LanroNET, a non-interventional, prospective study to assess the resource utilization and cost of lanreotide autogel 120 mg in Polish patients with neuroendocrine tumors – results of interim analysis

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Aim of the study: To examine characteristics and treatment patterns of symptomatic neuroendocrine tumors (NETs) patients who received lanreotide Autogel 120 mg (ATG120) administered as part of routine clinical practice.

Material and methods: Lanro-NET is a national, multicenter, non-interventional, observational study in the population of adult patients with symptomatic NETs treated with ATG120 for at least three months before inclusion. Data on demographic and clinical characteristics of the population, dosing interval regimen and aspects of administration were collected prospectively during 12 months. Costs were calculated from the perspective of public payer for the year 2014.

Results: Fifty-two patients were enrolled in the study. Primary tumors were located predominantly in gastrointestinal tract (51.2%), all tumors were metastatic. The most commonly reported disease symptoms were flushing and diarrhea (55.8% of patients). 86% of patients had undergone surgery, chemotherapy and radioisotope therapy were used in 11.6% and 46.5% of patients, respectively. During the 12-months observation 12 (28%) patients received ATG120 at an extended dosing interval (> 4 weeks), the mean number of days between injections was 31.75 (SD 6.74). The cost of ATG12 was estimated at 4273.17 PLN patient/month. In all patients ATG120 was administered by nurse, 51.6% of injections in out-patient setting, 48.4% – in hospital.

Conclusions: This study presents the current use of ATG120 in the population of Polish NETs patients in a realistic clinical settings. Finding that 28% of patients could be treated with extended dose intervals supports the potential for ATG120 of reducing treatment burden.

Key words: neuroendocrine tumors, lanreotide Autogel, clinical study, cost of treatment.

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Introduction

Neuroendocrine tumors (NETs) are a rare and heterogeneous group of neoplasms that originate from neuroendocrine cell compartments located in numerous different organ systems [1]. Unlike other solid tumors, they are able to over-secrete hormones and other biological substances normally secreted by neuroendocrine cells, resulting in characteristic syndromes. Because of their low incidence, there is a general lack of disease awareness, and prognosis in diagnosed patients varies widely, depending on grade (pro-

Table 1. Crucial studies evaluating the efficacy and safety of Somatuline ATG

Study	Patient population	Intervention	Comparator	Design	Primary endpoint	Results
Ruszniewski (2004) [8]	Patients with NETs with carcinoid syndrome	lanreotide ATG every 28 days; 90 mg for the first injections, then 60 mg, 90 mg or 120 mg depending on response to treatment	N/A	open, dose titration	number of diarrhea episodes, flushings and their severity	good tolerance of treatment, symptoms and biochemical markers reduction
Bajetta (2006) [9]	Patients with well differentiated NETs	lanreotide ATG 120 mg every 6 weeks	lanreotide PR 60 mg every 3 weeks	open, randomised	tumour markers and tumor size, symptoms assessment between baseline and week 18	good efficacy in NETs controlling
SymNET Ruszniewski (2014) [10]	NETs with carcinoid syndrome	somatuline ATG	N/A	open, cross-sectional	overall patient satisfaction regarding diarrhea control	79% of patients reported treatment satisfaction as regards control of diarrhea; 73% were satisfied with flushing control
ELECT Vinik (2014) [11]	NETs with carcinoid syndrome	lanreotide ATG 120 mg every 28 days	placebo	randomised controlled trial, parallel group for 16 weeks, followed by open-label extension	% of days octreotide required to control symptoms (rescue medication)	during initial phase, need for octreotide was less with Somatuline ATG than placebo (% of days in which octreotide was used –33.7% vs. 48.5% in placebo group, $p = 0.017$)

liferative rate), stage, and primary tumor site. For patients with diagnoses of localized NET, surgical resection is the treatment of choice. For patients with advanced disease, therapeutic options are limited [1]. First-line therapy in patients with advanced, functioning tumors usually involves somatostatin analogues: lanreotide and octreotide. These drugs, approved in the US and Europe for management of symptoms associated with NETs, are recommended by current guidelines [2–4], including recent Polish recommendations [5–7]. Lanreotide Autogel (lanreotide ATG) sustained release formulation – Somatuline Autogel (Ipsen Pharma) – has shown improvement in symptom control in numerous clinical studies. Crucial studies evaluating its efficacy and safety are presented in Table 1. The first study was a phase II/III trial investigating the use of lanreotide ATG in patients with NETs with carcinoid syndrome [8]. Among 71 patients who received lanreotide ATG for 6 months, 65% achieved a 50% or greater reduction in flushing episodes, and 18% had a 50% or greater reduction in diarrhea episodes [8]. The second study was a phase III randomized clinical trial that recruited patients with well-differentiated NETs and compared lanreotide ATG 120 mg with Somatuline PR formulation [9] (Table 1). The recently completed ELECT and SymNET trials considered the use of lanreotide ATG in carcinoid syndrome [10, 11] (Table 1).

In patients with hormonally active NETs, with advanced disease, treatment with somatostatin analogues may last for many years. However, a cost evaluation of treatment with lanreotide ATG has so far not been performed. The aim of this study was to examine characteristics and treatment patterns of symptomatic NETs patients who received lanreotide ATG 120 mg administered as part of routine clinical practice and to evaluate over the 24 months prospective follow-up resource utilization and costs of the treatment. This type of study provides evidence on the use of a drug in a realistic setting and can be used as a vehicle for addressing multiple post-approval objectives, e.g. optimizing product usage, documenting cost-effectiveness, and identifying best practice. The analysis of dosage regimen data (patients treated with lanreotide ATG 120 mg every 28 days or 42 days or 56 days during a 24-month period) supports better understanding of the cost and efficiency of treatment.

Material and methods

LanroNET is a national, multicenter, non-interventional, observational, prospective (24-month) study, conducted in accordance with the Declaration of Helsinki [12] and the International Ethical Guidelines for Epidemiological Studies, CIOMS, Feb 2008 [13]. This study also followed the recommendations of the International Epidemiological Association Guidelines for the Proper Conduct in Epidemiologic Research (Good Epidemiological Practice, GEP), Nov 2007 [14], and the International Society for Pharmacoepidemiology (ISPE) Good Pharmacoepidemiology Practices (GPP) Guidelines, April 2007 [15]. All patients gave written informed consent before entering the study.

Data were collected in accordance with the standard management of subjects with symptomatic NETs as applied in everyday practice (by particular site). Treatment monitoring, dose adjustment and all other medical decisions were made at the responsible physician's discretion,

Table 2. Baseline demographic and disease characteristics of the patients (analysed population)

Variable	Population (*n* = 43)
Mean (SD) age, years	60.1 (9.6)
Mean (SD) weight, kg	73.3 (16.0)
Sex	
Male, *n* (%)	19 (44.2)
Female, *n* (%)	24 (55.8)
Performance status (ECOG-WHO) *n* (%)	
0	13 (30.2)
1	19 (44.2)
2	8 (18.6)
3	1 (2.3)
NA	2 (4.7)
Origin of neuroendocrine tumor *n* (%)	
Small intestine	22 (51)
Pancreas	7 (16.3)
Colon/rectum	6 (14)
Bronchopulmonry system	2 (4.7)
Unknown	6 (14)
Proliferation grading *n* (%)	
G1	25 (58.1)
G2	7 (16.3)
G3	3 (7.0)
Not available	8 (18.6)
Prior treatment for neuroendocrine tumor *n*(%)	
Surgery	37 (86)
Somatostatin analogues	36 (83.7)
Chemotherapy	5 (11.6)
PRRT	20 (46.5)

according to routine practice at the study site. Eligible patients were adults (≥ 18 years of age) with symptomatic NETs treated with lanreotide ATG 120 mg for at least three months before inclusion. The decision to prescribe lanreotide ATG 120 mg was made prior to and independently from the decision to enroll the subject in this non-interventional study. Patients were excluded if they actively participated in any interventional NET clinical study. Patients who switched to treatment other than lanreotide ATG 120 mg exited the study at the moment of stopping lanreotide ATG 120 mg treatment and information of the recommended new therapy was recorded. Up to 8 weeks pause in lanreotide ATG 120 mg treatment for radioisotope therapy (PRRT) did not exclude the patient from the study.

Site selection was based on the ability to collect the data in electronic format, motivation to participate and fulfillment of all requirements of the protocol. Patients were included in the study during routine visits: outpatient visits or admissions to hospital. In order to avoid bias in recruitment of subjects, investigators were asked to include all consecutive subjects to achieve the recruitment target (target per centre) during a restricted and defined period. Relevant data collected prospectively were captured on an electronic case report form (eCRF).

An interim analysis was performed using patient observations conducted between June 2013 and June 2014 (data cut-off date was June 30, 2014). The following data were included: baseline patient characteristics (demographic details, clinical assessment, relevant medical history, prior therapies) and details of current treatment. The primary endpoint was to evaluate the resource utilization and cost of the treatment of symptomatic NETs patients in Poland with lanreotide ATG 120 mg including extended injection intervals in everyday clinical practice.

The mean time between injections was defined as the sum (across all recommended intervals) of the length of each recommended interval multiplied by the ratio between the time on that interval and the total time on lanreotide ATG 120 mg. Cost evaluation was performed from the perspective of the public payer, e.g. the National Health Fund, in 2014. Costs were assessed using a micro-costing approach, applying unit cost multipliers to the quantity of each type of resources consumed. Mean cost per patient in the 1-year time horizon resulted from the total cost divided by the number of patients included. Given the exploratory nature of the study, no formal statistical analysis was performed.

Results

Characteristics of the population

A total of 57 patients at 13 centers in different Polish regions were screened, and 52 were enrolled in the study. Of those, 9 patients were excluded from the analysis because of missing source data verification (SVD) of enrollment visits (7 patients) and failure in eCRF (2 patients), leaving 43 patients (19 men/24 women) for inclusion for analysis. Mean age in this population was 60.1 (SD 9.6) years. Other demographic characteristics of the study population are summarized in Table 2. According to ECOG (Eastern Cooperative Oncology Group) – WHO performance status criteria, 13 (30.2%), 19 (44.2%), 8 (18.6%), 1 (2.3%) and 2 (4.7%) patients were designated with status 0, 1, 2, 3, and 4, respectively (Table 2).

Primary tumors were located predominantly in the small intestine (51%), 16.3% of NETs occurred in the pancreas, 14% in the colon/rectum, and the bronchopulmonary system was the site of 4.7% of NETs. Primary tumor location was not documented/assessed in 6 patients (14%). All tumors were metastatic; the proportion of patients with 1 site and ≥2 sites of metastases was 18.6% and 81.4%, respectively.

The primary tumor could not be evaluated in 12 (27.9%) patients, and there were 2 (4.65%), 11 (25.6%), 12 (27.9%), and 4 (9.3%) tumors representing stages T1, T2, T3, and T4 (N/A in 2 patients; 4.65%). Regional lymph nodes could not be evaluated in 9 (20.9%) patients, in 4 (9.3%) patients regional lymph nodes were not involved, and in remaining patients the degree of regional lymph node involvement was N1 (22 patients), N2 (4 patients), and N3 (1 patients). Distant metastases were present in the majority of patients (*n* = 38, 88.4%), in 2 (4.7%) patients distant metastases could not be evaluated, and 1 (2.3%) patient had no distant metastases.

Proliferation indices were available for 35 (81.4%) tumors. Of these, 25 were considered well differentiated (G1), 7 moderately differentiated (G2), and 3 poorly differentiated (G3) according to the WHO classification [16].

Chromogranin A (CgA) and 5-hydroxyindoleacetic acid (5-HIAA) were the most frequently assessed pathological markers. Mean (SD)/median (min, max) CgA and 5-HIAA levels for all patients with baseline assessment (n = 38 and n = 25) were 955.9 (2610.1)/449.5 (23, 15532) ng/ml, and 42.9 (55.2)/28.1 (6, 268) µmol/day, respectively.

The most commonly reported symptoms of the disease were flushing and diarrhea (55.8% of patients), and abdominal pain (53.5% of patients). Fatigue was reported in 34.9% of patients, telangiectasia in 32.6%, hyperglycemia in 18.6%. Cushing syndrome and Zollinger-Ellison syndrome were reported in 2.3% and 2.3% of patients, respectively.

Most patients (86%) had undergone previous surgery; the mean time since surgery was 4.3 (SD: 4.0) years. Chemotherapy was used in the past in 11.6% of patients, PRRT in 46.5% of patients. Thirty-eight patients (83.7%) had been treated previously with somatostatin analogues. Among patients with G1 NETs (n = 25) the proportion of patients previously treated with surgery, PRRT, chemotherapy and somatostatin analogues was 96%, 44%, 8% and 100%, respectively, and the mean time since surgery was 3.57 (SD 2.7) years.

Pharmacotherapy and costs

At enrollment 34 patients (79.1%) were treated with lanreotide ATG 120 mg given every 4 weeks, and 9 patients (20.9%) received lanreotide ATG 120 mg at an extended dosing interval (> 4 weeks): 8 patients every 6 weeks, 1 patient every 8 weeks. During the 12-month prospective phase of the study the mean number of days between injections was 31.75 (SD 6.74), and the number of patients who received lanreotide ATG 120 mg at an extended dosing interval (> 4 weeks) increased to 12 (27.9%). Changes in dosing regimen of lanreotide ATG 120 mg were reported in 3 patients who had the dose frequency extended (from 4 to 5 weeks), in 1 patient treatment was switched from lanreotide ATG 120 mg to octreotide LAR because of temporary lack of lanreotide ATG 120 mg in this site, and 2 patients changed the treatment to PRRT.

The cost of lanreotide ATG 120 mg calculated based on reimbursement status and retail price of lanreotide ATG 120 mg being in force from 1 September 2014 [16] was 4338.52 PLN/patient/month at baseline and 4273.17 PLN/patient/month during the 12 months of the study (Tables 3, 4).

At baseline lanreotide ATG 120 mg was predominantly administered in hospital (n = 29, 67.4%) (Table 5). During the 12-month prospective phase of the study, 51.1% of injections were administered in an out-patient setting, and 48.4% in hospital (Table 6). In all patients lanreotide ATG 120 mg was administered by a nurse.

Table 3. Dosing regimen and cost of lanreotide ATG 120 mg at baseline (n = 43)

	Dose	Interval (weeks)	N. of patients		Cost/PLN/month*
Lanreotide ATG	120 mg	4	34	43	4 338.52
		6	8		
		8	1		

Retail and reference price of lanreotide ATG 120 mg – 4683.42 PLN/pack, full reimbursement [Obwieszczenie Ministra Zdrowia z dn. 22 sierpnia 2014 r. (poz.64)] [16]

Table 4. Dosing regimen and cost of lanreotide ATG 120 mg in the 12-months prospective phase of LanroNET (n = 43)

	Dose	Interval (weeks)	N. of patients		Cost/PLN/month*
Lanreotide ATG	120 mg	4	31	43	4273.17
		5	3		
		6	8		
		8	1		

Retail and reference price of lanreotide ATG 120 mg – 4683.42 PLN/pack, full reimbursement [Obwieszczenie Ministra Zdrowia z dn. 22 sierpnia 2014 r. (poz.64)] [16]

Discussion

This study presents the current use of lanreotide ATG 120 mg in the population of Polish NETs patients in a realistic clinical setting. This is an observational non-interventional study and there are no protocol-driven procedures or treatment patterns. The prospective design reduces recall bias, considered a weakness of retrospective trials. The study population, coming from 13 centers in different Polish regions, represents a wide cross-section of NET patients in our country and seems to be representative.

Interim analysis of results, mostly related to the primary objective of the study – the resource utilization and cost of treatment of symptomatic NET patients in Poland with lanreotide ATG 120 mg, from 12 months of observation, are presented. The demographic and clinical characteristics of the Polish population are, while not identical, at least comparable to those described in NET samples in other European countries [17–21]. Our data are close to most other epidemiological surveys with respect to age and gender of the population. The small intestine was the most pre-

Table 5. Administration of lanreotide ATG (setting, person, who administer lanreotide ATG) at baseline.

		Person, who administer lanreotide ATG n (%)				Total
		Physician	Caregiver	Patient	Nurse	
Setting of administration	Home	0	0	0	0	0
	Out-patient setting	0	0	0	14 (32.6)	14 (32.6)
	In-patient setting	0	0	0	29 (67.4)	29 (67.4)
Total		0	0	0	43 (100)	45 (100)

Table 6. Administration of lanreotide ATG (setting, person, who administer lanreotide ATG) during 12-months

		Person, who administer lanreotide ATG *n* (%)				Total
		Physician	Caregiver	Patient	Nurse	
Setting of administration	Home	0	0	0	0	0
	Out-patient setting	0	0	0	174 (51.6)	174 (51.6)
	In-patient setting	0	0	0	163 (48.4)	163 (48.4)
Total		0	0	0	337 (100)	337 (100)

n is the number of injections of lanreotide ATG 120 mg, percentage is the percentage of the total number of injections.

dominant NET location among Polish patients. A high percentage of NETs occurring in the small intestine has also been reported for many European countries, including Italy (24%) [18], Germany (22%) [17], Norway (26%) [20] and Sweden (35%) [19]. In the Polish study, similarly as in the German study [17], two differences from other published series are: the small number of lung tumors and the high percentage of cases of cancer of unknown primary tumor. The percentage of G3 tumors in our study was only 7%, which was lower than that observed in the German population (18%) [17]. This high percentage of poorly differentiated tumors probably does not indicate an unusually high prevalence, as grading available only for one third of the patients in the German study may have been performed preferentially for more malignant tumors, resulting in over-reporting of G3 tumors.

Our study showed that 86% of patients had undergone surgery. In contrast, only 58% of Norwegian patients received primary tumor surgery and 16% received palliative surgery [20], while in Germany surgery was the first treatment in 77.5% of patients [17]. The relatively high percentage of patients treated with PRRT (46.5%) seems to be very specific for the Polish population.

Some limitations of this study need to be considered. The decision on interval duration may in part reflect limitations in funding by the National Health Fund. Interim analysis does not present the effects of treatment, as it is focused on the primary end-points: resource utilization, costs per month and aspects of administration of lanreotide ATG 120 mg. Nevertheless, such effects will need to be presented in the final report.

So far, limited data have been published concerning dosing patterns and cost of somatostatin analogues used for treatment of NET patients in routine clinical practice. The only published pharmacoeconomic data comparing lanreotide versus octreotide in gastro-entero-pancreatic tumors come from the PHARMO Record Linkage System in the Netherlands [21]. A cost-minimization model was used to compare lifetime costs of both drugs used in routine clinical settings. Data for patients receiving outpatient dispensing long-acting lanreotide and octreotide in 2003–2010 were selected from the national database. A total of 92 patients were identified. Stratified by week, 17% of octreotide users received injections every 3 weeks, 67% every 4 weeks, 13% every 5 weeks, and 3% every 6 weeks. In comparison, 88% of lanreotide users received injections every 4 weeks and 13% every 6 weeks. Mean injection intervals were 27 ±8 days for octreotide and 31 ±10 days for lanreotide. This resulted in an average patient cost 7% less with lanreotide than octreotide based on the cost minimization model. In conclusion, this analysis suggested that long-acting lanreotide use reduced costs compared with long-acting octreotide. The driver of cost savings was the longer injection interval with lanreotide during stable treatment for NETs.

In our study, at enrollment 34 patients (79.1%) were treated with lanreotide ATG 120 mg given every 4 weeks, and 9 patients (20.9%) received lanreotide ATG 120 mg at an extended dosing interval (> 4 weeks): 8 patients every 6 weeks, 1 patient every 8 weeks. During the 12-month prospective phase, the mean number of days between injections was 31.75. This is in fact the same mean injection interval as that observed in the PHARMO database. Our study was non-interventional and non-comparable, so data related to octreotide treatment patterns are not available.

The possibility of extending dosing intervals of drugs administered in injections may positively influence patients' preference for treatment and compliance. A recent study evaluating the efficacy and safety of extended dosing intervals with lanreotide ATG 120 mg in patients with acromegaly previously controlled with conventional doses of octreotide LAR every 4 weeks demonstrated that extending dosing intervals was associated with patient preference over octreotide [22].

The cost of lanreotide ATG 120 mg calculated based on reimbursement status and retail price in force from 1 September 2014 was 4338.52 PLN/patient/month at baseline and 4273.17 PLN/patient/month during the 12 months of the study. This real cost of treatment is lower than the price of lanreotide ATG 120 mg with its wholesale gross price of 4683.42 PLN/pack. Findings that a substantial number of patients with functional NETs are treated with dose intervals longer than 28 days strongly support the potential for lanreotide ATG 120 mg to reduce the treatment burden. These findings are also in accordance with results of the Lanro-Study conducted recently among acromegaly patients in Poland, where during the 12-month prospective phase of the study 70 patients (50%) received lanreotide ATG120 at an extended dosing interval [23].

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