks only. Additional scenarios were conducted twice, and differed on the data cut-off date of the NETTER-1 trial (2015[1] versus 2016). The scenarios from the 2016 data cut-off date from the NETTER-1 trial will be reported in this section to align with the economic evaluation.

Review of the Submitter's MTC

Objective of Submitter's MTC

The objective of the Submitter's MTC was to compare efficacy measures, OS and PFS, between lutetium and relevant comparators for the treatment of GEP-NETS, including everolimus, lanreotide, Octreotide LAR, placebo and sunitinib.

Study Eligibility and Selection Process

The submitter conducted a systematic review to identify relevant studies for the MTCs. Eligibility criteria included phase II to phase IV randomized studies with greater than 15 adult patients with inoperable, gastro-entero-pancreatic neuroendocrine tumours (GEP-NETs) receiving lutetium compared to SSAs (octreotide/lanreotide), interferon, everolimus,

sunitinib, or chemotherapy. OS, PFS, time to second objective disease progression, adverse events, and quality of life were included as relevant outcomes. Studies were ineligible if they did not separate GEP-NETs by sub-analysis (i.e. Lung, liver, thyroid, etc.), and if NETs were undefined.

The search was performed on November 26, 2015 and subsequently updated on January 20, 2016 and September 02, 2017 using the following databases: Medline (OvidSP), Medline In-Process Citations & Daily Update (OvidSP), Embase (OvidSP), Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley), NIH Clinicaltrials.gov (internet), WHO International Clinical Trials Registry Platform (ICTRP) (internet). Hand-searching of reference lists was conducted to supplement the electronic searches. Relevant data, including study characteristics and outcome information, were extracted from eligible studies. Full-text screening for eligible studies occurred in duplicate by two independent analysts. The quality of all included studies were appraised using guidelines from NICE, the Centre for Reviews and Dissemination, and the Cochrane Collaboration. By identifying the relevant studies, the Submitter was able to perform an MTC by constructing networks through shared comparators. Multiple scenarios were conducted to take into account different patient characteristics. Overall, the Submitter's systematic review was conducted with good practice.

MTC Methods

The MTC was performed using a Bayesian framework which allows for the combination of the (log) hazard ratios, allowing for assumptions of transitivity, homogeneity, and exchangeability. The transitivity assumption posits that patients in a network are comparable enough that they could have been given any treatments involved in the network. The homogeneity between patients and other relevant trial characteristics must be high enough to justify synthesizing the relative treatment effect across trials. Variance around reported hazard ratios can be used to incorporate uncertainty around the estimated treatment effects. The submitter stated that a key assumption of the model was that the hazard was constant over the follow-up period in each arm of each trial; this would then imply that the populations of patients were all homogenous, and all patients had the same hazard rate. The exchangeability assumption aims to counter bias comparisons due to imbalanced distributions of variables between trials.

The Submitter presented two Poisson distributed random effects models, which allowed for the incorporation of corresponding between-trial variability; this model choice was used to more accurately reflect the uncertainty which was inherent in the model. The models incorporated patients with progressive GI-NETs, and included the NETTER-1 and RADIANT-4 trials. The Submitter conducted these models twice using data from both the 2015 and 2016 data cuts from the NETTER-1 trial. Only the models based on the 2016 data cut from the NETTER-1 trial will be discussed in this section.

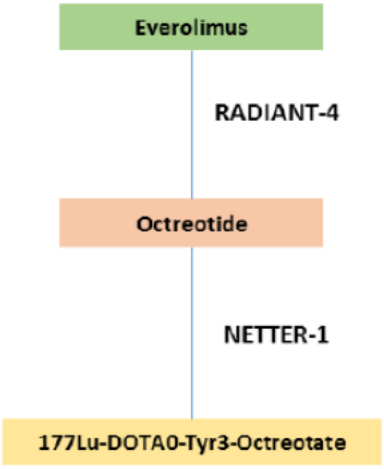
7.3 Findings[26]

Indirect Treatment Comparison

Results: MTC based on NETTER-1 CSR version 2: 2016-data cut

As previously stated, this MTC was performed for the progressive networks only. As such, the RADIANT-2 trial was excluded from the GI-NET analysis. The Submitter performed four network scenarios however only two were related to patients with GI-NETs; only scenarios related to GI-NET patients are reported here. The network scenarios include one scenario for GI-NET PFS data, and one scenario comparing GI-NET OS data. Figures 7.1 indicates the trials included in the network scenarios.

Figure 7.1: Scenario 1: Indirect Treatment Comparison Network for progressive GI-NET



Progression-Free Survival

Table 7.1 reports the data included in the GI-NET PFS addendum. Assumptions made for this network included the following: progressive patients only, assuming placebo in RADIANT-4 is the same as octreotide LAR in NETTER-1, SSR positive and negative patients respond the same to treatment, functional and non-functional patients respond the same to treatment, naïve and previously treated patients respond the same to treatment. A note of caution was made regarding the interpretation of these scenarios due to the number of assumptions that were made for each network scenario.

Table 7.1: Data included in the GI-NET PFS addendum

Study (Trial no.)	Intervention/comparator(s)	Label for MTC	PFS addendum Analysis population	Patient number (n)	Hazard ratio	Lower CI	Upper CI	P value
Advanced Accelerator Applications 2016 (NCT01578239 - NETTER-1)	177Lu-DOTATATE 29.6 GBq	177Lu-DOTATATE	ITT (Midgut NET)	117	0.214	0.139	0.331	<0.0001
	Octreotide LAR (60 mg)	Octreotide	ITT (Midgut NET)	114	NA	NA	NA	NA
Yao et al., 2015 (NCT01524783 - RADIANT-4)	Everolimus (10 mg) + BSC	Everolimus	sub-analysis ITT (GI-NET)	118	0.56	0.37	0.84	NR
	Placebo + BSC	Placebo	sub-analysis ITT (GI-NET)	57	NA	NA	NA	NA

Overall, lutetium did not demonstrate any statistically significant difference compared to everolimus, octreotide LAR or placebo. When ranked on probability of being best, lutetium was ranked first , suggesting it is the most effective treatment in GI-NET patients. However, caution is

warranted when interpreting these results due to the lack of statistically significant differences and many assumptions made for each network scenario.

Table 7.2: Results of Submitter's MTC Progressive GI-NET Scenarios for PFS

	Comparator			
Intervention		**Octreotide LAR/ placebo**	**Everolimus**	**177Lu-DOTATATE**
Octreotide LAR/ placebo	Estimate HR (95% CrI)	1 (1, 1)	0.56 (0.05, 6.97)	0.21 (0.02, 2.68)
Everolimus	Estimate HR (95% CrI)	1.79 (0.14, 21.77)	1 (1, 1)	0.37 (0.01, 13.61)
177Lu-DOTATATE	Estimate HR (95% CrI)	4.8 (0.37, 59.00)	2.69 (0.07, 93.28)	1 (1, 1)

HR, hazard ratio; P, probability; CrI, credible intervals

Overall Survival

Data included in the GI-NET OS analysis are in Table 7.3. Progressive patient studies were included. The GI-NET OS addendum compared the OS outcomes available for everolimus, octreotide LAR and lutetium in progressive NET patients because OS for GI-NET patients was not reported by the included studies. The following assumptions were made in the network: assumes all NET groups (midgut, colorectal, lung, GI-NET, P-NET) respond to the same treatment, placebo plus BSC in RADIANT-4 is equivalent to LAR in NETTER-1, SSR positive and negative patients respond the same to treatment, functional and non-functional patients respond the same to treatment, naïve and previously treated patients respond the same to treatment.

Table 7.3: Data included in the GI-NET OS addendum

Study (Trial no.)	Intervention/comparator(s)	Label for MTC	PFS addendum Analysis population	Patient number (n)	Hazard ratio	Lower CI	Upper CI	P value
Advanced Accelerator Applications 2016 (NCT01578239 - NETTER-1)	177Lu-DOTATATE 29.6 GBq	177Lu-DOTATATE	ITT (Midgut NET)	117	0.536	0.333	0.864	**0.0094**
	Octreotide LAR (60 mg)	Octreotide	ITT (Midgut NET)	114	NA	NA	NA	NA
Yao et al., 2015 (NCT01524783 - RADIANT-4)	Everolimus (10 mg) + BSC	Everolimus	ITT (FAS) (lung and GI-NETs)	205	0.64	0.4	1.05	0.037
	Placebo + BSC	Placebo	ITT (FAS) (lung and GI-NET)	97	NA	NA	NA	NA

There were no significant differences between any of the interventions when compared with lutetium or octreotide LAR. Lutetium was ranked as first, suggesting it is the most effective treatment in progressive NET patients. However, caution is warranted when interpreting these

results due to the lack of statistically significant differences and many assumptions made for each network scenario.

Table 7.4: Results of Submitter's MTC Progressive GI-NET Scenarios for OS

	Comparator			
Intervention		**Octreotide LAR/ placebo**	**Everolimus**	**177Lu-DOTATATE**
Octreotide LAR/ placebo	Estimate HR (95% CrI)	1 (1, 1)	0.64 (0.05, 8.04)	0.54 (0.04, 6.86)
Everolimus	Estimate HR (95% CrI)	1.56 (0.12, 19.23)	1 (1, 1)	0.84 (0.02, 29.49)
177Lu-DOTATATE	Estimate HR (95% CrI)	1.86 (0.15, 24.46)	1.20 (0.03, 43.73)	1 (1, 1)

HR, hazard ratio; P, probability; CrI, credible intervals

Critical Appraisal of the MTC

The quality of the MTC provided by the Submitter was assessed according to recommendations made by the International Society of Pharmaceoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons.[29] Details of the critical appraisal are presented below.

Table 7.5: ISPOR Questionnaire to Assess the Credibility of an Indirect Treatment Comparison or Network Meta-Analysis†	
ISPOR Questions	**Details and Comments‡**
1. Is the population relevant?	Yes, in part. The study populations of the included trials matched the review indication, which was to evaluate the efficacy of lutetium in adult patients with inoperable GEP-NETs. While initially the Submitter provided network scenarios that included both progressed and non-progressed patients, they provided a revised MTC analysis of GI-NET patients who had only progressed disease. However, it should be noted that OS was not reported separately for GI-NET patients in the RADIANT-4 trial, which may have biased the results of the network scenario when comparing OS between different treatments.
2. Are any critical interventions missing?	No. all relevant interventions were considered for this analysis.
3. Are any relevant outcomes missing?	Yes. The following outcomes were assessed: OS and PFS. Other relevant outcomes such as ORR, quality of life and safety were excluded from the Submitter's MTC.
4. Is the context (e.g., settings and circumstances) applicable to your population?	Yes. The settings of the included trials were similar, and applicable to the Canadian population.
5. Did the researchers attempt to identify and include all relevant randomized controlled trials?	Yes. The Submitter conducted a systematic review to identify eligible studies for the MTC.
6. Do the trials for the interventions of interest form one connected network of randomized controlled trials?	No. None of the two scenarios related to progressive GI-NET patients contain a closed loop.

Table 7.5: ISPOR Questionnaire to Assess the Credibility of an Indirect Treatment Comparison or Network Meta-Analysis[†]	
ISPOR Questions	**Details and Comments[‡]**
7. Is it apparent that poor quality studies were included thereby leading to bias?	Yes, in part. The Submitter critically appraised the quality of the studies included in the systematic review. Quality assessment was conducted according to criteria for assessment of risk of bias recommended by NICE, the Centre for Reviews and Dissemination, and The Cochrane Collaboration. However, the Submitter did not discuss how the quality of these trials could have impacted the results of the network comparisons.
8. Is it likely that bias was induced by selective reporting of outcomes in the studies?	Yes, in part. While the Submitter reported outcomes for OS and PFS, they did not consider any additional outcomes that may be considered relevant when comparing treatments. For example, safety and quality of life were not considered in the Submitter's MTC.
9. Are there systematic differences in treatment effect modifiers (i.e. baseline patient or study characteristics that impact the treatment effects) across the different treatment comparisons in the network?	Yes. Due to the number of assumptions being made in each network and the extreme variability across patient samples and trial characteristics, it is possible that the treatment comparisons were biased. The Submitter suggested that results be interpreted with caution.
10. If yes (i.e. there are such systematic differences in treatment effect modifiers), were these imbalances in effect modifiers across the different treatment comparisons identified prior to comparing individual study results?	Yes, the Submitter identified that numerous differences among the patient characteristics between the included trials existed. Conclusions drawn based on the network scenarios were suggested by the Submitter to be interpreted with caution due to the differences in trial characteristics, and the assumptions made for each network analysis.
11. Were statistical methods used that preserve within-study randomization? (No naïve comparisons)	Yes. A random effects Bayesian framework was implemented using Markov chain Monte Carlo methods.
12. If both direct and indirect comparisons are available for pairwise contrasts (i.e. closed loops), was agreement in treatment effects (i.e. consistency) evaluated or discussed?	Not applicable. No network scenarios contained a closed loop.
13. In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	Not applicable. None of the scenarios for progressive GI-NET patients contained a closed loop.
14. With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did the researchers attempt to minimize this bias with the analysis?	No.
15. Was a valid rationale provided for the use of random effects or fixed effect models?	Yes. The author stated that random effects models incorporate corresponding between variability and more accurately reflect the uncertainty inherent in the model.

Table 7.5: ISPOR Questionnaire to Assess the Credibility of an Indirect Treatment Comparison or Network Meta-Analysis[†]	
ISPOR Questions	**Details and Comments[‡]**
16. If a random effects model was used, were assumptions about heterogeneity explored or discussed?	Yes, in part. The Submitter explained assumptions related to their choice of models sued, and provided a list of assumptions for each network comparison. However, the Submitter did not discuss heterogeneity present between eligible trials and how this could have impacted the assumptions and results of the models. The Submitter concluded that interpretation of all results should be conducted with caution due to the high heterogeneity.
17. If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	No.
18. Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	Yes.
19. Are the individual study results reported?	Yes. The Submitter provided baseline characteristics of the trials and the HRs of the outcomes used in the NMA. The Submitter also reported efficacy data used in each network comparison from each trial.
20. Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analysis?	Not applicable. Neither of the two scenarios for progressive GI-NET patients contained a closed loop.
21. Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty?	Yes. The measures of uncertainty (95% credible intervals) were provided, where applicable.
22. Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	Yes. Interventions were ranked and treatment effects were reported along with 95% credible intervals.
23. Is the impact of important patient characteristics on treatment effects reported?	No. While no specific patient characteristics were specifically stated to have impacted the treatment effects, the author did suggest interpreting results with caution due to the high level of variability of patient characteristics between the included trials.
24. Are the conclusions fair and balanced?	Yes.
25. Were there any potential conflicts of interest?	Not reported. However, the Manufacturer of lutetium both wrote and performed the MTC, resulting in potential bias toward favourable conclusions for lutetium.
26. If yes, were steps taken to address these?	Not reported.
[†] Adapted from Jansen et al. Indirect Treatment Comparison/Network Meta-Analysis Study Questionnaire to Assess Relevance and Credibility to Inform Health Care Decision Making: An ISPOR-AMCP-NPC Good Practice Task Force Report. [‡]Bolded comments are considered a weakness of the ITC.	

Neither scenario detected any significant difference in PFS or OS among progressive GI-NET patients when comparing lutetium, octreotide LAR, everolimus and placebo. However, the NETTER-1 trial, demonstrated a strong statistically significant difference in PFS favouring lutetium over octreotide LAR. Since the NETTER-1 trial was phase 3 randomised controlled trial, the pCODR Review Team questioned why the Manufacturer's MTC could not detect a significant difference in PFS.

The random effects Poisson distribution model used by the Submitter takes into account variability between trials, and assumes that trial characteristics are similar enough to justify synthesizing relative treatment effects across trials. However, the Submitter identified that trial characteristics were greatly varied violating the assumption that there is enough homogeneity between trials used in the MTC. To assess robustness of networks with a closed loop, consistency testing can be performed, which would show that treatment effects estimated in the MTC are the same as actual treatment effects seen in the randomised controlled trials. However, as neither scenario 1 nor scenario 2 contained closed loops, consistency testing could not be performed. In addition, the assumptions of the two scenarios may also be too great to result in credible conclusions from the MTC. The lack of credibility due to unreasonable model assumptions may explain why neither scenario could detect a significant difference in PFS or OS among progressive GI-NET patients, especially while the phase 3 trial (NETTER-1) was able to detect a statistically significant difference in PFS. For the OS network, the submitter identified that OS was not reported separately for GI-NET patients in the RADIANT-4 trial, which resulted in mixed net population used for GI-NET. This may be another reason why there was a lack of statistically significant difference, whereas a significant difference was observed in the NETTER-1 trial.

7.3.1 Summary

The Submitter performed an ITC comparing outcomes associated with lutetium compared to relevant comparators for patients with progressive GI-NETs. Characteristics of patients in the included studies were substantially heterogeneous. The Submitter highlighted that patients varied on status of progressive or stable disease, presence or functional or non-functional and SSR positive or negative tumours, and whether they were previously treated or not. Overall, there were no statistically significant differences between lutetium, everolimus, octreotide LAR and placebo for PFS and OS. When ranked on probability of being best, lutetium was ranked first suggesting it is more efficacious compared to everolimus, octreotide LAR and placebo. The overall conclusions of the MTC are limited because of substantial heterogeneity in the studies and patient characteristics in the included studies. The results of the analyses should be interpreted with caution due to the number of assumptions that were made in the networks. Given these limitations, the comparative efficacy of lutetium to other comparators is uncertain.

7.4 Summary and Critical appraisal of the Manufacturer-submitted matching adjusted indirect comparison of lutetium to everolimus, sunitinib, and placebo in patients with P-NETs[27]

7.4.1 Objective

In the absence of RCTs comparing lutetium to relevant compactors, the Submitter undertook a review of clinical evidence and conducted an ITC in the form of a MAIC to evaluate the relative efficacy between lutetium and relevant comparators. The results of the MAIC were incorporated into the submitted economic evaluation to inform the cost-effectiveness estimates of lutetium for patients with P-NETs. The objective of this section is to summarize and critically appraise the methods and results of the manufacturer submitted MAIC comparing lutetium with relevant comparators (everolimus, sunitinib and placebo) for the treatment of advanced P-NETs.

7.4.2 Findings[27]

Rationale and Objectives

Multiple therapies are available for the treatment of patients with advanced P-NETs, including everolimus and sunitinib. The objective of the MAIC was to compare everolimus, sunitinib, and placebo to lutetium, as no head-to-head trials have been conducted comparing these relevant comparators to lutetium.

Source

The MAIC was performed by the submitter and has not been published or peer-reviewed. Three trials were used for this analysis: ERASMUS[30], RADIANT-3[11,31] and NCT00428597[12,32]. Individual patient level data was available from the ERASMUS trial for the Manufacturer to conduct their analysis, and published summary data was used for both the RADIANT-3 and NCT00428597 trials.

Systematic Review

The manufacturer conducted a systematic review to identify relevant randomised phase II to phase IV randomized studies with greater than 15 adult patients with inoperable, gastro-entero-pancreatic neuroendocrine tumours (GEP-NETs) receiving lutetium compared to SSAs (octreotide/lanreotide), interferon, everolimus, sunitinib, or chemotherapy. OS, PFS, time to second objective disease progression, adverse events, and quality of life were included as relevant outcomes. Details of the systematic review can be found in Section 7.1. Overall, the systematic review was conducted with good practice.

Methods

Trials included in MAIC

The following trials were included in the MAIC: ERASMUS[30], RADIANT-3[11,31] and NCT00428597[12,32]. The ERASMUS trial was a single arm trial enrolling a total of 1214 patients with GEP-NETs. All patients enrolled in the ERASMUS trial were given lutetium up to a cumulative intended dose of 750 to 800 mCi (27.8-29.6 GBq)[33]. Details of the ERASMUS trial are summarized in Section 8 of this report. RADIANT-3 was a randomized phase 3 trial

comparing everolimus to placebo. A total of 410 patients were enrolled in RADIANT-3 with 2017 and 2013 patients assigned to everolimus (10mg daily) and placebo, respectively. NCT00428597 was a randomized phase 3 trial comparing sunitinib (37.5mg once daily on a continuous dosing schedule) to placebo; this trial was terminated early on March 11, 2009 because it was determined by an independent Data Monitoring Committee that the study had met its primary endpoint in demonstrating improvement in PFS.[34]A total of 171 patients were enrolled in NCT00428597 with 86 and 85 patients assigned to sunitinib and placebo, respectively.

Matching Feasibility Assessment

In order to determine the feasibility of performing a MAIC analysis, the inclusion/exclusion criteria, and outcomes reported in each trial were reviewed and compared. Differences in baseline characteristics were noted when considering time from initial diagnosis, where the proportion of patients who reported a time from initial diagnosis of greater than five years were greater for RADIANT-3 compared to ERASMUS (31% for everolimus and 23% for placebo vs 16% in ERASMUS). Also, the median of time from initial diagnosis was longer for trial NCT00428597 compared to ERASMUS (2.4 years for sunitinib and 3.2 years for placebo vs. 1.24 years). There were also differences in time from disease progression to randomization between ERASMUS and RADIANT-3, and differences in previous treatments received from patients between ERASMUS and NCT00428597, where patients enrolled in NCT00428597 were more likely to have received surgery (88% for sunitinib and 91% for placebo vs 45% in the ERASMUS trial), and radiofrequency ablation, percutaneous ethanol injection which were not treatments reported in RADIANT-3 and ERASMUS. Patients enrolled in RADIANT-3 were more likely to have received somatostatin analogues compared to patient's enrolled in NCT00428597 and receiving either sunitinib or placebo (50% vs. 35% for sunitinib and 38% for placebo). It should be noted that patients who received therapy with short-acting somatostatin analogues were excluded from the ERASMUS trial. Within the NCT00428597 trial, patients receiving placebo were more likely to have undergone chemoembolization compared to patients receiving sunitinib (16% vs. 8%). Overall, patients enrolled in trial NCT00428597 were more likely to have undergone chemoembolization than patients enrolled in ERASMUS (13%), but less likely than patients enrolled in RADIANT-3 and receiving placebo (50%). Despite these differences in baseline characteristics, the Submitter conducted the MAIC analysis.

The inclusion and exclusion criteria between the trials were fairly similar, except that patients enrolled in the ERASMUS trial had measured performance statuses based on the Karnofsky scale, while patients in the RADIANT-3[11,31] and NCT00428597[12,32] trials measured performance status based on the WHO scale. In addition, patients with ECOG performance status of 2 were not included as part of the inclusion criteria for the NCT00428597 trial. Also, the Manufacturer stated that patients enrolled in RADIANT-3 had non-functioning tumors only while patients with functioning and non-functioning tumours were enrolled in ERASMUS and NCT00428597. The ERASMUS trial was not a randomized controlled trial, but rather a single arm study that initially enrolled patients with any GEP-NET. For this analysis, the submitter confirmed that data of patients with P-NETs from the ERASMUS trial were used.

Outcomes

The main outcomes of interest for the Submitter's MAIC were OS and PFS. Other outcomes of interest, such as ORR, quality of life, or safety, were not considered in the MAIC. The Manufacturer stated that definitions of progression were assumed to be the same across studies. PFS was defined as the time from randomisation to disease progression, or death from any cause. While the RADIANT-3 trial assessed PFS according to RECIST 1.0 criteria by

an investigator, trial NCT00428597 did not specify the version of RECIST criteria. The Manufacturer did not comment on the definitions of OS across trials. The time frames for calculation of OS across trials were determined be different across trials; OS was calculated until death or last day of follow-up for patients lost to follow-up in the ERASMUS[30] and RADIANT-3 trials[22,31], and until death or up to 22 months from start of study treatment in trial NCT00428597[34]. It is worth noting that trial NCT00428597 was terminated early, and OS was not mature at the time of data analysis. The median OS could not be estimated by Kaplan-Meier method for either treatment arm in the trial. The Submitter concluded, based on comparison of baseline characteristics, that there was good overlap between the study populations of the ERASMUS, RADIANT-3 and NCT00428597 trials.

Methods of Naïve Comparison

The Submitter conducted a naïve comparison of reconstructed everolimus, BSC and sunitinib data and ERASMUS Kaplan-Meier data to provide context and comparison with the population-adjusted estimates. Hazard ratios of OS and PFS were compared across trials.

Methods of MAIC

To identify relevant covariates, the Manufacturer identified covariates incorporated in a published MAIC by Signorovitch et al.[28] comparing everolimus to sunitinib including age, sex, performance status, time since diagnosis, number of disease sites, presence of distant metastases, prior use of somatostatin analogues and prior chemotherapy. The Manufacturer also incorporated expert clinical opinion to identify covariates of prognostic importance for patients with P-NETs. Since the ERASMUS trial measured performance status based on the Karnofsky scale, these scores were matched to the ECOG scale in the following way: Karnofsky score of 100 assigned to ECOG score of 0; Karnofsky score of 90 and 80 assigned to an ECOG score of 1; and a Karnofsky score of 70 and 60 were mapped to an ECOG score of 2. Through univariate analysis, covariates to be re-weighted within the ERASMUS trial were stated to be those which were statistically significant at the 20% level. The final list of covariates included age, ECOG performance status, previous chemotherapy and previous radiotherapy.

The weights for the MAIC were generated based on the probability that each patient would have been included in the comparator trial, creating an inverse propensity score. Weighted survival models were then used. Weights were used to compare OS and PFS between lutetium and comparators for each arm of the RADIANT-3 and NCT00428597 trials. The manufacturer stated that statistical analyses conducted in their MAIC were carried out in line with the NICE Decision Support Unit (DSU) guidelines, and their report met the requirements of the Quality of Effectiveness Estimates from Non-randomised Studies (QuEENS) checklist from the NICE DSU (Faria et al., 2015). Where individual patient level data was not available, the Guyot method was used to reconstruct individual time events and censoring times from the digitised Kaplan-Meier curves. An unanchored MAIC was conducted, which involves stronger assumptions that are generally regarded as unfeasible.[35] Due to the unanchored nature of the comparisons, the NICE DSU recommends that bias due to missing covariates be estimated, however the Manufacturer stated that they could not estimate residual bias due to lack of external studies to compare variance.

A survival analysis was conducted after the MAIC had been performed. Hazard ratios were estimated using cox proportional hazard models fitted to adjusted lutetium OS and PFS data from the ERASMUS trial, and reconstructed patient level data for everolimus, sunitinib and placebo.

Results

Naïve Comparison

Naïve comparisons of everolimus, placebo and sunitinib suggested that everolimus and sunitinib were both effective treatments for delaying the progression of P-NET tumours. The hazard ratio for overall survival for patients treated with everolimus was 0.94. Median survival times for everolimus in the RADIANT-3 trial and sunitinib in trial NCT0042859 were 44 months and 42 months, respectively, which were both greater than the median survival times for placebo in each trial (37.7 months in RADIANT-3 and 30 months in NCT0042859). Median survival for patients treated with lutetium was 66.9 months. The Submitter stated that the trial for sunitinib showed that 27% more patients survived receiving sunitinib compared to placebo. Hazard ratios for PFS for everolimus and sunitinib were 0.35 and 0.42, respectively. Median PFS was 11.3 months and 12 months for everolimus and sunitinib, respectively. The median PFS of everolimus and sunitinib were greater than median PFS for placebo in both the RADIANT-3 (4.6 months) and NCT0042859 (5.6 months). The median PFS of patients receiving lutetium was 30.9 months, which was greater than the median PFS observed for everolimus, sunitinib and placebo. The naïve comparison concluded that lutetium was the most effective treatment compared to everolimus, sunitinib and placebo.

Matching-Adjusted Indirect Comparison

After matching, there was successful balance between baseline characteristics between trials, however the sample size of patients from the ERASMUS trial was markedly reduced. Sample sizes of the ERASMUS trial were post-matching were between 17% and 36%. Median survival times suggested that lutetium was more effective than everolimus, sunitinib or placebo at delaying progression or death (Table 7.6). Hazard ratios estimated from the MAIC indicate lutetium as being advantageous over everolimus, sunitinib or placebo (Table 7.7). After adjustment of baseline characteristics, OS and PFS for lutetium was determined to be statistically significantly better compared to everolimus, sunitinib and placebo.

Table 7.6: Median survival times taken from reconstructed trials and estimated from Matching Adjusted Indirect Comparisons[26]

Comparator	Median PFS (pre-match)	Median PFS (post-match)	Median OS (pre-match)	Median OS (post-match)
NCT00428597 (Sunitinib)	12.0	12.0	42.0	42.0
Lutathera	30.9	24.5	66.9	96.5
NCT00428597 (BSC)	5.6	5.6	30.0	30.0
Lutathera	30.9	29.4	66.9	87.9
RADIANT-3 (everolimus)	11.3	11.3	44.0	44.0
Lutathera	30.9	19.7	66.9	56.4
RADIANT-3 (BSC)	4.6	4.6	37.7	37.7
Lutathera	30.9	20.9	66.9	64.3

Table 7.7: Hazard ratios estimated from Matching Adjusted Indirect Comparisons[26]

Comparator	Hazard ratio PFS [95% CI]	Hazard ratio OS [95% CI]
Lutathera versus. NCT00428597 (Sunitinib)	0.47 [0.25, 0.88]	0.50 [0.29, 0.84]

Lutathera versus. NCT00428597 (BSC)	0.12 [0.07, 0.21]	0.33 [0.20, 0.56]
Lutathera versus. RADIANT-3 (everolimus)	0.52 [0.34, 0.79]	0.61 [0.39, 0.98]
Lutathera versus. RADIANT-3 (BSC)	0.21 [0.13, 0.32]	0.56 [0.36, 0.90]

Critical Appraisal: Limitations and Sources of Biases

The quality of the manufacturer-submitted MAIC was appraised according to best practice principles outlined by Sigorovitch et al. 2012. The pCODR Methods Team noted the following:

- Performance status, while measured using the ECOG scale in RADIANT-3 and trial NCT0042859, was measured using the Karnofsky scale and then mapped to the ECOG scale for parity. Both performance measure scales are commonly used in the clinical practice, however there are multiple ways to map the scales to each other.
- MAIC analysis adjusted for four covariates, age, ECOG performance status, previous chemotherapy and previous chemotherapy. While the covariates were identified through expert clinical opinion and empirical investigation, the limited number of variables was questioned by the pCODR Review Team, as another published MAIC by Signorovitch et al[28]. was identified and determined a greater number of covariates as being relevant. This MAIC by Signorovitch et al. has been critically appraised by pCODR. The Manufacturer stated that their use of limited covariates was to avoid extreme weighting values that would greatly reduce effective sample size. It was noted that the effective sample size in the ERASMUS trial was markedly reduced as a result of the matching. It is possible that additional patient related factors measured between the trials, and uncontrolled for in the Submitter's MAIC impacted the estimates of efficacy between lutetium, sunitinib, everolimus and placebo. It is also possible that unmeasured patient factors between trials biased the estimates of efficacy due to unknown confounding.
- The Manufacturer reported that of the covariates controlled for in their analysis, age, ECOG status, and proportion of patients who received prior surgery or chemotherapy, the proportions of patients for age, ECOG status and prior surgery were similar across trials. However, the Manufacturer noted that the proportion of patients receiving prior chemotherapy was higher in the ERASMUS trial, which may have led to some of the differences estimated in the OS and PFS comparisons.
- Overall, there were differences noted in baseline patient characteristics across trials. For example, patients in the ERASMUS trial had their Karnofsky performances status scores matched to the ECOG scale (0, 1, and 2) for comparison to the RADIANT-3 and NCT00428597 trials. However, patients with ECOG performance status of 2 were not incorporated in the inclusion criteria of the NCT trial. This difference is expected not to have a great impact on the comparisons between the trials as the very few patients in each trial had patients recorded with an ECOG performance score of 2. While differences between other baseline characteristics did exist, the proportions and medians of the majority of variables between the trials were consistent.
- A main limitation of this analysis was that there was no common comparator between any of the comparisons to lutetium, as the ERASMUS trial was the only source of data for lutetium and was a single arm trial. Due to the unanchored nature of this analysis, the results of relative effect measures, in this case hazard ratios, must be interpreted with caution.
- Trial NCT00428597 ended early and OS data had not yet become mature. Median OS could not be estimated in this trial for either the sunitinib or placebo arms. Therefore, OS data used for comparison of treatment efficacy with sunitinib should be interpreted with caution; there is uncertainty in the estimates obtained through this MAIC analysis.

7.4.3 Summary

The Manufacturer submitted a MAIC comparing lutetium to everolimus, sunitinib and placebo for patients with advanced P-NETs. The Manufacturer's MAIC concluded that lutetium was the superior treatment compared to everolimus, sunitinib and placebo. As a result of the unanchored nature of the MAICs and the small sample sizes post-matching of the ERASMUS trial, all hazard ratios should be interpreted with caution. The overall conclusions of the MAIC are limited because of substantial heterogeneity in the studies and patient characteristics among the included studies. Given these limitations, the comparative efficacy of lutetium to other treatments is uncertain.

7.5 Critical appraisal of the published matching-adjusted indirect comparison of everolimus and sunitinib for advanced pancreatic neuroendocrine tumours [28]

7.5.4 Objective

In the absence of RCTs comparing lutetium to relevant compactors, the Submitter provided a published MAIC by Sigorovitch et al.[28] to evaluate the relative efficacy between lutetium and relevant comparators for P-NETs. While the MAIC conducted by Signorovitch et al.[28] does not include lutetium as a comparator, it was highlighted by the Manufacturer to provide greater context regarding relative efficacy between everolimus and sunitinib. The hazard ratios reported in this MAIC were used to inform the everolimus arm incorporated into the economic evaluation to help inform the cost-effectiveness estimates of lutetium for patients with P-NETs. The objective of this section is to summarize and critically appraise the methods and results of the published MAIC by Signorovitch et al.[28] comparing everolimus to sunitinib for patients with advanced P-NETs.

7.5.5 Findings

Rationale and Objectives

MAIC methods were used to compare everolimus with sunitinib to derive relative estimates of treatment effect for the P-NET subgroup as supportive evidence for the pCODR submission. The objective of the MAIC was to compare everolimus and sunitinib among patients with advanced P-NETs.

Source

The MAIC was performed by Sigorovitch et al.[28] Two trials were used for this analysis: one comparing everolimus to placebo (RADIANT-3[11]) and another comparing sunitinib to placebo (NCT00428597[12]). Cross-over was allowed in both trials form placebo to active treatment following disease progression. Individual patient data were available for the RADIANT-3 trial. Published summary data was used in the MAIC analysis for trial NCT00428597.

Systematic Review

It was not clear whether a systematic review was used to identify relevant literature to inform the MAIC.

Methods

Trials included in the MAIC

The following trials were included in the MAIC: RADIANT-3[11] and NCT00428597[12]. Both of these trials are described above. It should be noted that Sigorovitch et al. refers to trial NCT00428597 as A6181111; both of these trial identifiers are referring to the same trial and for consistency within this report, it will be referred to as NCT00428597. Both of these trials are described above.

Outcomes

Both trials reported PFS, defined as the time from randomization to the first documentation of disease progression according to RECIST version 1.0, or death from any cause. Overall survival was a secondary efficacy measure in both trials, however OS data were not mature in trial NCT00428597 as the trial was terminated early. Definitions of OS and PFS for both trials are described above.

For both RADIANT-3 and trial NCT00428597, safety assessments included documentation of adverse events with the use of the National Cancer Institute common Terminology Criteria for Adverse Events, version 3.0, hematologic and biochemical laboratory results, physical examination and vital-sign measurements.[11,12]

The authors noted that while imaging was conducted among both trials when progression was suspected or during scheduled assessments, the schedule for conducting imaging varied between the two trials. In RADIANT-3 imaging occurred every 12 weeks, while imaging occurred at weeks five, nine and every eight weeks thereafter. The authors concluded that RADIANT-3 and NCT00428597 trials were comparable to analyze in a MAIC.

Matching Feasibility Assessment [28]

The inclusion and exclusion criteria, baseline characteristics of included patients, and the outcomes reported in each trial were reviewed and compared (Table 7.8). The inclusion and exclusion criteria between the RADIANT-3 and NCT00428597 trials were similar. The authors reported that compared to baseline in trial NCT00428597, patients in RADIANT-3 were more likely to have an ECOG performance status of 0 (68.8% vs. 55.0%) and more likely to have used somatostatin analogues (49.2% vs. 36.3%), however patients were less likely to have previously used systemic chemotherapy (48.7% vs. 69.0%).

Methods of MAIC[28]

The manufacturer was able to use individual patient level data for the RADIANT-3 trial, and published aggregate data for trial NCT00428597. Since patients with an ECOG performance status of 2 were not included in trial NCT00428597, these patients were removed from the RADIANT-3 sample for the analysis. Baseline characteristics were compared between the two trials using t-tests and chi-square tests. Baseline characteristics adjusted for between the trials included age, sex, ECOG performance status (0 vs 1), time since diagnosis (≥3 years vs <3 years), number of disease sites (1, 2, or ≥3), presence of distant metastases, previous somatostatin analogues, and previous systemic chemotherapy.

Individual patients enrolled in RADIANT-3 were assigned weights to adjust baseline characteristics to match trial NCT00428597. Relative propensities were estimated using a logistic regression model that included all matched-on baseline characteristics as covariates. After matching PFS was compared for everolimus versus sunitinib, comparing each drug to placebo. A Cox proportional hazards model was used to fit to RADIANT-3 and

then was compared to the published hazard ratio for sunitinib using the method of Bucher et al. in the matched samples. The authors stated that due to the crossovers to active therapy within the trials, drug effects on OS can be obscured and complicate indirect comparisons making comparisons to relative effect measures, such as hazard ratios, invalid. The authors conducted a MAIC to compare OS between everolimus and sunitinib, however the placebo arm data were not used due to the crossover. Individual patients in the everolimus arm in RADIANT-3 were assigned the same weights previously used to match baseline values to trial A6, and figure OS data were used from the sunitinib arm in trial NCT00428597. Using a weighted cox proportional hazards model and weighted Kaplan-Meier estimates, these OS data were used to compare OS between everolimus and sunitinib.

MAIC Results[28]

After matching, baseline characteristics between RADIANT-3 and trial NCT00428597 matched exactly (Table 7.8). With the placebo arms serving as a common comparator, everolimus was associated with similar PFS compared to sunitinib; although, this comparison was not statistically significant (HR=0.84, 9%CI=0.46-1.53, p=0.578). However, the authors noted that the trials measuring OS and PFS for everolimus and sunitinib were both powered to detect differences with placebo, and not each other. Therefore, cross trial comparisons of OS and PFS between everolimus and sunitinib are limited.

The analysis for OS excluded the placebo arms due to the crossovers; in this analysis everolimus was associated with similar OS compared to sunitinib; (HR=0.81, 95%CI=0.49-1.31, p=0.383). Everolimus was associated with longer OS compared to the placebo arm in trial NCT00428597 (HR=0.61, 95%CI=0.38-0.98, p=0.042), but not compared to sunitinib (HR=0.81, 95%CI=0.49-1.31, p=0.383); It should be noted that OS data were not mature in trial NCT00428597 due to the early stopping of the trial. Median OS was also not reached for patients randomized to everolimus in RADIANT-3.

Table 7.8: Baseline characteristics pre-and post-matching

Baseline characteristics[a]	RADIANT-3 study sample		A6181111
	Pre-match	Post-match	As reported
Median age (years)[b]	58.0	56.5	56.5
Age > 64 years	27.4	26.3	26.3
Female	44.9	52.0	52.0
WHO or ECOG[c] performance status of 0	68.8[d]	55.0	55.0
Time since diagnosis ≥3 years	46.7	48.0	48.0
Number of disease sites			
1	28.2	31.4	31.4
2	36.8	33.7	33.7
≥3	35.0	34.9	34.9
Presence of distant metastases	96.2	94.7	94.7
Previous somatostatin analogues	49.2[d]	36.3	36.3
Previous systemic chemotherapy	48.7[d]	69.0	69.0

Notes:
[a]Reported as percentages, unless otherwise noted.
[b]For A6181111, 56.5 is the midpoint between reported medians on the active (56) and placebo (57) arms.
[c]An ECOG performance status of 0 was equated to a WHO performance status of 0.
[d]$P < 0.05$ for comparison vs. A6181111.

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Table 7.9: Comparisons of PFS and OS

Comparison	Before matching			After matching		
	HR	95% CI	P-Value	HR	95% CI	P-Value
Progression-free survival						
Everolimus vs. Placebo	0.38	0.29-0.49	<0.001	0.35	0.24-0.52	<0.001
Sunitinib vs. Placebo	0.42	0.26-0.66	<0.001	0.42	0.26-0.66	<0.001
Everolimus vs. Sunitinib[a]	0.90	0.53-1.53	0.695	0.84	0.46-1.53	0.578
Overall survival						
Everolimus vs. Placebo in A6181111	0.53	0.35-0.78	0.002	0.61	0.38-0.98	0.042
Everolimus vs. Sunitinib	0.69	0.46-1.05	0.087	0.81	0.49-1.31	0.383

Notes:
[a]Comparison based on the HR for everolimus vs. placebo divided by the HR for sunitinib vs. placebo.

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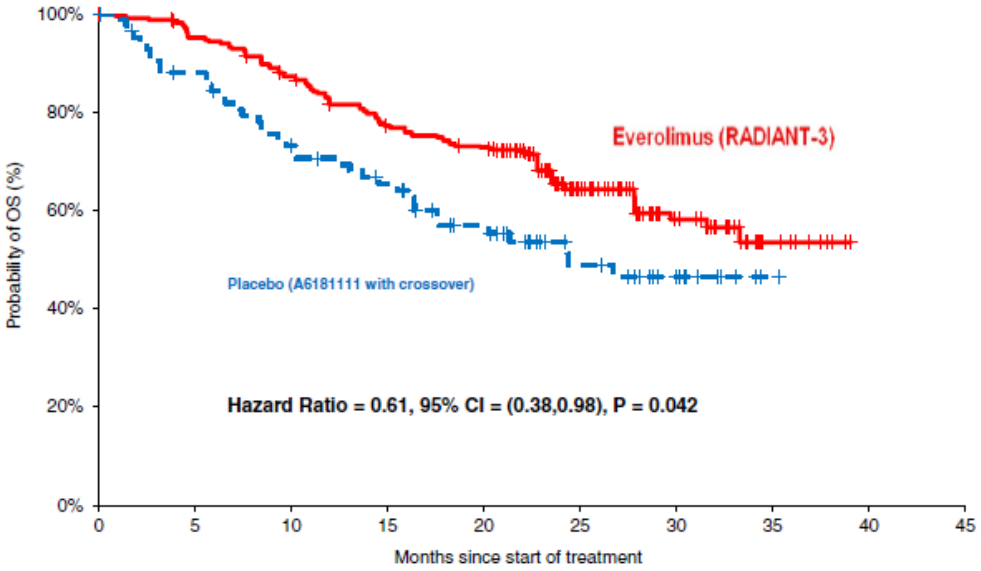
Figure 7.2: OS of Everolimus vs Placebo in NCT00428597 after matching



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After matching, everolimus was associated with significantly higher placebo-adjusted rates of peripheral edema (OR=4.24; p=0.011), and fever (OR=3.22; p=0.049) compared to sunitinib; almost all of these events were of grade 1 or 2 in severity in the everolimus arm. Occurrences of peripheral edema and fever of grade 3 or 4 were stated not to differ significantly between everolimus and sunitinib. Placebo-adjusted rates of neutropenia (OR = 0.15; p = 0.049) and hypertension (OR = 0.19; p = 0.021) were significantly lower with everolimus and sunitinib, with over one-third of these events in the sunitinib arm being of grade 3 or 4. Other adverse events did not show statistically significant differences at the 5% level. The authors noted that no adjustments for multiple comparisons were made, making these analyses exploratory. These comparisons of side effects between everolimus and sunitinib should be made with caution.

Critical Appraisal: Limitations and Sources of Biases

The quality of the manufacturer-submitted MAIC was appraised according to best practice principles outlined by Signorovitch et al. 2012.[36] The pCODR Methods Team noted the following:

After adjusting for baseline characteristics, everolimus was associated with longer OS versus placebo in trial A6, although crossover to sunitinib after progression was noted. Compared to sunitinib, everolimus was associated with similar PFS and OS. The authors concluded that a clinical significant improvement existed among patients with advanced pNET receiving everolimus compared to placebo when considering OS. Although, the authors noted that the true effect of everolimus on OS compared to placebo is likely to be underestimated based on this MAIC analysis due to the crossover in the placebo arm, or the early stopping that occurred in trial NCT00428597[12]. The authors acknowledged that after adjusting for baseline characteristics reduces the potential for observed characteristics to bias cross trial comparisons; however, the authors did not report how the sample sizes were affected after matching. For example, whether sample sizes were reduced.

While comparison of adverse events were made between everolimus and sunitinib, these analyses were not adjusted for multiple comparisons. Therefore, the authors suggested interpreting any conclusions related to side effects with caution, and that these analyses should be considered exploratory. The authors also noted that trial NCT00428597[12] did not report many side effects that were reported in RADIANT-3, therefore no comparison could be made. The authors also noted that while each respective study, RADIANT-3 and trial NCT00428597[12], were powered to calculate within-trial differences in PFS, MAIC conducted by Signorovitch et al[28]. was most likely underpowered to detect cross-trial differences in adverse event risk.

The MAIC conducted by Signorovitch et al.[28] balanced baseline characteristics of both RADIANT-3[11] and trial NCT00428597[12] by adjusting their analysis with a number of covariates to reduce potential for bias between cross trial comparisons of outcomes. However, adjustment could only be made for variables that were present between both RADIANT-3[11] and trial NCT00428597[12]. Even with adjustment of baseline characteristics, the comparison of hazard ratios for OS were not possible due to the crossover form placebo to active therapy in both RADIANT-3[11] and trial NCT00428597[12].

Other limitations noted by the authors included bias related to unobserved variables that may confound cross-trial comparisons of hazard ratios.[28]

In addition, scheduled imaging for detection of disease progression differed between the trials. The impact of this difference on outcome measure comparisons was suggested to be limited, since comparisons were based on hazard ratios relative to placebo. Also, imaging schedules were consistent between placebo and active therapy arms within each trial, limiting direct impact of comparisons of OS.

For a true comparison of everolimus to sunitinib, a head-to-head randomized trial is needed. In the absence of such data, indirect comparisons of treatments must be used. However, uncertainty in clinical effect estimates exist and the results should be interpreted with caution.

7.5.6 Summary

The Manufacturer identified a published MAIC conducted by Signorovitch et al.[28] comparing everolimus, sunitinib and placebo among patients with advanced P-NETs. The efficacy outcomes were used to inform the everolimus arm incorporated into the economic evaluation. The authors concluded that PFS was statistically significantly better for everolimus and sunitinib compared to placebo. OS was also determined to be statistically significantly better for everolimus compared to placebo. However, the authors concluded that everolimus and sunitinib were not statistically significantly different between each other when comparing either OS or PFS. Everolimus and sunitinib were concluded to have similar PFS and OS. The authors highlighted that both trials, RADIANT-3[11] and NCT00428597[12], which included everolimus and sunitinib, respectively, were powered to compare efficacy measures to placebo and not another active treatment; therefore, cross trial comparisons should be interpreted with caution. While the authors conducted comparisons of adverse events between trials, they noted that no adjustments for multiple comparisons were made and that these analyses should be considered exploratory; conclusions regarding comparisons of side effects between everolimus and sunitinib should be made with caution. Despite the good practices conducted by the authors, the results may still be biased due to unmeasured baseline characteristics, cross-over that was present in both studies, and lack of power for cross trial comparisons of everolimus and sunitinib. Results of the MAIC conducted by Signorovitch et al.[28] should be interpreted with caution.

8 COMPARISON WITH OTHER LITERATURE

This section describes how the evidence summarized in the pCODR systematic review compares with published literature or other findings. The reimbursement request is for patients with unresectable advanced or metastatic somatostatin receptor-positive GEP-NETs of the foregut, midgut and hindgut. The pivotal trial identified in the systematic review, NETTER-1, included patients with only midgut tumours. The CGP identified the ERASMUS trial as a relevant study, which evaluated the safety and efficacy of ^{177}Lu-dotatate in patients with somatostatin receptive positive GEP-NETS (i.e., not limited to midgut tumours) that included multiple tumour types.[30] The CGP considered the ERASMUS trial to be a relevant study even though it did not meet the criteria for the systematic review. The purpose of this section is to summarize and critically appraise the ERASMUS trial.

8.1 Study Design

The ERASMUS trial is an investigator sponsored, phase 1/2 non-randomized, open-label, single group study evaluating the safety and efficacy of ^{177}Lu-dotatate in patients with different somatostatin receptor-positive tumour types, including pancreatic NETs (P-NETs), foregut, including bronchial NETs, midgut NETs, and hindgut NETs.[30]

8.2 Study Population

In total, the ERASMUS trial enrolled 1214 patients between January 2000 and December 2012. The majority of patients were enrolled in the Netherlands (67%, n=810); the remaining patients were referred to international or non-Dutch patients (33%, n=404). Most patients in the ERASMUS trial had GEP-NETs of the foregut, midgut, hindgut, bronchus, and P-NET. Patients treated with ^{177}Lu-dotatate in the ERASMUS trial received ^{177}Lu-dotatate through compassionate access. The protocol used by investigators was developed from industrial protocols used in previous studies with similar radiolabeled peptides, including ^{111}In-DTPA^{0}-Octreotide and ^{90}Y-DOTA^{0}-Tyr^{3}-Octreotide.[30]

Patients included in the ERASMUS trial met the following eligibility criteria[4,30,37]:

- Presence of histology proven GEP-NET, which included bronchial carcinoid tumours
- Presence of somatostatin receptors on known tumour lesions as demonstrated by OctreoScan within six months of the first dose of radiolabeled ^{177}Lu-dotatate. The uptake on the OctreoScan was to be at least as high as normal liver uptake on planar imaging.
- Life expectancy >12 weeks.
- Adequate laboratory values including: serum creatinine ≤150 µmol/L and a calculated (Cockroft's formula), or preferably a measured creatinine clearance, based on two 24-hour urine collections, of ≥40 mL/min, Hb concentration ≥5.5 mmol/L, WBC ≥2x10^{9}/L, platelets ≥75x10^{9}/L, total bilirubin ≤3 x ULN, and serum albumin >30g/L
- Karnofsky Performance Score ≥50
- No prior treatment with other radiolabeled somatostatin analogs

Exclusion criteria included having the following:

- Possible surgery with curative intent
- Surgery, radiotherapy, chemotherapy, or other investigational therapy within three months prior to the start of ^{177}Lu-dotatate therapy

- Known brain metastases, unless these metastases have been treated with stabilized for at least six months prior to study start. Patients with a history of brain metastases must have a head CT scan with contrast to document stable disease prior to study start
- Uncontrolled congestive heart failure
- Any patient receiving therapy with short-acting SST analogues in whom these analogues cannot be interrupted for 12 hours before and 12 hours after the administration of the radiolabelled SST analogues, or any subject receiving therapy with long-acting SST analogues in whom these analogues cannot be interrupted for at least six weeks before the administration of the radiolabelled SST analogue, unless the uptake on the OctreoScan during continued SST analogue medication is at least as high as normal liver uptake on planar imaging.

8.3 Intervention and Assessments

Patients were treated with ^{177}Lu-dotatate up to a cumulative dose of 750 to 800 mCi (27.8 to 29.6 GBq, which corresponds to a radiation dose of 2 Gy to the bone marrow); if the radiation dose to the kidneys exceeded 23 Gy, the cumulative dose was reduced to 500 to 700 mCi. Every six to 13 weeks, patients were treated with ^{177}Lu-dotatate via four intravenous administrations at 200 mCi (7.4 GBq). Some patients may not have received a cumulative dose of 800 mCi for the following reasons: patients may have had lower starting doses, patients may have experienced dose limiting toxicity resulting in dose reduction or discontinuation, patients may not have received the fourth treatment because their kidney dosimetry data based on planar images indicated they would exceed the 23 Gy kidney threshold dose limit if administered with full dose, patients requested an end to their treatment with ^{177}Lu-dotatate, presence of morbidity, variations in the amount of ^{177}Lu delivered to the hospital Radiopharmacy for preparation of ^{177}Lu-dotatate, or death. ^{177}Lu-dotatate was co-administered via a second pump system along with granisetron (3 mg) or ondansetron (8 mg), which was injected intravenously, and an infusion of amino acids (lysine 2.5%, arginine 2.5% in 1 L 0.9% NaCl; 250 mL/h).[30]

Routine hematology, liver and kidney function tests were performed before each therapy and at follow-up visits. Patients also received a CT scan or MRI within three months before beginning ^{177}Lu-dotatate therapy, and then every six to eight weeks, three months, and six months following their last treatment, and then every six months afterward or until disease progression occurred. [30]

8.4 Statistical Analyses

Data presented for the ERASMUS trial in this section is from the Statistical Analysis Plan (SAP) provided by the Submitter, AAA which was based on both retrospective and prospective collected data. It should also be noted that the SAP for the ERASMUS study was not formally prespecified, therefore no formal statistical and sample size planning occurred for this trial. Data were analysed during two separate periods. The first analysis period occurred in 2011/2012 and included 615 patients enrolled between January 2000 and March 2007, with a follow-up cut-off date of February 2010. The second analysis period included follow-up data from the 615 patients included at the first analysis as well as new patients enrolled between March 2007 and December 2012, resulting in the analysis of 1214 patients. In addition, the second data analysis included a subgroup of 53 patients with GEP-NETs; these patients were enrolled in the control arm of the ^{177}Lu-DOTA0-Tyr^3-Octreotate + Xeloda study protocol (these patients received ^{177}Lu-DOTA0-Tyr^3-Octreotate alone).[30]

The Submitter, AAA, contracted an independent CRO to verify the ERASMUS study source data retrospectively and to generate a SAS database for statistical analysis. The authors conducted an analysis of variance (ANOVA), paired t tests, chi square tests (or Fisher's exact test if applicable), Pearson's correlation tests, and logistic regression. Log-rank tests and Cox regression models were used for survival analysis.[37]

8.5 Outcomes of Interest

The primary objectives of the ERASMUS trial were to determine the overall response rate (ORR), duration of response (DoR) in patients with SSTR positive tumours treated with ^{177}Lu-dotatate as assessed by investigators using RECIST 1.1 criteria, as well as safety. Analysis of ORR and DoR included descriptive analyses including proportion and binomial exact confidence intervals (95% CI), and number of non-missing value, quartiles, arithmetic mean, standard deviation, minimum, median and maximum, respectively. The Kaplan-Meier method was used to assess median DoR and 95%CI.[30] The Kaplan-Meier method was also used to analyze PFS and OS. An alpha of 0.05 was specified as the threshold for meeting statistical significance. [33]

Two sensitivity analyses were conducted by the submitter. The first sensitivity analysis was conducted to assess the impact of patients without baseline tumour measurements on the ORR, as the initial assessment of ORR did not include those patients. The second sensitivity analysis incorporated investigator notes made throughout the trial regarding patient progression or death when calculating ORR, OS and PFS. The results of the second sensitivity analysis are not reported here.

It is worth mentioning that while originally assessed using SWOG criteria, throughout the trial the response assessment criteria was altered to be evaluated by RECIST criteria for regulatory purposes, and to provide comparison with the NETTER-1 trial.[4,30]

Quality of life (QoL) was assessed using the QLQ-C30 questionnaire or all patients enrolled in the study (see Section 1.2.3 for details regarding patient enrollment). For patients enrolled after March 2007, QoL was assessed using the QLQ-C30 and QLQ-GI.NET21 questionnaires. Missing data were imputed according to the official scoring manual.

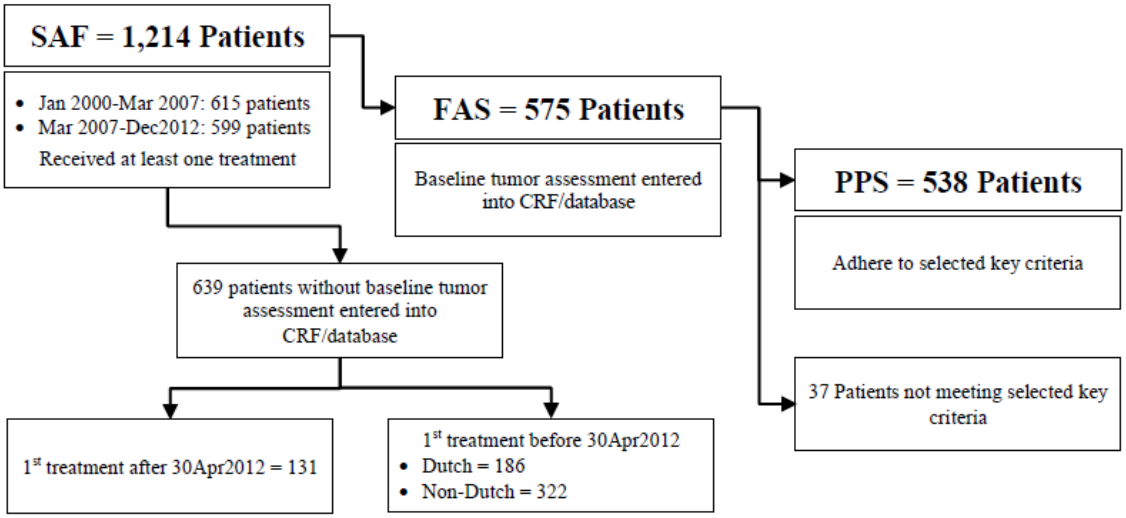
8.6 Analysis Sets and Patient Disposition

The Safety Analysis Set (SAF) [n=1214] included all patients who were enrolled in the ERASMUS trial and who had a baseline tumour assessment recorded. The Full Analysis Set (FAS) [n=575] included all patients enrolled and who received at least one treatment with ^{177}Lu-dotatate. See Figure 8.1. These subgroups were not pre-specified.

For the analysis of safety, the SAF will be summarized. The results reported in this section are from patients who were enrolled until the end of the second analysis in December 2012.

Within the SAF, a total of 1214 patients were enrolled; 615 patients were enrolled between January 2000 and March 2007, and 599 patients were enrolled between March 2007 and December 2012. Therefore, the SAF included all patients. Within the FAS, all patients who were enrolled and had at least one valid baseline tumour assessment were included (n=575).

Figure 8.1: Patient Subgroups in the ERASMUS trial[30]



An exploratory analysis was conducted post-hoc on a subset of patients from the FAS dataset with progressive mid-gut NETs, comparable to the NETTER-1 phase 3 trial comprised of 118 patients.

8.7 Results

8.7.1 Demographic Characteristics

The proportion of males and females, mean age, and median BMI were similar across both the FAS and SAF (Table 1). Among the entire patient sample (SAF, n=1214) slightly over half of patients were male (54.2%, n=658) with a mean age of 58.4 years (range 16-90); one patient was reported as being younger than 18 years of age with a non-GEP-NET tumour. In the entire SAF dataset, 19.4% and 12.6% of patients were previously treated with chemotherapy and radiotherapy, respectively. Nearly half of the sample (48.9%) had previously received surgery. Most of the patients in the SAF dataset were Dutch (n=810). The mean age for Dutch patients in the SAF dataset was 59.7 years (range 18-90). The Dutch population in the SAF dataset contained 51.6% males (n=418).[4,30]

Table 8.1: Demographic Characteristics of ERASMUS study, FAS and SAF subsets [4]

Demographic Parameters	FAS N=578	SAF		
		Dutch N=811	Non-Dutch N=403	Total SAF N=1214
Sex: male, %	58	52	60	54
Age (years), median (range)	59 (16, 86)	60 (18, 90)	56 (16, 85)	58 (16, 90)
≥ 65 years, %	31	36	21	31
BMI (kg/m^2), median (range)	24 (15, 45)	24 (15, 97)	24 (15, 37)	24 (15, 97)
Region, % Dutch	85	-	-	67
Karnofsky Performance Score, %				
100	32	25	32	27
90	38	36	35	36
80	20	23	15	21
70	6	8	5	7
≤ 60	4	5	3	4
Missing	0	3	10	5
Median (range)	90 (40, 100)	90 (40, 100)	90 (40, 100)	90 (40,100)

A breakdown of tumour subtype in the SAF and FAS populations is provided in Table 8.2. Most patients in both subgroups had a midgut or P-NET tumour. In the SAF population, 56.8% of patients received a cumulative dose of 177Lu-dotatate of 800mCi or greater, and 20.9% of patients received a cumulative dose between greater than or equal to 600mCi and 800mCi of lutetium. For patients in the P-NET, hindgut NET, midgut NET and foregut NET subgroups within the SAF population, 60.7%, 61.8%, 61.7%, and 63.0% received a cumulative dose of 800 mCi or greater, respectively. For patients in the P-NET, hindgut NET, midgut NET and foregut NET subgroups within the SAF population, 21.5%, 14.7%, 20.5%, and 11.1% of patients received a cumulative dose between 600 mCi and 800 mCi.[30] In the FAS population, 76.3% and 21.3% of patients received a cumulative dose of 800mCi and between greater than or equal to 600mCi and 800mCi of 177Lu-dotatate, respectively.

Table 8.2: Breakdown of tumour subtype in the SAF population, n=1214, and FAS population, n=578[4]

Tumour subtype	**SAF N (%)**	**FAS N (%)**
Midgut NET	410 (34)	218 (38)
P-NET	331 (27)	169 (29)
Bronchial NET	53 (4)	21 (4)
Hindgut NET	34 (3)	12 (2)
Foregut NET	27 (2)	12 (2)

8.8 Efficacy Outcomes

8.8.1 Response Outcomes

The mean follow-up periods were 13.5 months (SD: 19.1) and 41.1 months (SD: 36.9) for the non-Dutch and Dutch patients in the SAF dataset.

Within the FAS population, the ORR was 41.2% (95%CI, 37.2-45.2). The median duration of response (DOR) was 12.1 months (95% CI, 11.0-15.9).

Within the FAS population based on RECIST criteria, including both Dutch and non-Dutch patients, 3.3%, 37.9%, 50.1% and 3.5% of patients experienced a complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD), respectively; 5.2% of patients were non-evaluable.

The ORR by tumour subgroup are described in Table 8.3. ORR of the pancreatic NET, foregut NET, hindgut NET, unknown NET, bronchial NET, and midgut NET subgroups were generally consistent with that of the overall FAS population. The ORR of the bronchial (ORR=33.3%, 95%CI, 13.2-53.5) and midgut NET (OR=33.0%, 95%CI, 26.8-39.3) subgroups were lower than the ORR FAS population The ORR of the pancreatic NET (OR=59.5%, 95%CI, 52.1-67.0) subgroup was higher than the ORR of the FAS population. However, the sample size of the other subgroups should be taken into consideration, as all subgroups, except for pancreatic, midgut, and unknown subgroups, had sample sizes of less than seven patients.

The mean duration of response (DoR) was 11.2 months for midgut NET, 13.3 months for P-NET, 17.8 months for hindgut NET, 18.7 month for foregut NET, and 23.8 months for bronchial NET.

Table 8.3: Objective response rate according to RECIST 1.1 by tumour subgroup; FAS (N=575)[30]

	Patients	NE		ORR* 95% CI			
Tumor Type	**N**	**N**	**%**	**N**	**%**	**Lower**	**Upper**
Pancreatic NET	168	10	6.0	100	59.5	21.7	78.3
Foregut NET	12	0	0	6	50.0	26.8	39.3
Hindgut NET	13	1	7.7	6	46.2	19.1	73.3
Unknown NET	86	5	5.8	35	40.7	52.1	67.0
Bronchial NET	21	1	4.8	7	33.3	13.2	53.5
Midgut NET	218	10	4.6	72	33.0	30.3	51.1
Other	19	1	5.3	6	31.6	0.0	25.6
Thyroid Carcinoma	20	1	5.0	3	15.0	0.0	30.7
Paraganglioma	18	1	5.6	2	11.1	10.7	52.5

After conducting sensitivity analyses to determine how the non-Dutch patients lost to follow-up would affect the ORR in the FAS population, it was noted that the Dutch and non-Dutch patient showed similar ORR. The ORR for Dutch and non-Dutch patients in the FAS population were 41.0% and 42.7%, respectively. While the ORR was relatively similar among Dutch and non-Dutch patients overall, there were differences in ORR between the different tumour subgroups See table 4.[30]

Table 8.4: Objective response rate as assessed by RECIST 1.1, by tumour type – Dutch and non-Dutch; FAS (N=575)[30]

	Dutch			Non-Dutch		
	Pts	ORR*		Pts	ORR*	
Tumor Type	N	NE	%	N	NE	%
All tumors**	493	202	40.9	82	35	42.6
Foregut NET	12	6	50.0	21.1	0	-
Midgut NET	183	63	34.4	35	9	25.7
Hindgut NET	13	6	46.1	0	-	-
Pancreatic NET	133	75	56.4	35	25	71.4
Bronchial NET	19	7	36.8	2	0	0
Unknown NET	80	34	42.5	6	1	16.7
Paraganglioma	16	2	12.5	2	0	0
Thyroid Carcinoma	20	3	15.0	0	-	-
Other	17	6	35.3	2	-	-

*Objective Response Rate: ORR (Partial Response + Complete Response)

**There were 23 (4.7%) Dutch patients with non-evaluable (NE) tumours and (8.5%) non-Dutch patients with NE tumours

The median DOR among the Dutch patients was 4.6 months in the non-Dutch patients, and 15.2 months in the Dutch patients; The authors note that the high amount of patients lost to follow-up in the non-Dutch population was due to a large difference in the DOR between the Dutch and non-Dutch patients.

An exploratory evaluation was conducted evaluating tumour response among a subgroup of patients with progressive midgut tumours (n=118), comparable to the NETTER-1 phase 3 study. The ORR among these patients was 33%. The median DOR was 9.9 months. Within the FAS population of progressive midgut patients (n=39), the objective response rate was 33.0% (95%CI, 24.7-42.3).

8.8.2 Sensitivity analysis

A sensitivity analysis was conducted in order to determine the influence of the inclusion of patients without baseline tumour measurements had on the ORR. The ORR for the SAF population, without inclusion of patients without baseline measurements, was 41% (95%CI, 37-45); after inclusion of patients without baseline measurements, the ORR reduced to 20% (95% CI, 17-22). A reduction in ORR was also observed among all tumour subtypes. For patients with midgut carcinoid tumours within the FAS population, the ORR of 33% (95%CI, 25-41) was reduced to 17% (95%CI, 12-21). [30] A review by the FDA concluded that as the ascertainment of bias from inclusion of patients without baseline tumour scans is not possible, the results for the SAF population should be considered over the results of the FAS population as they yield more conservative estimates of ORR[4]. It should also be noted that the estimate for ORR in the SAF population for the midgut subgroup (17%) is in line with the ORR for the NETTER-1 trial (15% by BICR).[7]

Table 8.5: ERASMUS ORR and DoR for SAF and FAS populations for selected tumour subgroups[4]

Tumor Type	Analysis Set	Study Phase*	ORR				DoR**		
			ORR, n (%)	95% CI	CR, n (%)	PR, n (%)	Median	95% CI	Range
All	FAS	All	247 (42.7)	(38.7, 46.9)	20 (3.5)	227 (39.3)	19.4	(16.6, 23.7)	(0.0+, 95.0+)
		1	162 (46.6)	(41.2, 51.9)	17 (4.9)	145 (41.7)	17.2	(14.0, 21.3)	(0.0+, 95.0+)
		2	85 (37.0)	(30.7, 43.5)	3 (1.3)	82 (35.7)	25.3	(17.0, 37.1)	(0.0+, 70.3+)
	SAF***	All	247 (20.3)	(18.1, 22.7)	20 (1.6)	227 (18.7)	19.4	(16.6, 23.7)	(0.0+, 95.0+)
		1	162 (26.3)	(22.9, 30.0)	17 (2.8)	145 (23.6)	17.2	(14.0, 21.3)	(0.0+, 95.0+)
		2	85 (14.2)	(11.5, 17.2)	3 (0.5)	82 (13.7)	25.3	(17.0, 37.1)	(0.0+, 70.3+)
GEP-NET and Bronchial	FAS	All	198 (45.7)	(41.0, 50.6)	19 (4.4)	179 (41.3)	20.1	(16.7, 24.4)	(0.0+, 95.0+)
		1	138 (48.1)	(42.2, 54.0)	16 (5.6)	122 (42.5)	17.7	(15.3, 23.0)	(0.0+, 95.0+)
		2	60 (41.1)	(33.0, 49.5)	3 (2.1)	57 (39.0)	35	(17.0, 38.0)	(0.0+, 70.3+)
	SAF	All	198 (23.2)	(20.4, 26.1)	19 (2.2)	179 (20.9)	20.1	(16.7, 24.4)	(0.0+, 95.0+)
		1	138 (29.5)	(25.4, 33.8)	16 (3.4)	122 (26.1)	17.7	(15.3, 23.0)	(0.0+, 95.0+)
		2	60 (15.5)	(12.0, 19.5)	3 (0.8)	57 (14.7)	35	(17.0, 38.0)	(0.0+, 70.3+)
P-NET	FAS	All	108 (63.9)	(56.2, 71.1)	14 (8.3)	94 (55.6)	23	(16.6, 32.6)	(0.0+, 86.4+)
		1	70 (68.6)	(58.7, 77.5)	12 (11.8)	58 (56.9)	19.4	(12.2, 24.4)	(0.0+, 86.4+)
		2	38 (56.7)	(44.0, 68.8)	2 (3.0)	36 (53.7)	35	(16.7, 38.0)	(0.0+, 70.3+)
	SAF	All	108 (32.6)	(27.6, 38.0)	14 (4.2)	94 (28.4)	23	(16.6, 32.6)	(0.0+, 86.4+)
		1	70 (40.2)	(32.9, 47.9)	12 (6.9)	58 (33.3)	19.4	(12.2, 24.4)	(0.0+, 86.4+)
		2	38 (24.2)	(17.7, 31.7)	2 (1.3)	36 (22.9)	35	(16.7, 38.0)	(0.0+, 70.3+)
Midgut	FAS	All	70 (32.1)	(26.0, 38.7)	4 (1.8)	66 (30.3)	17.2	(13.1, 23.0)	(0.0+, 95.0+)
		1	61 (36.1)	(28.9, 43.8)	4 (2.4)	57 (33.7)	17.2	(11.5, 23.0)	(0.0+, 95.0+)
		2	9 (18.4)	(8.8, 32.0)		9 (18.4)	17	(16.6, NR)	(0.0+, 39.6+)
	SAF	All	70 (17.1)	(13.6, 21.1)	4 (1.0)	66 (16.1)	17.2	(13.1, 23.0)	(0.0+, 95.0+)
		1	61 (23.1)	(18.2, 28.7)	4 (1.5)	57 (21.6)	17.2	(11.5, 23.0)	(0.0+, 95.0+)
		2	9 (6.2)	(2.9, 11.4)		9 (6.2)	17	(16.6, NR)	(0.0+, 39.6+)

8.8.3 Overall Survival

Across all tumour subtypes (FAS), the median OS was 64.4 months (95%CI, 57.0-73.8). Within the FAS population, the median OS was 71.4 months (95%CI, 63.2-not estimable) and 56.8 months (95%CI, 50.9-73.6) for pancreatic NET and midgut NET, respectively. Median overall survival was not calculable for hindgut and foregut NETs.

OS was an exploratory analysis. The median OS among only Dutch patients within the FAS population was 63.4 months (95%CI, 56.8-73.6), approximately one month shorter than the median OS of the SAF population (OS=64.4 months, 95%CI, 50.2-60.3).

After sensitivity analyses were conducted among all patients included in the SAF population (n=1214), the median OS was lower compared to the FAS population. The median OS was 54.7 months (95%CI, 50.2-60.3). The authors concluded that the sensitivity anlysis showed that patients excluded from the FAS population had an impact on the OS results, as lower median OS was observed among the SAF population compared to the FAS population. Regardless of this difference, the authors noted that clinical benefit of lutetium remains highly relevant even in the worse case scenario. [30]

8.8.4 Progression Free Survival

PFS was an exploratory outcome. Across all tumour subtypes (FAS), the overall median PFS was 28.0 months (95%CI, 25.0-30.3) (Table 8.6). Within the FAS population, the median PFS was 30.8 months (95%CI, 25.0-36.2), 29.3 months (95%CI, 22.3-39.0), and 28.8 months (95%CI, 24.1-33.7) for pancreatic NET, hindgut NET, and midgut NET, respectively. Median PFS was not estimable for foregut net. Among the Dutch population, the median PFS was 28.0 months (95%CI, 25.0-30.3), similar to that of the overall population. [30]

Table 8.6: Summary statistics of median PFS as assessed by RECIST 1.1: overall and tumour subtypes; FAS (N=575)[30]

	No. of Patients			Median Progression Free Survival - 95% CI		
	Total	Events	%	Months	Lower	Upper
Overall	575	369	64.2	28.0	25.0	30.3
Pancreatic NET	168	95	56.6	30.8	25.0	36.2
Hindgut NET	13	8	61.5	29.3	22.3	39.0
Unknown NET	86	54	62.8	29.0	24.0	36.9
Midgut NET	218	154	70.6	28.8	24.1	33.7
Paraganglioma	18	6	33.3	24.8	15.4	.
Bronchial NET	21	15	71.4	18.3	10.3	25.4
Other	19	17	89.5	14.5	11.9	25.0
Thyroid carcinoma	20	16	80.0	9.6	8.0	28.9
Foregut NET	12	4	33.3	.	21.2	.

8.8.5 Time to Progression

Across all tumour subtypes (FAS), the median time to progression was 33.7 months (95%CI, 30.5-36.9). Within the FAS population, the median times to progression were 33.9 months (95%CI, 30.0-40.1), 29.3 months (95%CI, 22.3-39.0), and 40.0 months (95%CI, 33.2-46.1) for pancreatic NET, hindgut NET, and midgut NET, respectively. Time to progression was not calculable for foregut NET. Within the Dutch population, time to progression was similar to the FAS population, 33.7 months (95% CI, 30.5-36.9). [30]

8.8.6 Quality of Life

The FDA reported that QoL data was not considered in their decision making process for review of 177Lu-dotatate for GEP-NETs, as the QoL data was incomplete and flawed which prevented them from drawing inferences.[4] Overall results related to quality of life are reported below.

Using the QLQ-C30, improvements in disease symptoms (including side effects of treatment, self-image, disease related worries, social functioning, communication and sexuality) were defined as a 10% or more increase from baseline. Patients with a score of less than 10% at baseline were excluded from the analysis. Quality of life was also measured using the QLQ-C30 and QLQ-GI.NET21 questionnaires for patients enrolled after March 2007. Improvement in global health status score was observed in 34.4% of patients in the SAF population using the QLQ-C30; 24.3% of patients reported worsened scores.[30]

8.8.7 Safety

Safety data were not collected prospectively during the ERASMUS trial. Instead, AAA, employed an independent CRO to review and verify the medical charts of all patients enrolled in the ERASMUS trial. Serious adverse reactions were determined by identifying all serious adverse events possibly related to treatment with 177Lu-dotatate. The authors of the ERASMUS protocol stated that there was under reporting of adverse events in the ERASMUS trial due to the difference in rates of serious adverse events between the Dutch and non-Dutch patients, and the high rate of losses-to-follow-up of non-Dutch patients. All safety data reported are in regards to the SAF population (n=1214). [30]

Approximately half of all patients enrolled in the ERASMUS trial experienced at least one treatment emergent serious adverse event (SAE) (51.8%; 629/1214). The most frequently occurring serious adverse events according to system organ classes were

those related to surgical and medical procedures (18.2%, n=221), and gastrointestinal disorders (18.0%, n=218). Other system organ classes affected by greater than 5% of the SAF population included general disorders and administration site (14.4%, n=175), blood and lymphatic system disorders (14.2%, n=172), infections and infestations (7.7%, n=93), metabolism and nutrition disorders (7.5%, n=91), neoplasms, including those which were benign, malignant and unspecified including infected neoplasms (6.9%, n=84), nervous system disorders (5.6%, n=68), hepatobiliary disorders (5.4%, n=65), and respiratory thoracic and mediastinal disorders (5.4%, n=65). [30]

SAEs of the highest frequencies included pancytopenia (8.0%), anaemia (4.4%), diarrhea (4.7%), abdominal pain (5.8%), vomiting (3.8%), nausea (3.2%) and thrombocytopenia (3.0%). Additionally, myelodysplastic syndrome was identified as occurring for 1.4% of patients (n=17). Death occurred in 4.5% of patients. The authors of the ERASMUS protocol concluded that 41.1% of patients experienced at least one SAE that was not related to lutetium, while 15.9% of patients experienced at least one SAE that was possibly or probably related to lutetium. [30]

As per investigator opinion, 449 patients (41.1%) experienced at least one SAE unrelated to the receipt of 177Lu-dotatate, while 193 patients (15.9%) experienced at least one serious adverse event that possibly or probably could have been related to 177Lu-dotatate. SAEs thought to have probably been related to 177Lu-dotatate occurred among 131 patients (10.8%). The greatest proportion of serious adverse events thought to have probably been related to 177Lu-dotatate occurred among patients with midgut NETs (Table 8.7), followed by P-NET, hindgut NET, and foregut NET. However, this should be viewed with caution given the significant differences in sample size. [30]

Table 8.7: Overall summary of incidence of serious adverse events per tumour subtype and relationship to study medication; SAF (n=1214)[30]

		Fore-gut NET	Mid-gut NET	Hind-gut NET	P-NET
Total no. of subjects		27	410	34	331
No. of Subject with	**Any**	10 (37.0)	230 (56.1)	13 (38.2)	166 (50.2)
	Unrelated	8 (29.6)	188 (45.9)	10 (29.4)	132 (39.9)
	Possibly	1 (3.7)	19 (4.6)	1 (2.9)	29 (6.3)
	Probably	2 (7.4)	47 (11.5)	3 (8.8)	34 (10.3)

Source: Table 14.3.1.2.1 (see Appendix 16.2.7)
P-NET: Pancreatic NET; UNK NET: unknown NET

Compared to the non-Dutch population, which experienced an incidence of SAEs of 29.5%, the incidence of SAEs was 63.0% among the Dutch population. SAEs considered to be unrelated to 177Lu-dotatate occurred in 21.8% of patients in the non-Dutch population, while 7.2% were considered to be possibly related. Among the Dutch population, 50.7% of SAEs were considered unrelated to 177Lu-dotatate, while 20.2% were considered possibly related. [30]

Twenty-five deaths were recorded to have occurred within the 30-day period after the last dose of 177Lu-dotatate was administered; the study investigators determined that all of these deaths were unrelated to the study treatment. In total, 450 deaths (37.1%) were recorded in the SAF population, including 401 deaths in the Dutch population

(n=810), and 49 deaths in the non-Dutch population (n=404). No deaths due to treatment with ^{177}Lu-dotatate were reported. [30]

Limitations

A number of methodological issues have been identified by the pCODR Methods team that limit the ability to provide reliable conclusions regarding the use of ^{177}Lu-dotatate across all GEP-NETS. Specific limitations of the ERASMUS trial are stated below.

- The ERASMUS study was a single arm study with no active treatment or placebo controlled groups. As a result, a direct comparison of the efficacy and safety of 177Lu-dotatate relative the relevant comparators is not possible.
- The development of the statistical analysis plan, and collection of the data for the ERASMUS study occurred post-development of the statistical analysis plan. No formal statistical and sample size planning occurred for this trial. Data for the ERASMUS trial were verified and analysed retrospectively by an independent CRO.
- The open-label nature of the trial may have introduced ascertainment bias affecting the reporting or measurement of efficacy or safety parameters, as both patients and researchers had knowledge of the treatment (^{177}Lu-dotatate) that patients were receiving. As patients were treated as part of compassionate care access and followed protocol according to their attended institution rather than protocol of a randomized controlled trial, it is possible that diagnostic, treatment and investigational processes were not being conducted consistently across all institutions.
- Only 578 of 1214 patients (48%) had recorded baseline assessments. There were systemic differences in the data retrieved from Dutch and non-Dutch patients. Many of the non-Dutch patients did not have recorded baseline tumour assessments, and were lost to follow-up resulting in attrition bias. As patients without baseline tumour assessments were not included in efficacy analyses, results are subject to selection bias.
- Due to differential reporting of adverse events, the ERASMUS study is subject to reporting bias.
- There was no formal statistical analysis plan designed for the ERASMUS trial, as the trial was initially not meant to enroll a large number of patients. Due to the lack of formal planning there cannot be certainty as to whether the ERASMUS trial was appropriately powered to detect significant changes to efficacy measures.
- Safety data were not collected in a case report form, nor were they reported to a dedicated safety officer on an ongoing bases. The researchers of the ERASMUS trial employed an independent CRO to conduct a retrospective review of medical charts of all patients enrolled in the trial.

Conclusions

Within the SAF population the objective response rate, overall response, progression free survival and time to progression were 41.2% (95%CI, 37.2-45.2), 64.4 months (95%CI, 57.0-73.8), 28.0 months (95%CI, 25.0-30.3) and 33.7 months (95%CI, 30.5-36.9), respectively. After sensitivity analyses, there were overall reductions of the results of efficacy measures, mainly due to the differential amount of patients lost to follow-up between the Dutch and non-Dutch patients.

Safety data reported for the ERASMUS trial included all patients. However, the discrepancy between the reported side effects between Dutch and non-Dutch patients was apparent due to the differences in amount of missing data and patients lost to follow-up among the non-Dutch population; for example, serious adverse events were reported among 63.0% of Dutch patients and 29.5% of non-Dutch patients. While the data from the ERASMUS trial indicates that ^{177}Lu-dotatate

may be efficacious for multiple GEP-NET subtypes, the results should be interpreted with caution due to the many inherent trial-related limitations.

9 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Gastrointestinal Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on ^{177}Lu-Dotatate (Lutathera) for GEP-NETs. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the CADTH website (www.cadth.ca/pcodr).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report.

The Gastrointestinal Clinical Guidance Panel is comprised of five clinicians. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the CADTH website (www.cadth.ca/pcodr). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY AND DETAILED METHODOLOGY

1. Literature search via OVID platform

#	Searches	Results
1	(Lutathera* or lutate or AE221IM3BB or 177Lu-dota* or 177Ludota* or 177Lutetium).ti,ab,ot,kf,kw,hw,nm.	1473
2	((177* or 177-Lu* or 177Lu* or Lu-177* or Lu177* or Lu) adj5 ((Dota* adj3 octreotate) or dota-tate or dotatate or ludotatate or oxodotreotide)).ti,ab,ot,kf,kw,hw,nm.	1402
3	((177* or 177-Lu* or 177Lu* or Lu-177* or Lu177*) adj5 lutetium*).ti,ab,ot,kf,kw,hw,nm.	3263
4	or/1-3	4056
5	exp Neuroendocrine tumors/	239761
6	((neuroendocrine adj3 (tumo?r* or carcinoma* or neoplas* or cancer* or sarcoma* or malignan*)) or carcinoid* or gastinoma* or insulinoma* or glucagonoma* or VIPoma* or paraganglioma* or argentaffinoma* or somatostatinoma* or polypeptidoma or NET).ti,ab,kf,kw.	308089
7	or/5-6	491999
8	exp Digestive System/ or exp Digestive System Neoplasms/ or exp Lung/ or exp Lung Neoplasms/	4356242
9	(gastrointestin* or GI or digestive or intestine* or intestinal* or gastroentero* or foregut or fore-gut or thymoma or thymic or thymus or esophag* or lung? or pulmonary or respiratory or liver or gallbladder or spleen or stomach or pancreat* or pancreas*or gastric or duodenal or duodenum* or midgut or mid-gut or appendix or appendic*or ileum or ileal or jejunum or jejunal or cecal or c?ecum or hindgut or hind-gut or bowel? or colic or rectal or rectum or colorectal or colon* or anus or anal).ti,ab,kf,kw.	7809486
10	or/8-9	8976598
11	(GEP-NET? or GEPNET?).ti,ab,kf,kw.	1515
12	7 or 10 or 11	9329912
13	4 and 12	2474
14	13 use medall,cctr	554
15	*oxodotreotide lu 177/	40
16	(Lutathera* or lutate or AE221IM3BB or 177Lu-dota* or 177Ludota* or 177Lutetium).ti,ab,kw,dq.	1366
17	((177* or 177-Lu* or 177Lu* or Lu-177* or Lu177* or Lu) adj5 ((Dota* adj3 octreotate) or dota-tate or dotatate or ludotatate or oxodotreotide)).ti,ab,kw,dq.	1306
18	((177* or 177-Lu* or 177Lu* or Lu-177* or Lu177*) adj5 lutetium*).ti,ab,kw,dq.	949
19	or/15-18	2416
20	exp Neuroendocrine tumor/	239761
21	((neuroendocrine adj3 (tumo?r* or carcinoma* or neoplas* or cancer* or sarcoma* or malignan*)) or carcinoid* or gastinoma* or insulinoma* or glucagonoma* or VIPoma* or paraganglioma* or argentaffinoma* or somatostatinoma* or polypeptidoma or NET).ti,ab,kw.	307428
22	or/20-21	491426
23	exp digestive system/ or exp digestive system cancer/ or exp lung/ or exp lung cancer/	4187899
24	(gastrointestin* or GI or digestive or intestine* or intestinal* or gastroentero* or foregut or fore-gut or thymoma or thymic or thymus or esophag* or lung? or pulmonary or respiratory or liver or gallbladder or spleen or stomach or pancreat* or pancreas*or gastric or duodenal or duodenum* or midgut or mid-gut or appendix or appendic*or ileum or ileal or jejunum or jejunal or cecal or c?ecum or hindgut or hind-gut or bowel? or colic or rectal or rectum or colorectal or colon* or anus or anal).ti,ab,kw.	7744523
25	or/23-24	8893201
26	(GEP-NET? or GEPNET?).ti,ab,kw.	1513
27	22 or 25 or 26	9252306
28	19 and 27	1671
29	28 use oemezd	1171
30	29 and conference abstract.pt.	622
31	limit 30 to yr="2013 -Current"	435

32	29 not 30	549
33	14 or 32	1103
34	remove duplicates from 33	820
35	31 or 34	1255
36	limit 35 to english language	1215
37	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Clinical Study or Adaptive Clinical Trial or Equivalence Trial).pt.	1099106
38	(Clinical Trial or Clinical Trial, Phase I or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV).pt.	849276
39	Multicenter Study.pt.	316679
40	Clinical Studies as Topic/	148894
41	exp Clinical Trial/ or exp Clinical Trials as Topic/ or exp "Clinical Trial (topic)"/	2583038
42	Multicenter Study/ or Multicenter Studies as Topic/ or "Multicenter Study (topic)"/	454337
43	Randomization/	173864
44	Random Allocation/	190784
45	Double-Blind Method/	385187
46	Double Blind Procedure/	144976
47	Double-Blind Studies/	249756
48	Single-Blind Method/	72145
49	Single Blind Procedure/	30219
50	Single-Blind Studies/	73988
51	Placebos/	310605
52	Placebo/	309472
53	Control Groups/	110887
54	Control Group/	110795
55	Cross-Over Studies/ or Crossover Procedure/	131003
56	(random* or sham or placebo*).ti,ab,hw,kf,kw.	3822381
57	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	757071
58	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.	2761
59	(control* adj3 (study or studies or trial* or group*)).ti,ab,hw,kf,kw.	8350581
60	(clinical adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	5773076
61	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.	90223
62	(phase adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	440046
63	((crossover or cross-over) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	179641
64	((multicent* or multi-cent*) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	656284
65	allocated.ti,ab,hw.	168884
66	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.	108385
67	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	23077
68	(pragmatic study or pragmatic studies).ti,ab,hw,kf,kw.	869
69	((pragmatic or practical) adj3 trial*).ti,ab,hw,kf,kw.	10223
70	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.	15893
71	trial.ti,kf,kw.	834168
72	or/37-71	13137596
73	exp animals/	44372466
74	exp animal experimentation/	2162463
75	exp models animal/	1612167
76	exp animal experiment/	2162463
77	nonhuman/	5219803
78	exp vertebrate/	43155746
79	animal.po.	0

80	or/73-79	46002663
81	exp humans/	35720203
82	exp human experiment/	397938
83	human.po.	0
84	or/81-83	35721632
85	80 not 84	10281938
86	72 not 85	10602650
87	36 and 86	487

2. **Literature search via PubMed**
   A limited PubMed search was performed to capture records not found in MEDLINE.

Search	Query	Items found
#8	Search **(#6 AND #7)**	59
#7	Search **publisher[sb]**	530755
#6	Search **(#2 OR #3 OR #4 OR #5)**	1185
#5	Search **(((177*[tiab] OR 177-Lu*[tiab] OR 177Lu*[tiab] OR Lu-177*[tiab] OR Lu177*[tiab]) AND lutetium*[tiab]))**	305
#4	Search **(((177*[tiab] OR 177-Lu*[tiab] OR 177Lu*[tiab] OR Lu-177*[tiab] OR Lu177*[tiab] OR Lu[tiab]) AND (Dota*[tiab] AND octreotate[tiab]) OR dota-octreotate[tiab] OR dotaoctreotate[tiab] OR dota-tyr3*[tiab] OR dotatyr3*[tiab] or dota-tate[tiab] OR dotatate[tiab] OR ludotatate[tiab] OR oxodotreotide[tiab]))**	882
#3	Search **((Lutathera*[tiab] OR lutate[tiab] OR AE221IM3BB[tiab] OR 177Lu-dota*[tiab] OR 177Ludota*[tiab] OR 177Lutetium[tiab]))**	276
#2	Search **"Lutetium-177" [Supplementary Concept]**	30

3. **Cochrane Central Register of Controlled Trials (Central)**
   Searched via Ovid

4. **Grey Literature search via:**

Clinical Trial Registries:

U.S. NIH ClinicalTrials. gov
http://www.clinicaltrials.gov/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Search: Lutathera, lutetium Lu177 dotatate (and spelling variations)

Select international agencies including:

Food and Drug Administration (FDA):
http://www.fda.gov/

European Medicines Agency (EMA):
http://www.ema.europa.eu/

Search: Lutathera, lutetium Lu177 dotatate (and spelling variations), neuroendocrine tumours

Conference abstracts:

American Society of Clinical Oncology (ASCO)
http://www.asco.org/

European Society for Medical Oncology (ESMO)
https://www.esmo.org/

Search: Lutathera, lutetium Lu177 dotatate (and spelling variations)– last 5 years

Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (July 2018) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Lutathera/lutetium Lu177 dotatate, and neuroendocrine tumours or gastrointestinal terms.

Methodological filters were applied to limit retrieval to any type of clinical trial. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents, but not limited by publication year.

The search is considered up to date as of April 29, 2019.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicaltrials.gov and Canadian Partnership Against Cancer Corporation - Canadian Cancer Trials), and relevant conference abstracts. Conference abstracts were retrieved through a search of the Embase database limited to the last five years. Abstracts from the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) were searched manually for conference years not available in Embase. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. One member of the pCODR Methods Team independently made the final selection of studies to be included in the review.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

Data Analysis

No additional data analyses were conducted as part of the pCODR review.

Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups, by the Provincial Advisory Group (PAG), and by Registered Clinicians.

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