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SUMMARY WITH CRITICAL APPRAISAL

Lanreotide for the Treatment of Neuroendocrine Tumours: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines

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Context and Policy Issues

Neuroendocrine tumors (NETs) are rare tumors most commonly found in the gastrointestinal systems.[1] However, NETS can also originate in other areas, including the pancreas, lungs, ovaries, thyroid, pituitary, and adrenal glands.[2] According to a 2014 report by the Carcinoid Neuroendocrine Tumour Society (CNETS) of Canada, the annual incidence of clinically significant NETs is approximately 2.5 to 5 per 100,000, with prevalence estimated to be 35 per 100,000.[3] NETs are classified as functional or nonfunctional tumours, with functional NETs secreting hormones that cause hormonal symptoms whereas non-factional NETs may or may not produce hormones and do not cause hormonal symptoms.[4]

Many patients diagnosed with NETs have inoperable disease and require medical therapy to control disease progression and relieve symptoms arising from the excessive production of hormones in functional NETs.[5] With 90% of gastroenteropancreatic neuroendocrine tumors (GEP-NETs) expressing somatostatin receptors,[6] somatostatin analogs (SSAs) play a fundamental role in the treatment of GEP-NETs.[7,8] They exert their antiproliferative and antisecretory effects by binding to somatostatin receptors on tumor cell membranes.[6,8] Currently, octreotide and lanreotide are the two SSAs available in Canada.

This review aims to summarize evidence regarding the clinical and cost-effectiveness, as well as guidelines for the use of lanreotide autogel in the treatment of NETs in adult patients.

Research Question

1. What is the clinical effectiveness of lanreotide for the treatment of neuroendocrine tumours in adults?
2. What is the cost-effectiveness of lanreotide for the treatment of neuroendocrine tumours in adults?
3. What are the evidence-based guidelines associated with lanreotide for the treatment of neuroendocrine tumours in adults?

Key Findings

Evidence from the included studies[1,9,10] suggests that lanreotide autogel has antiproliferative activity and is effective at controlling symptoms of carcinoid syndrome (CS), with a favorable safety and tolerability profile in patients with NETs. One randomized controlled trial (RCT) in the included systematic review (SR),[9] reported that the overall median progression free survival (PFS) of lanreotide autogel dosed at 120 mg every four weeks was 32.8 months in patients with well-differentiated or moderately differentiated G1 of G2 GEP-NETs compared with 18 months of placebo. A subgroup of patients with pancreatic NETS (pNETs) in that study had a median PFS of 29.7 months. One small (n=30) non-randomized study[1] reported that the 5-year overall survival (OS) was 87.5% with lanreotide autogel versus 65.6% with octreotide. One RCT[10] found that the odds of

success or partial success in treating diarrhea associated with CS were significantly higher with lanreotide than with placebo (OR = 2.4; 95% CI: 1.1, 5.3). One non-randomized study,[11] found that the majority of patients treated with lanreotide autogel were either 'completely' or 'rather satisfied' with the control of diarrhea (76%) or flushing episodes (73%). One economic evaluation[12] conducted in Europe estimated that the overall annual cost-savings for using lanreotide autogel versus octreotide long-acting release (LAR) to treat patients with acromegaly or NETs ranged from EUR € 1.9 million to € 7.07 million, with the savings driven by lower price, reduced administration time, and lower risk of clogging associated with lanreotide autogel. The literature search did not identify any evidence-based guidelines with recommendations specific for the use of lanreotide in the treatment of NETs.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Filters were applied to limit the retrieval to health technology assessments, SRs, meta-analyses, economic studies, non-randomized studies, RCTs, and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2012, and July 20, 2017.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed, and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults patients (>18 years) diagnosed with any type of neuroendocrine tumour (NET); including those originating in the pancreas, lung, and other areas and both functional (produce hormone) and non-functional (do not produce hormone) tumours
Intervention	Lanreotide (Somatuline Autogel)
Comparator	Q1-2: Octreotide; Placebo; No treatment Q3: No comparator
Outcomes	Q1: Clinical effectiveness (e.g., symptom control, quality of life, tumour management [e.g., progression-free survival, overall survival, etc.]); safety Q2: Cost effectiveness (e.g., incremental cost per QALY or health benefit gained) Q3: Guidelines
Study Designs	HTA/Systematic Reviews/Meta-Analyses, Randomized Controlled Trials, Non-Randomized Studies, Economic Evaluations, Guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published before January 1, 2012.

Critical Appraisal of Individual Studies

The included SR[9] was critically appraised using the Assessment of Multiple Systematic Reviews (AMSTAR) tool,[13] the RCT,[10] the non-randomized studies[1,11] were critically evaluated using the Downs and Black checklist,[14] and the economic evaluation[12] was assessed using the Drummond tool.[4] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study was narratively described.

Summary of Evidence

Quantity of Research Available

A total of 442 citations were identified in the literature search. Following the screening of titles and abstracts, 402 citations were excluded, and 40 potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search. Of the 41 potentially relevant articles, 36 publications were excluded for various reasons, while five articles met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

A detailed summary of the characteristics of included studies has been presented in Appendix 2

Evidence of Clinical Effectiveness

One SR,[9] one RCT,[10] and two non-randomized studies[1,11] with evidence of clinical effectiveness were identified.

Study Design

The SR[15] included 40 primary studies including two randomized studies. Thirteen of these primary studies were published as abstracts. The RCT[10] had three phases— a 16-week randomized, double-blind (DB), placebo-controlled phase, a 32-week initial open-label (OL) phase, and a long-term open-label extension (LTOLE) phase. One of the non-randomized studies was a retrospective cohort study,[1] and the other non-randomized study[11] was described as a multinational, observational, non-interventional study.

Country of Origin

The SR[9] was authored by reviewers from Australia, France, Germany, Spain, and the United Kingdom (UK). The RCT was a multinational study with the sites in 12 countries (Brazil, Croatia, Czech Republic, Latvia, India, Poland, Russia, Serbia, South Africa, Turkey, Ukraine, and the United States of America). One non-randomized study[1] was

conducted in Italy, while the other[11] used data from centers in eight countries (Czech Republic, France, Hungary, Israel, Italy, Poland, Spain, and the UK).

Patient Population

The primary studies included in the SR[9] had a total of 913 patients diagnosed with grade 1 or grade 2 GEP-NETs disease. One hundred and fifteen patients with histologically confirmed NETs or a NET of unknown location with liver metastases participated in the RCT.[10] Patients in the RCT were eligible if they had a history of CS (flushing and diarrhea); positive somatostatin receptor status; naïve to somatostatin antagonists (SSA) or responsive to octreotide LAR (≤30 mg/4 weeks) or short-acting octreotide (≤600 µg daily). One non-randomized study[1] included 30 patients with ^{68}Gallium-DOTA-TOC-PET/CT positive, histologically confirmed measurable metastatic pulmonary carcinoids (PCs). The other non-randomized study[11] involved 273 NETs patients with CS-related diarrhea who had been receiving lanreotide autogel for >3 months.

Interventions and Comparators

The SR[9] included non-comparative studies as well as studies which compared lanreotide with placebo. The RCT[10] randomized patients to receive lanreotide autogel at a dose of 120 mg or a matched placebo every four weeks. Short-acting octreotide was designated as the rescue medication for all patients who had breakthrough symptoms. The non-randomized studies[1,11] had no comparator arms. In one non-randomized study,[1] some patients (n=10) were treated with lanreotide autogel 120 mg every four weeks, and the others (n=20) received octreotide LAR 30 mg every four weeks.[1] Patients in the other non-randomized study[11] received lanreotide autogel at doses ranging from 60 mg to 120 mg every four weeks. From here on, this report refers to lanreotide as lanreotide autogel 120 mg unless otherwise stated.

Outcomes

The outcome measure of interest in the SR[9] included PFS, time to disease progression (TTP), tumour response, and OS. In the RCT,[10] the adjusted mean percentage of days with rescue octreotide use for symptom control during the 16-week DB phase was the primary endpoint while control of flushing episodes was a secondary outcome. Median PFS was the outcome measure of interest in one non-randomized study.[1] In the other non-randomized study,[11] the primary outcome was patient-reported satisfaction with diarrhea control whereas secondary outcomes included overall changes in diarrhea symptoms, satisfaction with symptoms of flushing and patients quality of life (QoL) evaluated using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and QLQ-G.I.NET 21 questionnaires. Assessments of outcomes were done after patients had received lanreotide for greater than 3 months.

Evidence of Economic Effectiveness

A detailed summary of the characteristics of the economic evaluation has been provided in Appendix 2

One economic evaluation[12] was identified which assessed cost-savings of using lanreotide compared to octreotide LAR to manage patients with acromegaly and NETs. The analysis considered administration of the drugs by either hospital-based or community-based nurses in France, Germany and the UK. A decision-tree model was used with a health care payer perspective which included only direct medical costs, such as drug consumption and costs

of administration. The main assumptions were that the first (initial) dose was lost if clogging occurred, for which reason a second injection was performed. The analysis also assumed 85% compliance rate. The base case (Scenario A) depended on a multicenter quantitative study which investigated the time needed to prepare and administer of lanreotide and octreotide LAR as well as nurse practitioner perceptions of the success rate of these products in France, Germany, the UK, and the USA. Two scenario analyses (Scenarios B and C), which assumed a higher or lower risk of clogging at first injection and a longer or shorter drug administration time, were simulated to assess uncertainty.

Summary of Critical Appraisal

A detailed summary of the critical appraisal of the included studies is available in Appendix 3.

The SR[9] clearly stated the objectives study and the main outcomes of interest. The comprehensiveness of the literature search for studies to include in the SR[9] was uncertain since only one electronic database was searched. Of the 40 primary studies included in the SR,[9] two were RCTs, of which only one reported relevant results. The remaining studies included 13 conference abstracts and mostly non-randomized studies (retrospective, open-label prospective, and case studies) which provided limited details. The methods of study selection and data extraction were not adequately described, and the scientific quality and the likelihood of publication bias of included studies were not assessed. Thus, the quality of the SR[9] was low. However, the SR[9] included the pivotal phase-3 DB, placebo-controlled RCT (the CLARINET study[5]) upon which lanreotide was approved for the treatment of NETs.

The RCT[10] included in this review defined its objectives. Inclusion and exclusion criteria and the characteristics of the study patients were provided. The patients were randomly allocated to treatment groups, with participants, staff, and outcome assessors blinded to the assigned treatment. The baseline demographic and clinical characteristics were similar across study groups. The intervention and control, as well as the main outcomes, were defined. Efficacy analyses were conducted on the intention-to-treat population, whereas safety assessments were based on the safety population. However, the RCT[10] included only patients with well-controlled symptoms. Thus, it is unknown if the patients in this study were representative of the general population of patients with CS treated in clinical practice. While short-acting octreotide was the official rescue medication for breakthrough diarrhea, its use in this regard was not standardized and enforced. Patients used it at doses and frequency of their choosing, and there was no restriction on using other rescue medications. Therefore, it is uncertain whether the variability in the types and manner of use of rescue medications influenced the reported findings.

One non-randomized study[1] provided details of its objectives, inclusion and exclusion criteria, the index intervention, and the outcomes to be measured. Validated tools were used to measure outcomes, appropriate statistical analyses were applied, and the main findings were reported clearly. However, it was a small (n=30) retrospective cohort study including only ten patients who were treated with lanreotide, without adequate reporting of their specific demographic and medical characteristics. Further, patients were excluded if they had undergone prior treatments for either metastatic or localized disease. Therefore, the generalizability of the study findings, as they relate to lanreotide, is uncertain.

Another non-randomized study[11] assessed the real-world patient experience with the management of CS symptoms. A sample size determination was performed to ensure the

study was adequately powered to detect statistically significant differences. However, only 80% of the estimated number of patients could be enrolled to participate in the study because of slow recruitment. Considering that the subjective patient-reported outcomes of the study[11] were assessed at a single clinical visit for each patient, the comprehensiveness of the study findings and their generalizability are unknown.

Overall, the economic evaluation[12] met the requirements of most relevant items in the Drummond assessment tool. However, the evaluation was conducted in Europe and was based on euro-indexed historical cost estimates that were not discounted. Thus, the generalizability of the cost-saving findings in the Canadian context is unknown.

Summary of Findings

A detailed summary of findings from the included studies is available in Appendix 4.

What is the clinical effectiveness of lanreotide for the treatment of neuroendocrine tumours in adults?

A. Efficacy

Overall Progression Free Survival

One SR[9] reported that the median PFS was 32.8 months for patients with well-differentiated or moderately differentiated grade 1 (G1) or grade 2 (G2) GEP-NETs who received lanreotide every four weeks versus 18 months for those who received placebo. The results were taken from the DB and the OLE phases of the phase-3 D placebo-controlled RCT (CLARINET study[5]) which was the only RCT in the SR with adequately reported findings. An open-label phase II study included in the SR[9] reported a median PFS of 12.9 months for lanreotide every four weeks in patients with progressive GEP-NETs. Based on an included long-term (9 years) retrospective study, the SR[9] reported that patients with metastatic midgut NETs who received lanreotide, had 93%, 75% and 59% PFS at the end of years 1, 3, and 5 were, respectively. The doses of lanreotide in that study were between 60 mg to every four weeks.

One included non-randomized study[1] reported a median PFS of 10.1 months with lanreotide versus 11.1 months with octreotide

Progression Free Survival in patients with pancreatic Nets (pNETs)

The SR[9] reported that the median PFS was 29.7 months for pNETs patients treated with lanreotide every four weeks. The finding was from a subgroup analysis of data from both the DB and the OLE phases of the CLARINET study.[5]

Progression Free Survival in patients with lung NETs

One included non-randomized study[1] reported that in patients with metastatic lung NETs who were treated with SSA drugs as first-line therapy, the median PFS was 10.1 months with lanreotide of every four weeks and 11.1 months with octreotide LAR 30 mg every four weeks.

Tumour Response and Time To Disease Progression

The SR[9] reported that the tumour response among patients treated with lanreotide every four weeks was 66% compared with 53% of patients who received placebo. The TTP for

patients who had switched from placebo to lanreotide due to disease progression was 14.0 months. Both the tumour response and TTP results were based on the CLARINET study.[5] None of the other included clinical studies[1,10,11] of this review reported TTP or tumour response data for the subgroup of patients with pNETs or lungs NETs.

Overall survival

The SR[9] found no significant difference in OS between the placebo and the lanreotide. The results were based on the CLARINET study[5] and may be due to complications introduced by crossover from placebo to lanreotide, and uncertainty over subsequent treatment after disease progression. In the retrospective study,[1] the OS of patients with metastatic midgut NETs who were treated with lanreotide at doses between 60 mg and every four weeks was 96%, 78%, and 72%, at years 1, 3, and 5, respectively. One included non-randomized study[1] reported that the 5-year OS was 87.5% with lanreotide versus 65.6% with octreotide. None of the other included studies[1,10,11] of this review had OS data for the subgroup of patients with pNETs or lungs NETs.

NETs-related diarrhea and flushing control

One RCT[10] found that the odds of success or partial success at treating CS-related diarrhea were significantly higher with lanreotide every four weeks than with placebo (OR = 2.4; 95% CI: 1.1, 5.3). Full or partial treatment success was defined as no need for, or ≤3 days' use of short-acting octreotide as rescue medication for diarrhea in weeks 12 to 15. The adjusted mean percentage of days with rescue octreotide use was 33.7% with lanreotide compared with 48.5% in the placebo group. In the non-randomized study,[11] majority of patients treated with lanreotide were either 'completely' or 'rather satisfied' with control of diarrhea (76%) or flushing episodes (73%) at the assessment visit. Physician records indicated a mean reduction of 2.1 stools per day (95% CI: 1.7, 2.5) at the evaluation visit compared to the beginning of treatment with lanreotide. The difference was statistically significant.

Quality of Life

One non-randomized study[11] reported that 70% of patients who were satisfied with diarrhea control reported "good", "very good", or "excellent" QoL compared with 39% of patients who were dissatisfied or 48% of patients who were neither satisfied nor dissatisfied with diarrhea control.

B. Safety

From three included studies[1,9,10] the most frequently (>5%) reported AEs among patients treated with lanreotide were steatorrhea, diarrhea, abdominal pain, cholelithiasis, nausea, vomiting, and flatulence. One study,[11] did not report any adverse drug reactions or safety cases. Where the comparisons were made, the incidence of AEs in the lanreotide group was not significantly different from the placebo group.[9,10] AEs were mostly mild to moderate. However, the RCT[10] found one patient (1.69%) in the lanreotide group with invasive ductal breast carcinoma and one patient (1.79%) in the placebo group with cerebral ischemia withdrew from the study. According to the authors, these serious AEs were not related to the treatment.

What is the cost-effectiveness of lanreotide for the treatment of neuroendocrine tumours in adults?

One economic evaluation[12] reported cost-saving outcome for using lanreotide versus octreotide LAR to treat patients with acromegaly of NETs in France, Germany, and the UK. In the base case (Scenario A) the mean cost savings per each successful use of lanreotide were €35, €91, and €143 for France, Germany, and the UK, respectively. The overall annual cost-savings were estimated to range between €1.9 million and €7.07 million. The lower, price, reduced risk of clogging and shorter administration time associated with lanreotide drove the cost-savings. The costs related to the setting of drug administration were similar and small (3%). They did not contribute significantly to the differences in the expenses of using lanreotide or octreotide LAR for acromegaly or NETs in this evaluation.

What are the evidence-based guidelines associated with lanreotide for the treatment of neuroendocrine tumours in adults?

The literature search did not identify any evidence-based guidelines with recommendations specific for the use of lanreotide in the treatment of NETs. However, there were a few minimal consensus documents on the treatment NETs with SSAs (see Appendix 5). Regardless of the originators, all the identified consensus statements were in agreement about the effectiveness of octreotide and lanreotide in controlling clinical syndromes in functional NETs, and their antiproliferative effect in well-differentiated NETs. The antiproliferative and CS symptom control activities of octreotide and lanreotide is considered a class effect.[16] Even so, it has been argued by some authors that since the pivotal trial of octreotide (PROMID[17]) did not include patients with pNETs or G2 midgut NETs, the scientific evidence supporting the use of lanreotide in the treatment of pNETs of G1 and G2, regardless of hepatic tumor burden, may be more reliable.[7,16] Their reasoning is that these patient populations had encouraging efficacy results in the CLARINETstudy[5] of lanreotide. However, none of the identified consensus documents had a statement of preference for one SSA over the other, and there was no definite statement regarding using the two drugs interchangeably or strictly according to approved label.

Limitations

A small number of studies were identified for this review without any evidence-based clinical guideline with recommendation specific to the use of lanreotide in the treatment of NETs. The SR[9] was of low methodological quality and reported relevant findings from only one RCT and three non-randomized primary studies, despite including 40 publications. The heterogeneity in study designs, patient population, and definitions of outcomes did not permit a meta-analysis, thus the SR[9] did not allow for pooled effects estimates.

The use of rescue medication without standardization complicated the interpretation of the findings from the RCT.[10] The other two included studies[1,11] were non-randomized with high potential for bias. In one small (n=30) non-comparative retrospective cohort study[1] only ten patients were treated with lanreotide. In another non-randomized study[11] designed to assess real-practice patients' experience, the primary efficacy outcome included patient-reported outcomes, and the freedom of patients to choose and use rescue medication without investigators' control further complicates the possibility of an objective assessment of the study findings. Overall, the economic evaluation was well-done. However, its generalizability to Canadian context is unknown because it was conducted in Europe using historical euro-indexed cost estimates.

Conclusions and Implications for Decision or Policy Making

This review included one SR,[9] one RCT,[10] and two non-randomized studies[1,11] which provided evidence of clinical effectiveness of lanreotide for the treatment of NETs. The SR,[9] reported an overall median PFS of 32.8 months with lanreotide every four weeks versus 18 months with placebo in patients diagnosed with well-differentiated or moderately differentiated G1 of G2 GEP-NETs. The findings were based on the CLARINET study[5] from which the median PFS was 29.7 months in a subgroup of pNET. An open-label phase II study included in the SR[9] reported median PFS of 12.9 months in patients with progressive GEP-NET treated with lanreotide every four weeks. The tumour response rate reported in the SR[9] was 66% with lanreotide every four weeks versus 53% with placebo. One included non-randomized study[1] reported that the 5-year OS was 87.5% with lanreotide versus 65.6% with octreotide. The included RCT[10] found that the odds of success or partial success in treating diarrhea associated with CS were significantly higher with lanreotide than with placebo (OR = 2.4; 95% CI: 1.1, 5.3; P = .036). One non-randomized study,[11] found that the majority of patients treated with lanreotide were either 'completely' or 'rather satisfied' with the control of diarrhea (76%) or flushing episodes (73%). The QoL was reported as good, very good, or excellent in 70% of these satisfied patients compared with 39% of patients who were dissatisfied, or 48% of patients who were neither satisfied nor dissatisfied. Lanreotide was safe and well-tolerated, with an incidence rate of AEs similar to placebo. The most frequently (>5%) reported AEs with lanreotide were steatorrhea, diarrhea, abdominal pain, cholelithiasis, nausea, vomiting, and flatulence. One economic evaluation[12] estimated that the overall annual cost-savings for using lanreotide versus octreotide LAR to treat patients with acromegaly or NETs ranged between € 1.9 million and € 7.07 million. The lower price, reduced administration time, and lower risk of clogging associated with lanreotide drove the cost-savings. The literature search did not identify any evidence-based guidelines with recommendations specific for the use of lanreotide in the treatment of NETs.

In general, the evidence from four included studies[1,9,10] of this review suggests that lanreotide has an antiproliferative effect and is effective for controlling CS symptoms, with a favorable safety and tolerability profile in patients with NETs. Lanreotide may be a cost-saving SSA option for the management of NETs.[12] However, a current economic evaluation considering the Canadian health care system is required to ascertain the cost benefit.

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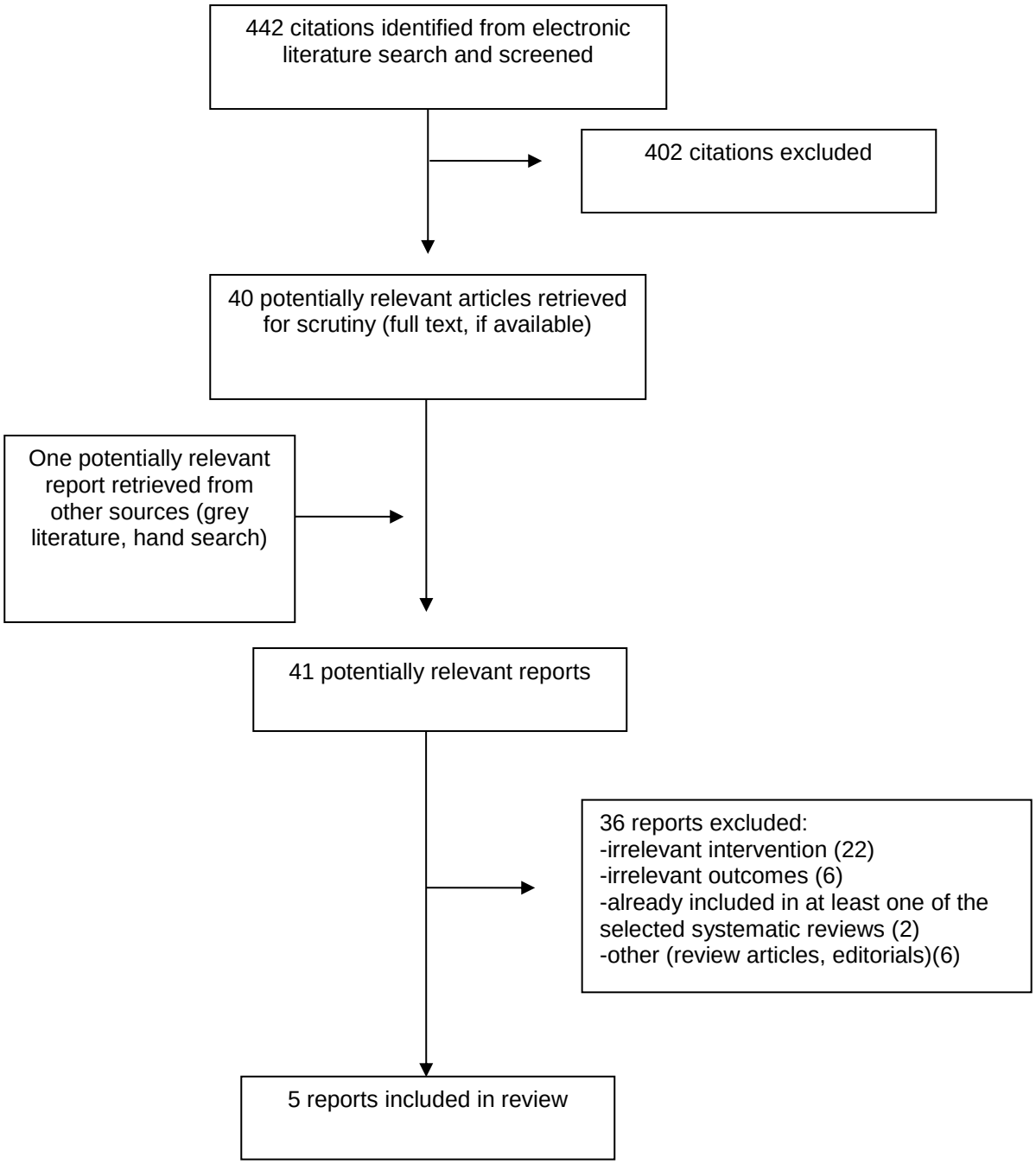
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 1: Characteristics of Included Clinical Studies

Author, Publication Date, Country	Study Design	Population	Intervention	Comparator(s)	Outcomes
Michael, 2017[9] **Multinational**	A systematic review of 27 full-length publications and 13 congress abstracts. All the congress abstracts and 14 publications (including one RCT) reported on the efficacy of lanreotide Autogel.	A total 913 patients with grade 1 or grade 2 GEP-NETs disease (Ki-67 <10%) were involved in the studies which assessed Lanreotide Autogel	Lanreotide Autogel, 120 mg every 4 or 6 weeks	Placebo/None	Antiproliferative Efficacy • PFS • TTP • Tumor response, • OS and • disease markers, Safety • AEs, • Toxicity • Tolerability
Vinik, 2016[10] **Multinational (Brazil, Croatia, Czech Republic, Latvia, India, Poland, Russia, Serbia, South Africa, Turkey, Ukraine, and the U.S.)**	A 3-phase study encompassing a 16-week randomized, DB, placebo-controlled phase, a 32-week initial OL phase, and the LTOLE	A total of 115 patients (mean age 58.6 years) with histologically confirmed NETs or a NET of unknown location with liver metastases, and a history of CS (flushing and diarrhea); positive somatostatin receptor status; SSA-naïve or responsive to conventional octreotide LAR doses (≤30 mg/4 weeks) or short-acting octreotide (≤600 µg daily); absence of tumor progression on two sequential CT or MRI scans ≥3 months apart, and last scan ≤6 months of study entry.	Lanreotide 120 mg every four weeks (with short-acting octreotide for use as rescue medication for breakthrough symptoms). Mean (SD) duration of treatment with lanreotide in the DB phase was 14.4 (3.9) weeks.	Placebo	**Efficacy** *Primary endpoint* Adjusted mean percentage of days with rescue octreotide use for symptom control during the 16-week DB phase, based on patients' diary records. The proportion of patients who successfully or partially responded to the DB treatment. Success and partial success were defined, respectively, as no need for, or ≤3 days of, rescue medication between weeks 12 and 15. Secondary endpoints Average daily frequency of diarrhea and flushing events and percentage of days with non-octreotide rescue medications use, the proportion of patients who rolled over early into the initial OL phase; change from baseline to week 12 in HRQoL **Safety** AEs, SAEs, WDAE
Bongiovanni, 2017[1]	A retrospective cohort study	30 patients (median age 65.5 years; range, 47 to	First-line SSA treatment (octreotide LAR	None	Median PFS (overall and for ^{18}FDG-PET/CT positive and ^{18}FDG-

Author, Publication Date, Country	Study Design	Population	Intervention	Comparator(s)	Outcomes
Italy		82 years) with histologically confirmed measurable metastatic PCs typical and atypical); All patients were ^{68}Gallium-DOTA-TOC-PET/CT-positive. 16 (53.3%) patients had undergone surgery for localized disease, whereas 14 patients (46.6%) presented with locally advanced or metastatic cancer.	30 mg or lanreotide 120 mg) every four weeks. The median treatment duration was 10.0 months (range, 2.0 to 59.0 months).		PET/CT negative patients) 5-year OS
Ruszniewski, 2016[11] **Multinational (Czech Republic, France, Hungary, Israel, Italy, Poland, Spain, and the UK)**	A multinational, observational, non-interventional[a] study conducted at 45 secondary or tertiary care centres in eight countries.	273 patients (age range 31 to >70 years) diagnosed with NETs and receiving lanreotide for longer than 3 months. Almost all patients (271/273) had some metastases. Patients were eligible if they had a history of diarrhea related to CS.	Lanreotide Autogel at doses of 60–120 mg every four weeks.[a] The median duration of lanreotide treatment was 10.9 (range: 3 to 215) months)	None	Patient-reported outcomes Primary Satisfaction with diarrhea control on the day of the visit. Secondary I. Diarrhea severity and associated impact on daily activities; II. Overall change in diarrhea symptoms at the time of the visit compared with before treatment initiation; III. Feelings and consequences of diarrhea on daily life; IV. Satisfaction with flushing control; and V. Patients' QoL

AEs = adverse events; CS = carcinoid syndrome; GEP = gastroenteropancreatic; HRQoL = health related quality of life; LTOLE = long-term open-label extension; NETs = neuroendocrine tumours; OL = open-label; OS = overall survival; PFS = progression-free survival; pNETs = pancreatic NETS; QoL = quality of life; RCT = randomized controlled trial; SAEs = serious adverse events; TTP = time to progression; UK = United Kingdom; WDAEs = withdrawal due to adverse events

a "The study did not impact on usual clinical management. Patients' clinic attendance and the exact prescription of lanreotide or any other concomitant medications was unrestricted and in accordance with routine clinical practice. The decision to prescribe lanreotide was made prior to, and independently from, the decision to enroll patients in the present study."11

Table 2: Characteristics of Included Cost Studies

First author, Publication Year, Country	Type of Analysis, Perspective	Intervention, Comparator	Study Population	Time Horizon	Main Assumptions
Marty, 2012[12] **France, Germany, UK**	Cost saving analysis using a decision-tree model. It was based on a multicenter quantitative study to investigate the time needed for preparation and administration of the lanreotide Autogel and octreotide LAR, as well as nurse practitioner perceptions of the success rate of these products. The analyses used a health care payer perspective, including only direct medical costs, such as drug consumption and administration costs.	Lanreotide Autogel, octreotide LAR	Patients receiving with treatment somatostatin receptor ligands for acromegaly and NETs	A year (cost per patient per year)	• First dose was assumed to be lost in case of clogging and a second injection was performed. • 85% compliance rate • The risk of clogging at first injection and the time for drug administration were set for 3 scenarios as follows; **Scenario A (Base case)** ○ Clog Risk lanreotide 0% octreotide 2.6%; Admin. Time lanreotide 1.1 min octreotide 5.5 min **Scenario B** ○ Clog Risk lanreotide 1.0% octreotide 1.9%; ○ Admin. Time lanreotide 1.5 min octreotide 3.0 min **Scenario C** ○ Clog Risk lanreotide 0% octreotide 3.3%; ○ Admin. Time lanreotide 1.1 min octreotide 8.0 min

GEP = gastroenteropancreatic; NETs = neuroendocrine tumours;

Appendix 3: Critical Appraisal of Included Publications

Table 3: Strengths and Limitations of Systematic Review using the AMSTAR tool

Strengths	Limitations
Michael, 2017[9]	
• The objectives of the SR were clearly stated. • The main outcomes of interest were defined • A table of included studies with study characteristics was provided. • The SR included the pivotal phase-3 DB, placebo-controlled RCT which was the basis of approval for lanreotide Autogel for the treatment of NETs. • The authors declared sources of potential conflicts of interest	• Only one electronic source was searched for relevant literature. Although searches were also done in four congresses (ASCO, ENETS, ESMO, and NANTS) from 2013 to 2016, is uncertain whether the literature search for this SR was comprehensive enough. • The methods of study selection and data extraction were not adequately described, though the authors stated that two reviewers reviewed titles, abstracts, and full-length articles. • With only two RCT, most of the included studies had retrospective designs or were small open-label prospective studies. Thus there was a high potential for bias. • The scientific quality of included studies and the likelihood of publication bias were not assessed. Thus, it is unknown how well the conclusions of the SR reflect the quality of its primary studies. • Pooling of findings could not be done because the primary studies varied widely in designs, patient population, and definitions of outcomes, among others. • The SR was industry funded. Some authors had a consulting or advisory relationship with or offered expert testimony on behave of the industry. Others received research funding or honoraria, were employees of industry, shareholders, or inventors and holders of patent and intellectual property rights on the intervention.

ASCO = American Society of Clinical Oncology, DB = double-blend, ESMO = European Society for Medical Oncology, ENETS = European Neuroendocrine Tumor Society; NANTS = North American Neuroendocrine Tumor Society, NETs = RCT = randomized controlled trial, SR = systematic review

Table 4: Strengths and Limitations of Randomized Controlled Trial and Non-Randomized studies using the Downs and Black checklist

Strengths	Limitations
Vinik, 2016[10]	
• The objectives and main outcomes in the study were clearly defined • Inclusion and exclusion criteria were well-defined, and the characteristics of included patients, as well as the nature of the interventions and control being examined, were described. • Sample size calculation was done to ensure the study was adequately powered to detect statistically significant differences in outcome between the study	• Only patients with well-controlled symptoms were eligible to be included in the study. Thus, it is unknown whether the patients in this study were representative of the general population patients with carcinoid syndrome treated in clinical practice • Patients used short-acting octreotide before the initiation of the study, and unstandardized use of short-acting octreotide to control breakthrough diarrhea was permitted during the study. Therefore, the likelihood of

Strengths	Limitations
arms. • Patients were randomly allocated to treatment groups, with participants, staff, and outcome assessors blinded to the assigned treatment. • Baseline demographic and clinical characteristics were similar across study groups. • Efficacy analyses were conducted on the ITT population [a], whereas safety assessments were performed in the safety population [b]. • The authors declared they had no interests that may be relevant to the work.	the differences in patient exposure to octreotide contributing to differences in diarrhea events or global health status cannot be ruled out • Patients were permitted to use other antidiarrheal medications, apart from short-acting octreotide, for symptom control. The absence of standardization in the rescue medication use undermines the rigor of using it as an outcome measure.
Bongiovanni, 2017[1]	
• Overall, the study was reported in detail, with clearly described objectives, inclusion and exclusion criteria, interventions to be used, and the main outcomes to be measured. • The main findings of the study were clearly described with estimates of variability for outcomes, where applicable. • Outcomes were measured with well-known validated tools and methods, and appropriate statistical analyses were applied. • The authors declared no conflict of interests	• A retrospective study with potential for recall bias. • The sample size was small (n=30) and the study was designed to evaluate the effects of SSA in general with only one third (10/30) of the population treated with lanreotide autogel. • The criteria for choosing patients for treatment with octreotide LAR and others with lanreotide autogel were not described. Though overall baseline patients' characteristics were described, the specifics of the characteristics of the patients who received lanreotide are unknown. Thus it is unknown if the ten patients in this study who were treated with lanreotide autogel were representative of the patient's population in clinical practice. • Patients who had undergone prior treatments for either metastatic or localized disease were excluded. Thus, it is unknown if the findings of this study are generalizable in patients with NETs who are not naïve to therapy.
Ruszniewski, 2016[11]	
• Objectives of the study and the details of the intervention were clearly defined • The study assessed of the real-world patient experience of CS-symptom management • A sample size determination was performed to ensure the study was adequately powered to detect statistically significant differences. However, only 80% of the estimated number of patients could be enrolled to participate in the study because of slow recruitment. • The main findings of the study were clearly described with estimates of variability for outcomes, where applicable. • Efficacy analyses were based on both the ITT and per protocol populations. Thus the potential for bias in reported results due to variability in study population from baseline was minimized. • Validated QoL questionnaires were used in the study, and the main patient-reported outcome data were	• The main focus of the study was to evaluate patient-reported outcomes, such as patient satisfaction with diarrhea control, which are very subjective. Also, the patient-reported outcomes were assessed only at one clinical visit, which may not be enough to report a patient's treatment comprehensively. • Being a real-world study, the inclusion criteria were not very restrictive, allowing entry to the general population of NETs patients with variable treatment duration, doses and dosing interval for lanreotide. It is uncertain whether such variability contributed to the reported findings. • The settings of the study were described as "specialist centres". It is unclear if the expertise and services available for the evaluations could be replicated in non-specialized settings. • The study was industry funded, and the authors had consulting or advisory relationships with industry.

Strengths	Limitations
corroborated by objective data from medical records. • The authors disclosed potential sources of conflict of interests	

AEs = adverse events; CS = carcinoid syndrome; GEP = gastroenteropancreatic; HRQoL = health related quality of life; LTOLE = long-term open-label extension; NETs = neuroendocrine tumours; OL = open-label; OS = overall survival; PFS = progression-free survival; pNETs = pancreatic NETS; QoL = quality of life; RCT = randomized controlled trial; SAEs = serious adverse events; TTP = time to progression; UK = United Kingdom; WDAEs = withdrawal due to adverse events ITT = intention-to-treat

a Defined as all randomized patients, regardless of receipt of or adherence to allocated treatment.

b Defined as all randomized patients who received at least one injection of study treatment, according to actual treatment received.

Table 5: Strengths and Limitations of Economic Studies using Drummond

Strengths	Limitations
Marty, 2012[12]	
• The research question and its economic importance were stated. • The alternatives interventions being compared and the rationale for choosing them were clearly described. • Details of the decision-tree model used in the evaluation were given, and the viewpoint of the analysis was clearly stated. • The primary outcome measure and the sources of cost-saving estimates were clearly stated. • In addition to the base case analysis, two extreme scenarios, one favorable and the other unfavorable, were analyzed to assess uncertainty. • A sensitivity analysis was performed for hospital-based and community-based nurses' wages to assess the uncertainty in annual rates of salary and price index across countries where the studies were conducted. • The authors report no conflicts of interest in this work	• The authors stated that this cost-consequence study was based on a multicenter quantitative study. However, details of the design and characteristics of the study were not provided, though a summary of results was given. • The ranges over which variables were varied in the scenario analyses were not justified. • The study depended on history cost estimates which were not discounted, and no explanation was given for why this was not done. • Despite declaring no conflict of interest, the authors acknowledged an unrestricted grant from industry to support this study. • The study was conducted in three European countries with cost stated in euros. Taken together with the historical cost estimated used, there is uncertainty whether the findings will be generalizable in the Canadian context.

Appendix 4: Main Study Findings and Author's Conclusions

Table 6: Summary of Clinical Findings of Included Studies

Main Study Findings	Author's Conclusion
Michael, 2017[9]	
A. Efficacy **1. Findings from RCT** *a. The DB phase, lanreotide Autogel 120 mg/4 weeks versus placebo* • At 24 months, 65% (95% CI: 54.0, 74.1) of patients who received lanreotide had not had disease progression compared with 33% (95% CI: 23.0, 43.3) of in the placebo group. For the placebo group, the median PFS was 18 month. The median PFS had not been reached in the lanreotide group at 24 months. • Tumour response, as determined by partial response or stable disease using RECIST version 1.0 criteria, was 66% in patients treated with lanreotide compared with 53% of those in the placebo group. *b. The OLE phase with lanreotide Autogel 120 mg/4 weeks* • The median PFS was 32.8 (95% CI: 30.9, 68.0)[6] months for patients treated with lanreotide in the DB phase and continued into the OLE phase. For patients who had switched from placebo to lanreotide due to disease progression, time to further progression was 14.0 months. • The median PFS was 29.7 months for pNETs patients treated with lanreotide in both the DB and the OLE phases of the study. • The OS did not differ significantly between the placebo and the lanreotide groups. This could be due to complications introduced by crossover from placebo to lanreotide, and uncertainty over subsequent treatment after disease progression . **2. Findings from Non-Randomized primary studies.** Studies in this category varied widely regarding designs and populations. Most of the studies increased the dose of lanreotide in the course of the investigations, did not report median PFS, and used unstandardized ways to assess the tumour response. Reported outcomes included the following • An open-label phase II study of lanreotide 120 mg/4 weeks in patients with progressive GEP-NETs (n=30) reported a median PFS of 12.9 months, with 89% of patients achieving tumour stabilization. • In a retrospective study of patients with well-differentiated digestive NETs (n=68), treatment with lanreotide Autogel at a median dose of 90 mg/4 weeks resulted in PFS > 80 months in patients with ≤25% liver involvement compared with 15 months for those with >25% liver involvement. The difference was statistically significant (*P* = 0.005).	"Current clinical evidence shows that lanreotide Autogel has good antiproliferative activity with favorable safety and tolerability in patients with GEP-NETs, suggesting it should be considered as an early first-line treatment in this population. Further studies are needed to assess the potential benefits of higher doses and the use of lanreotide Autogel in combination therapy and as maintenance therapy in the absence of disease progression following other therapies."[15] Page 1

Main Study Findings	Author's Conclusion
• A long-term (9 years) retrospective study of patients with metastatic midgut NETs (n=69) treated with lanreotide Autogel at doses varying from 60 mg to 120 mg/4 weeks, the OS at years 1, 3, and 5 was 96%, 78%, and 72%, respectively. Radiographic PFS at these time points were 93%, 75%, and 59%, respectively. **B. Safety** • The most common TRAEs of lanreotide were diarrhea (25.7%), abdominal pain (13.9%), cholelithiasis (9.9%), and hyperglycemia (4.95%). They were mild or moderate in most cases, with no clinically significant trends, and no significant differences between treatment groups.	
Vinik, 2016[10]	
• Efficacy • The adjusted mean percentage of days with rescue octreotide use was 33.7% (95% CI: 25.0, 42.4) with lanreotide compared with 48.5% (95% CI; 39.6, 57.4) in the placebo group. The absolute difference of –14.8% (95% CI: –26.8, –2.8) was significantly lower (*P* = 0.017) and in favor of lanreotide. • Treatment with lanreotide was associated with the significantly greater proportion of patients than placebo with full treatment success (40.7% vs. 23.2%) or partial treatment success (6.8% vs. 5.4%). • Compared with no treatment, the odds of success or partial success were significantly higher with lanreotide than with placebo (OR = 2.4; 95% CI: 1.1, 5.3; *P* = .036). Full or partial treatment success was defined as no need for, or ≤3 days' use of short-acting octreotide as rescue medication in weeks 12 to 15. • The (adjusted mean (SE) daily frequency of diarrhea events was 1.34 (0.13) with lanreotide versus 1.55 [0.14] in the placebo group. The difference was not statistically significant (–0.21; 95% CI: –0.58, 0.15; *P* = 0.25). • At week 12, there was a greater improvement from baseline in global health status/QoL, gastrointestinal symptoms, and endocrine symptoms in patients receiving lanreotide, compared with lesser improvement or no change with placebo. Although the adjusted treatment differences favored the lanreotide group, the wide 95% CIs (not shown) indicate they did not reach the level of significance. • Safety • The incidence of AEs was similar and generally low in both groups. The most frequent AEs (lanreotide vs. Placebo) were nausea (5 [8.6%] vs. 5 [8.8%],), vomiting (4 [6.9%] vs. 2 [3.5%]), abdominal pain (5 [8.6%] vs. 8[14.0%]), and flatulence (3 [5.2%] vs. 1 [1.8%]). • The reported incidence of serious AEs were 2 (3.4%) for lanreotide versus 5 (8.8%) for placebo. Serious AEs	"Lanreotide depot/autogel is effective for the control of CS symptoms in patients (SSA-naïve or experienced) with NETs."[10] Page 1068

Main Study Findings	Author's Conclusion
resulted in the withdrawal of one patient each from the lanreotide (invasive ductal breast) carcinoma and placebo (cerebral ischemia) groups. But these were not considered treatment-related	
Bongiovanni, 2017[1]	
30 patients with metastatic PC received first-line[a] SSA treatment (20 with 30 mg octreotide LAR and 10 with lanreotide 120 mg/ 28 days) for a median duration of 10 months (range: 2.0 to 59.0 months). **A. Efficacy** • Partial response was observed in one (3.3%) patient and 26 patients (86.6%) showed stable disease. The median duration of both responses was 12 months. • The median overall PFS was 11.1 months (95% CI: 7.0, 15.0). There was no significant difference between the median PFS with lanreotide (10.1 months) and with octreotide (11.1 months). • Patients with negative ^{18}FDG-PET/CT had median PFS of 15.2 months (95% CI: 7.6 months, not reached) compared with 7.0 months (95% CI: 4.0, 10.1) for those with positive ^{18}FDG-PET/CT. • No differences were observed in median PFS with respect to TTF-1 value, histologic subtype, and presence of extrahepatic metastases. • The median OS was 74.0 months, with a 5-year OS of 87.5% with lanreotide versus 65.6% with octreotide. **B. Safety** • Reported AEs were steatorrhea (46.6%), diarrhea (26.6%), and symptoms of grade 3 cholelithiasis (n=1). Steatorrhea and diarrhea were treated with symptomatic drugs and the SSA treatment was interrupted for the patient with symptoms of cholelithiasis	• "SSAs showed antitumor activity in terms of disease control rate and PFS and proved safe, even in patients with poor Eastern Cooperative Oncology Group status. ^{18}FDG-PET/CT would appear to be a prognostic factor."[1] Page 415 • "…our findings confirm the activity and safety profile of both octreotide and lanreotide in nonfunctioning PCs and provide valuable information on the prognostic significance of ^{18}FDG-PET/CT."[15] Page 418
Ruszniewski, 2016[11]	
Primary Endpoint: CS–related diarrhea control • Both the ITT and PP analyses showed that 76% of patients were either 'completely' or 'rather satisfied' with diarrhea control at the assessment visit. • Satisfaction with diarrhea control was lower (66%) among patients with additional contributing factors compared with those without (80%) *Secondary Endpoints* • Overall, 79% of patients reported improved diarrhea after lanreotide treatment, with the proportion of patients reported having 'mild', 'minimal', or 'no diarrhea' increasing from 33% at initiation to 75% after treatment. • Physicians recorded that patients had significantly lower daily stool frequency at study visit than at lanreotide initiation. The mean (SD) stools/day	"In conclusion, lanreotide Autogel/Depot is an effective and convenient treatment for patients with NETs and associated CS. This is supported by the PRO measures of symptom control used in this study, which were consistent with physician-rated measures during the study. PRO measures were also consistent with previous clinical data."[11] page 6

Main Study Findings	Author's Conclusion
decreasing from 4.7 (3.0) to 2.6 (2.5); a mean reduction of 2.1 stools/day (95% CI: 1.7, 2.5) • Of patients who reported experiencing significant flushing episodes at initiation of lanreotide treatment, 73% were 'completely' or 'rather satisfied' with the control of flushing at study visit. • 70% of patients (140/200) who were satisfied with diarrhea control reported good, very good, or excellent QoL as determined by EORTC QLQ-C30 global scores compared with 39% of patients (7/18) who were dissatisfied, or 48% of patients (22/46) who were neither satisfied nor dissatisfied with diarrhea control.	

[18]FDG-PET/CT = fluorine-18 fluorodeoxyglucose-positron emission tomography/computed tomography; AE = adverse events; CI =confidence interval; CS = carcinoid syndrome; DB = double-blind; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaires–Core 30; GEP = gastroenteropancreatic; ITT = intention to treat; NETs = neuroendocrine tumours; OLE = open-label extension; OR = odds ratio; OS = overall survival; PC = pulmonary carcinoids; PFS = progression-free survival; pNETs = pancreatic NETS; PP = per-protocol; PRO = patient-reported outcomes; QoL = quality of life; RCT = randomized controlled trial; RECIST = response evaluation criteria in solid tumors; SD = standard deviation; SSAs = somatostatin analogs; TRAEs = treatment-related adverse events; TTF-1 = thyroid transcription factor 1; TTP = time to progression;

[a] All the patients underwent second-line treatment with chemotherapy (n=6) or peptide receptor radionuclide therapy (n=23), and 12 patients received an unidentified third-line therapy.

Table 7: Summary of Cost Findings

Main Study Findings	Author's Conclusion
Marty, 2012[12]	
• Mean cost savings per successful injection due to lanreotide Autogel were as follows: ○ **Scenario A (base case)** € 35, € 91, and € 143 for France, Germany, and the UK, respectively. ○ **Scenario B** € 12.7, € 51.9, and € 126.8, respectively, for **France, Germany, and the UK, respectively** ○ **Scenario C** € 44.8, € 108.0, and € 150.5, respectively, for **France, Germany, and the UK**. • The overall annual savings were €1.9 million for France, € 5.735 million for Germany, and EUR € 7.07 milllion for the UK. • Cost saving due to the reduced clogging incidence and shorter administration time associated with lanreotide were 100% in France, 32% in Germany, and 20% in the UK. • The administration costs were similar for both the hospital and community settings, and estimated to be 3% of the drug cost.	"Administration costs as a whole might be important to take into account when comparing costly drugs which must be administered by injection. Simulations of reduction in risk of clogging and shorter administration times for Somatuline Autogel® (lanreotide) versus Sandostatin LAR®, on top of lower retail drug prices, predict substantial cost savings in the countries studied, ie, France, Germany, and the UK."[12] Page 43

EUR = euros, UK = United Kingdom

Appendix 5: Additional References of Potential Interest

Consensus guidelines with mini-consensus statements for the use of somatostatin analogues including lanreotide in NETs

1. Bednarczuk T, Bolanowski M, Zemczak A, Baldys-Waligorska A, Blicharz-Dorniak J, Boratyn-Nowicka A, et al. Neuroendocrine neoplasms of the small intestine and appendix - management guidelines (recommended by the Polish Network of Neuroendocrine Tumours). Endokrynol Pol. 2017;68(2):223-36.
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