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ORIGINAL RESEARCH

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Pharmacological and safety profile of a prolonged-release lanreotide formulation in acromegaly

Sebastian Neggers[a], Corin Badiu[b], Betina Biagetti[c], Lucie Durand-Gasselin[d], Anne Petit[e], Patrick Petrossians[f], Benjamin Regnault[g], David Rich[h], Zulfiya Shafigullina[i], Sergey Shustov[i] and Anna Vydrych[i]

[a]Medicine and Endocrinology, Erasmus University Medical Center, Erasmus University Rotterdam, Rotterdam, Netherlands; [b]Department of Endocrinology National Institute of Endocrinology, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania; [c]Department of Endocrinology, Hospital Universitari Vall d'Hebron, Barcelona, Spain; [d]Clinical Pharmacokinetics & Pharmacometrics, Ipsen Innovation, Les Ulis, France; [e]Drug Product Development & Industrialization, Ipsen PharmSciences, Dreux, France; [f]Department of Endocrinology, University Hospital of Liège, Sart Tilman Campus, Liège, Belgium; [g]Ipsen, Boulogne-Billancourt, France; [h]Global Development, Rare Diseases, Ipsen BioInnovation, Abingdon, UK; [i]Department of Endocrinology, North-Western State Medical University Named after I.I Mechnikov, St. Petersburg, Russia

ABSTRACT

Background: Patients with acromegaly require lifelong medication; a longer dosing interval would reduce treatment burden. This study investigated the pharmacokinetics, pharmacodynamics and safety profile of a new prolonged-release formulation (PRF) of lanreotide every 12 weeks.

Research design and methods: In this multicenter, open-label, dose-ascending study, cohorts of nine patients with acromegaly received single doses of lanreotide PRF according to a 3 + 3 + 3 scheme in order to determine the maximum tolerated dose (MTD). Following a 12-week treatment period, patients were followed up for a further 12 weeks. Serum lanreotide, insulin-like growth factor-1 and growth hormone concentrations were analyzed. Adverse events were monitored throughout the study.

Results: The MTD was not reached. Peak lanreotide serum concentration values were similar in all cohorts, whereas area under the curve values from time zero to 85 days increased but were not dose-proportional. The apparent elimination half-life of lanreotide PRF was approximately 54–63 days, in line with the expected prolonged-release characteristics. Growth hormone and insulin-like growth factor-1 levels were generally stable.

Conclusions: The safety and tolerability profile was in-line with the known safety profile of lanreotide autogel. Lanreotide PRF was well tolerated and the pharmacokinetic profile suggests that a dosing interval of 12 weeks could be achievable.

Clinical trial registration: www.clinicaltrials.gov identifier is NCT02396953; EudraCT 2014–002389-62.

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Acromegaly; lanreotide prolonged-release formulation; maximum tolerated dose; pharmacokinetics; pharmacodynamics; somatostatin analogues

1. Introduction

Traditionally, first-line treatment for acromegaly is neurosurgery, followed by medical treatment and radiotherapy if tumor control is not achieved [1]. Medical therapy can enable approximately 50% of patients to achieve biochemical control (normal insulin-like growth factor-1 [IGF-1] levels) [2] and ≥20% tumor volume shrinkage in 63–75% of patients [3]. First-generation somatostatin analogues (octreotide and lanreotide) are the primary medical treatment for acromegaly [4,5]. Recommended dosing intervals for lanreotide are every 7, 10, or 14 days for lanreotide long-acting (LA) and every 28 days for lanreotide autogel [6,7]. As lifelong medication is necessary to control acromegaly, a longer dosing interval would reduce the burden associated with frequent injections for patients [8,9].

Extending the dosing interval to 8 weeks is feasible with lanreotide autogel 120 mg in patients who have achieved adequate disease control with lanreotide autogel 60, 90 or 120 mg or octreotide long-acting release (LAR) 10 or 20 mg every 4 weeks [10–13]. With 8-week dosing intervals, the mean lanreotide serum trough concentration (C_{trough}) (the lowest concentration before the next dose) at steady state can be maintained above 1.13 ng/mL, which is the concentration required to reduce growth hormone (GH) concentrations to ≤2.5 ng/mL and achieve adequate disease control [10,14,15]. Patients also prefer less frequent injections [11], indicating that adherence to treatment may improve with extended dosing intervals.

Previous pharmacokinetic (PK) and pharmacodynamic (PD) modeling in acromegaly have indicated that lanreotide efficacy is driven by threshold serum concentrations rather than overall exposure [16]. Administration of 120 mg every 56 days could achieve a similar GH reduction to that achieved with 60 mg every 28 days [17]. Although higher doses of lanreotide autogel may extend the dosing interval, associated increases in peak serum concentrations (C_{max}) may affect the safety and tolerability profile. Therefore, with the aim of safely increasing the lanreotide dosing interval to 12 weeks, a prolonged-

CONTACT Sebastian Neggers s.neggers@erasmusmc.nl Medicine and Endocrinology, Erasmus University Medical Center, Erasmus University Rotterdam, Doctor Molewaterplein 40, Rotterdam 3015 GD, Netherlands

Supplemental data for this article can be accessed here.

release formulation (PRF) was developed to deliver a higher dose vs. lanreotide autogel. The PRF includes a hydrosoluble co-solvent with lubricating properties, which is non-viscous and nontoxic when administered via a deep subcutaneous route at the clinical doses selected. Preliminary studies in dogs demonstrated that the co-solvent enabled higher concentrations of lanreotide to be injected with a limited increase in C_{max} and a higher terminal elimination half-life ($t_{½}$) than lanreotide autogel (indicating slow depot release) (Ipsen Data on File ALL-ALL-001244).

The primary study objectives were to identify the maximum tolerated dose (MTD) and to investigate the PK of a single lanreotide PRF dose in patients with acromegaly. To reach the 12-week target, doses three times greater than those commonly prescribed for the treatment of acromegaly with lanreotide autogel (60, 90, and 120 mg) were selected to assess the duration of efficacy with regards to control of IGF-1 levels with each dose. The secondary study objectives were to investigate the safety, tolerability, and PD of a single dose of lanreotide PRF. The results are reported in line with the Transparent Reporting of Evaluations with Non-randomized Designs (TREND) guidelines (supplementary materials S1).

2. Patients and methods

2.1. Patients

Patients were recruited from 10 countries (Belgium, Czech Republic, France, Italy, Lithuania, Netherlands, Romania, Russia, Spain and the UK). Eligible patients were 18–75 years old, diagnosed with acromegaly, treated with a stable dose of either octreotide LAR or lanreotide autogel for ≥3 months immediately prior to study entry, with confirmation of disease control during this period (age-adjusted IGF-1 < 1.3 × upper limit of normal [ULN]). Patients were excluded from the study if they had received radiotherapy within 2 years prior to study entry (to render an effect of radiotherapy on study outcome highly unlikely, while enabling recruitment); dopamine agonist and/or GH receptor antagonist therapy or pituitary surgery within 3 months prior to study entry; estrogen hormone replacement therapy; clinically significant hepatic, pancreatic or renal abnormalities; symptomatic gallstones; uncontrolled cardiovascular disease; uncontrolled diabetes (HbA_{1c} ≥9%); or diabetes treated with insulin for <6 months prior to study entry. Further criteria are described in the supplementary materials (S2).

2.2. Study treatment

Lanreotide PRF utilizes a hydrosoluble co-solvent in order to maintain concentrations of lanreotide *in vivo* above the efficacy threshold for longer than with lanreotide autogel. Each patient received a single dose of lanreotide PRF, administered by a healthcare professional as a deep subcutaneous injection from a prefilled syringe, with a target injection time of <1 minute. Patients were assigned to a dose group regardless of dosing of prior medication for acromegaly. Each cohort was split into smaller groups (n = 1–3) that received sequential treatment according to the staggered treatment scheme that was dependent upon the data review committee (DRC) assessment of safety data from the preceding group. After all patients within a cohort had reached Visit 5 (Week 2 post-dose), the DRC reviewed the safety data from the entire cohort and determined whether the study should progress to the ascending dose cohort. Patients were dosed and reviewed as shown in Figure 1(a). The staggered treatment schemes were modified from 3 + 3 + 3 to 1 + 2 + 2 + 2 + 2 scheme in Cohort 2 and 2 + 2 + 2 + 3 in Cohort 3 due to the results of a parallel study (EudraCT 2015–004338-85) in which two out of four healthy volunteers injected with 180 mg lanreotide PRF experienced abdominal pain on the day of injection. Elevated levels of hepatic and pancreatic enzymes (amylase, lipase, aspartate transaminase and alanine transaminase), classified as dose-limiting toxicities, were reported in these patients (Ipsen Data on File ALL-ALL-001243).

2.3. Study design

This was a multicenter, open-label, dose-ascending, 24-week study of lanreotide PRF: 180 mg (Cohort 1), 270 mg (Cohort 2), and 360 mg (Cohort 3) (NCT02396953; EudraCT 2014–002389-62). Based on prior clinical experience with this type of study and patient population, nine patients per cohort were considered sufficient to meet the study objectives using an adaptive 3 + 3 + 3 decision rule (in Cohort 2 on a 1 + 2 + 2 + 2 + 2 and in Cohort 3 on a 2 + 2 + 2 + 3 decision rule) focusing *a priori* on patient safety, described above.

Following study enrollment, if a patient's GH or IGF-1 levels increased and caused symptoms, or further disease control was needed, the patient was withdrawn from the study. It was anticipated that all patients would be withdrawn prior to the end of the study due to elevated IGF-1 levels above the upper limit of the age-normalized range.

Patients were assessed post-treatment on Days 1, 2, 3, and 5, then once weekly for 4 weeks, and then bi-weekly for 10 weeks. One interim analysis was conducted after the 26th patient had completed Visit 12.

2.4. Endpoints

The primary safety endpoint was the MTD of a single dose of lanreotide PRF. The primary pharmacological endpoint was the PK properties of a single dose of lanreotide PRF. PD endpoints included serum concentrations of IGF-1, GH, free triiodothyronine (FT3), free thyroxine (FT4), thyroid-stimulating hormone (TSH), and prolactin (PRL). Safety and tolerability endpoints included treatment-emergent adverse events (TEAEs), vital signs, physical examination, 12-lead electrocardiogram (ECG) QT-corrected interval, clinical laboratory assessments (including glycosylated hemoglobin [HbA_{1c}] and estimated glomerular filtration rate [eGFR]), gallbladder echography, putative antibodies to lanreotide, and evaluation of injection-site reactions. Acromegaly symptoms were also recorded as an indication of efficacy.

2.5. Assessments

Blood samples were collected for the determination of serum lanreotide, IGF-1, FT3, FT4, TSH, and PRL (up to end of study)

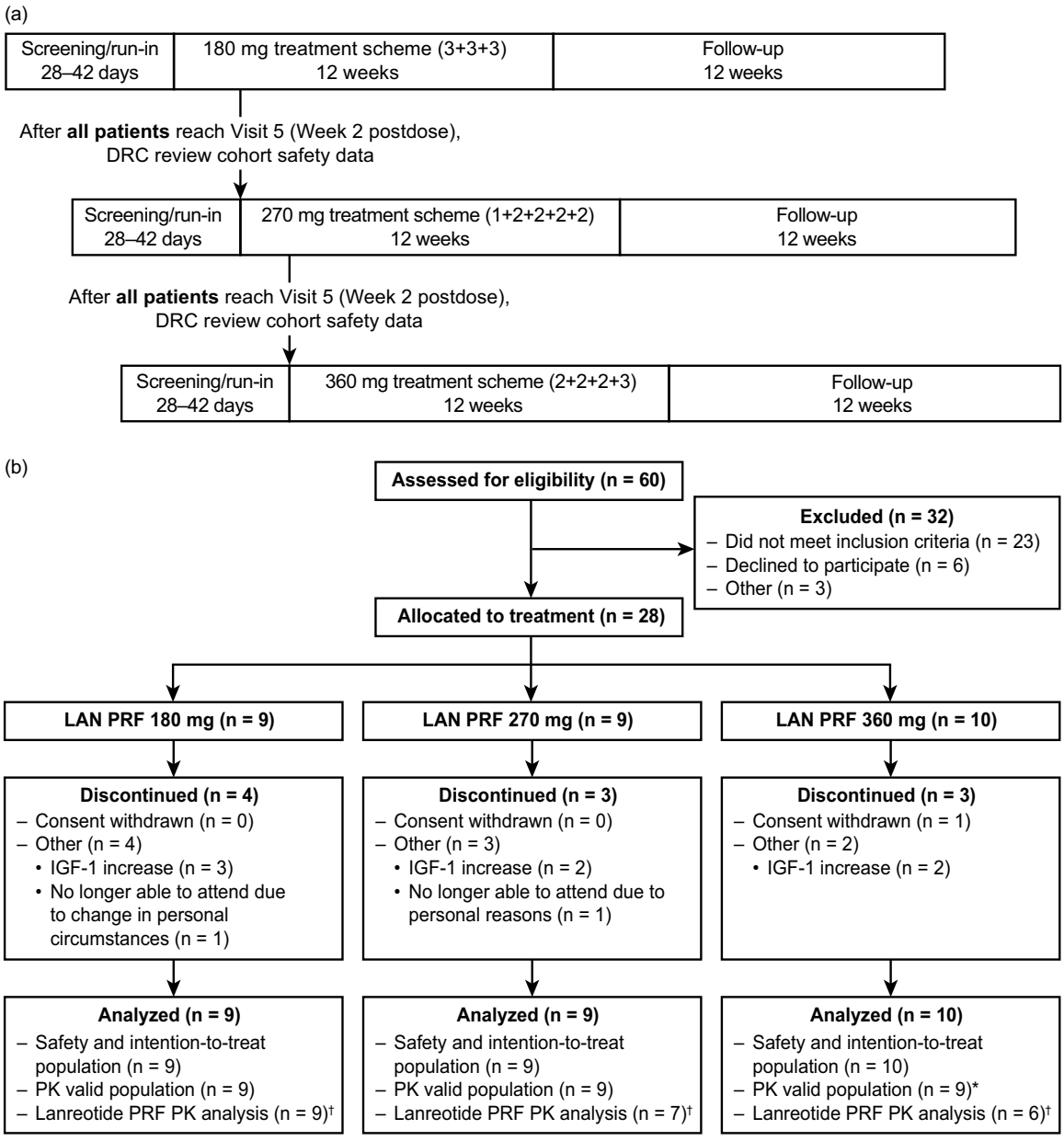

Figure 1. Study design. (a) Staggered treatment schemes. (b) CONSORT flowchart of patient enrollment, discontinuations and analysis. *One patient was excluded because no serum lanreotide PRF concentrations were available following lanreotide PRF administration on Day 1 due to a protocol deviation; †overall, 22 patients met the criteria to be included in the lanreotide PRF PK analysis, as described in the statistical methods.

DRC, data review committee; IGF-1, insulin-like growth factor-1; LAN-PRF, lanreotide prolonged-release formulation.

and serum GH (up to Week 13) to monitor lanreotide PRF efficacy. The reference ranges of the central laboratory were used for all analyzed parameters. Lanreotide serum concentrations were determined using a specific and sensitive radioimmunoassay (Kymos Pharma Services, Barcelona, Spain) and used in the non-compartmental PK analysis performed at Biotrial (Rennes, France). Non-compartmental PK calculations were performed using Phoenix WinNonlin® 7.0 (Pharsight Corporation, Palo Alto, California, USA).

The following serum PK parameter assessments were planned for lanreotide: C_{max}, time to maximum serum concentration (T_{max}), area under the curve for serum concentration from time zero to infinity ($AUC_{0-\infty}$), apparent terminal elimination half-life ($t_{½}$), apparent terminal elimination rate constant (λ_z), mean residence time, apparent clearance (CL/F), apparent volume of distribution (V/F), C_{trough} on day 85, and area under curve (AUC) from time zero to 85 days (AUC_{0-85}).

During the initial screening, IGF-1 levels of three patients were measured at local centers using LIAISON® (DiaSorin, Saluggia, Italy). Thereafter, to ensure continuity, all IGF-1 assays were performed with the central laboratory IMMULITE® 2000 (Siemens Healthineers, Erlangen, Germany) platform. During the study, production of the original ('old') IMMULITE® reagent ceased and a standardized reagent ('new,' tested for concordance) was used from February 2017. Summary statistics were performed by reagent type (old and new).

TEAEs were monitored using direct, non-leading questioning by the investigator or by spontaneous reports by the patient throughout the study from the time of informed consent. All toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03 (June 2010). TEAEs were defined as any AE that occurred between treatment initiation and 3 months after study treatment end that was not present prior to receiving treatment, or was present prior to receiving treatment but the intensity increased or became serious, or the intensity was the same but the drug relationship became associated during the active phase of the study.

2.6. Statistical analyses

The sample size was based on prior clinical experience with this type of study and patient population, and considered sufficient to meet the study objectives. The primary safety endpoint was analyzed using the safety population (all treated patients who had ≥1 post-baseline safety assessment). The primary PK endpoint was analyzed using the PK valid population (all treated patients who had no major protocol deviations affecting the PK variables and sufficient data to estimate the main PK parameters [C_{max}, T_{max} and AUC]). The lanreotide statistical dataset included all patients from the PK valid population who were not pre-treated with lanreotide as this would impact the statistical analyses (due to differences in lanreotide levels relative to octreotide pre-treated patients).

For each cohort and dataset, descriptive statistics and an exponential regression model over the 180 to 360 mg dose range were used to determine linear dose proportionality for C_{max}, $AUC_{0–85}$ and $AUC_{0–\infty}$ for lanreotide PRF and dose independence for $t_{½}$, CL/F and V/F. Descriptive statistics for $AUC_{0–\infty}$, CL/F, V/F and mean residence time were not performed when <33% of lanreotide values followed the PK calculation predetermined rules (Supplementary materials S2). No formal statistical testing was planned for the safety or PD parameters. Statistical evaluation not related to PK was conducted by Chiltern international Ltd. (Slough, UK), using Statistical Analysis System (SAS®) software version 9.2 (SAS Institute, Cary, NC, USA). Statistical evaluation related to PK parameters was conducted by Biotrial (Rennes, France).

2.7. Ethics statement

The study was conducted in accordance with the Declaration of Helsinki (2013), the International Council for Harmonisation Consolidated Guideline on Good Clinical Practice and Independent Ethics Committee (IEC)/Institutional Review Board (IRB) and informed consent regulations. The patient information leaflet, informed consent form and study protocol were approved by an IEC/IRB and written, informed consent was obtained from patients in their native language prior to enrollment. A list of the IECs/IRBs is provided in the supplementary materials (S3).

3. Results

3.1. Patients

In total, 60 patients were screened at 22 investigational sites between 31 March 2015 and 28 November 2017, 28 patients were enrolled into the study (n = 9, n = 9 and n = 10 in the 180 mg, 270 mg, and 360 mg cohorts, respectively) (shown in Figure 1(b)). An additional patient was included as the last two patients were enrolled simultaneously and it was not considered ethical to deny study entry to a patient who wanted to take part and had successfully completed the screening process. Demographics and baseline characteristics were generally well balanced between cohorts (Table 1). Of the participants, 100% were Caucasian, 13 (46.4%) were male and the median (range) age was 55.5 (37–72) years. Prior medication for acromegaly was used by all 28 patients (100%) and included octreotide/octreotide acetate in 23 patients (82.1%), and lanreotide/lanreotide acetate in five patients (17.9%). Previous pituitary surgery and/or radiotherapy for acromegaly was received by 24/28 (85.7%) of patients; 19 [67.9%] patients had received pituitary surgery only, one patient [3.6%] had received radiotherapy only, and four [14.3%] patients had received both previous surgery and radiotherapy (Table 1). The median (range) time since last surgery (n = 23) was 8.2 (1–26) years and since last radiotherapy (n = 5) was 6.4 (4–14) years. Overall, five patients (17.9%) and 22 patients (78.6%) had micro- (≤10 mm) and macro-adenoma (>10 mm), respectively; the size of tumors was not measured beyond screening. The acromegaly symptoms most frequently presenting at screening were joint pain (n = 19; 67.9%) and asthenia (n = 16; 57.1%).

Overall, 18 patients completed the study. The median study duration was similar for each cohort (28.1, 28.1, and 28.5 weeks for the 180 mg, 270 mg, and 360 mg cohorts, respectively). Two patients withdrew due to personal reasons and one withdrew consent. Overall, 25% (n = 7) of enrolled patients were withdrawn due to increased IGF-1 levels, which were above the ULN. Of these seven patients, two patients in the 180 mg cohort were withdrawn at Week 9; two patients in the 270 mg cohort and one in the 360 mg cohort were withdrawn at Week 13; and one patient from the 180 mg and one from the 360 mg cohort were withdrawn at Week 17. Patients were included in the analysis as shown in Figure 1(b). A total of 67 major protocol deviations were reported for 21 patients (n = 7 for each cohort); 63 of the 67 occurrences were due to tests or examinations not being performed. Procedural deviations included three occurrences related to incorrect informed consent forms, and one occurrence of the Visit 13 and early withdrawal assessments being performed after the patient had started regular treatment again. None of the protocol deviations were considered to affect the outcome results of the study.

3.2. Primary endpoints

There were no dose-limiting toxicities during the study duration, and the MTD of lanreotide PRF was not reached. The lanreotide PRF PK parameters are presented next to the previously reported single-dose PK parameters of lanreotide autogel [18] in Table 2. A rapid initial release of lanreotide was observed after deep subcutaneous administration of lanreotide PRF, with peak serum concentration reached at a median of 6 hours in all cohorts. After reaching peak levels, lanreotide concentrations decreased slowly according to

Table 1. Demographics and baseline disease characteristics (safety population).

	LAN PRF 180 mg (n = 9)	LAN PRF 270 mg (n = 9)	LAN PRF 360 mg (n = 10)	All (n = 28)
Sex, n (%)				
Male	3 (33.3)	4 (44.4)	6 (60.0)	13 (46.4)
Female	6 (66.7)	5 (55.6)	4 (40.0)	15 (53.6)
Age in years, median (range)	56.0 (46, 72)	49.0 (41, 63)	55.5 (37, 72)	55.5 (37, 72)
BMI at screening in kg/m^2, median (range)	27.5 (21, 36)	28.8 (23, 40)	27.7 (26, 41)	28.4 (21, 41)
Type 2 diabetes mellitus, n (%)	3 (33.3)	2 (22.2)	2 (20.0)	7 (25.0)
Years since diagnosis, median (range)	8.0 (5, 27)	9.3 (2, 24)	9.2 (1, 17)	8.7 (1, 27)
Size of pituitary tumor at diagnosis, n (%)				
<10 mm	2 (22.2)	1 (11.1)	2 (20.0)	5 (17.9)
≥10 mm	6 (66.7)	8 (88.9)	8 (80.0)	22 (78.6)
Previous disease therapies, n (%)[a, b]				
Pituitary surgery	7 (77.8)	7 (77.8)	9 (90.0)	23 (82.1)
RT for acromegaly	2 (22.2)	3 (33.3)	0 (0.0)	5 (17.9)
Octreotide LAR[c]	9 (100.0)	7 (77.8)	7 (70.0)	23 (82.1)
20 mg	3 (33.3)	4 (44.4)	6 (60.0)	13 (46.4)
30 mg	5 (55.5)	2 (22.2)	0 (0.0)	7 (25.0)
40 mg	1 (11.1)	0 (0.0)	1 (10.0)	2 (7.1)
60 mg	0 (0.0)	1 (11.1)	0 (0.0)	1 (3.6)
Lanreotide autogel[c]	0 (0.0)	2 (22.2)	3 (30.0)	5 (17.9)
90 mg	0 (0.0)	0 (0.0)	2 (20.0)	2 (7.1)
120 mg	0 (0.0)	2 (22.2)	1 (10.0)	3 (10.7)
Years since last RT				
n	2	3	0	5
Median (range)	5.5 (5, 6)	12.5 (4, 14)	0	6.4 (4, 14)
Years since last surgery,				
n	7	7	9	23
Median (range)	7.0 (4, 26)	9.1 (1, 24)	8.4 (1, 12)	8.2 (1, 26)
IGF-1 ng/mL, median (range)				
IMMULITE 2000 (old reagent)	133.0 (39, 264)	170 (129, 220)	247.5 (212, 302)	189.5 (39, 302)
Missing	0	0	6	6
IMMULITE 2000 (new reagent)	–	129.5 (115, 144)	155.0 (94, 286)	144.0 (94, 286)
Missing	9	7	0	16
GH ng/mL, median (range)	0.59 (0.06, 2.99)	0.56 (0.13, 3.55)	1.03 (0.25, 8.01)	0.75 (0.06, 8.01)

Demographics and baseline characteristics were generally well balanced between cohorts. The central lab's reference ranges were used for all analyzed parameters including GH and IGF-1. Percentages are based on the number of included patients per cohort and overall.
[a]Patients treated with both surgery and RT: cohort 1, n = 2; cohort 2, n = 2; cohort 3, n = 0.
[b]Patients who had no surgery or RT: cohort 1, n = 2; cohort 2, n = 1; cohort 3, n = 1.
[c]All screened patients.
BMI, body mass index; LAN, lanreotide; LAR, long-acting release; PRF, prolonged-release formulation; RT, radiotherapy; SD, standard deviation. Time since diagnosis, last surgery, and last RT is the time in years relative to screening.

first-order kinetics (shown in Figure 2). Mean lanreotide C_{max} values were similar in all cohorts, showing no trend for a dose proportional increase, whereas mean AUC_{0-85} values appeared to increase, but less than dose-proportionally. Mean $t_{½}$ values were independent of the dose administered. Based on the maximum values reported for $t_{½}$ (180 mg: 35.0–80.2 days; 270 mg: 42.6–74.7 days; 360 mg: 49.5–79.1 days), steady-state PK of lanreotide PRF would be expected at around 60 weeks. This is a conservative estimate, taking into account that in some cases the $t_{½}$ was too long to be accurately calculated and therefore not included.

3.3. Secondary endpoints

3.3.1. Serum GH and IGF-1 levels

Serum GH levels remained stable from screening to Week 13 (end of scheduled analysis) in all three cohorts: mean (SD) change from baseline to Visit 12 was 0.667 (0.473), 0.684 (0.863), and 0.003 (1.761) ng/mL for Cohorts 1–3, respectively (shown in Figure 3(a)). Despite some patients withdrawing due to increased IGF-1 levels, overall mean IGF-1 levels were relatively stable across the study when using either the old (mean [SD] change from baseline to Visit 18: 104.2 [82.7] ng/mL) or new standardized IMMULITE 2000 reagent (mean [SD] change from baseline to Visit 18: 61.0 [62.2] ng/mL), and when calculated in relation to the ULN adjusting for age and gender (mean (SD) change from baseline to Visit 18: 47.7 [39.5] and 27.6 [31.5] x ULN for old and new standardized IMMULITE 2000 reagent, respectively; shown in Figure 3(b-c)). In total, seven patients were withdrawn from the study due to increased IGF-1 levels (three patients from Cohort 1, and two patients each from Cohorts 2 and 3). Cohort 1 was analyzed with the old assay reagent, Cohort 2 was analyzed with the old and new assay reagents and Cohort 3 was partly analyzed with the old assay reagent (data not shown) and completely analyzed with the new assay reagent. Samples tested with both the old and new standardized IMMULITE reagents showed a high correlation (Pearson's correlation coefficient: p = 0.968, slope = 0.5845).

3.3.2. Serum FT3, FT4, TSH and PRL levels

High-dose lanreotide may affect the production of FT3, FT4, TSH and PRL [19,20] therefore serum levels of these hormones were explored, however, this study was not powered to formally assess if higher doses of lanreotide could correct previous pituitary deficiencies. At screening or Visit 2 pre-dose, a total of 13 patients across all cohorts were deficient in at least one of these hormones; levels remained stable in five patients and were transient in eight patients. Overall, for all four parameters, mean serum concentrations were within the

Table 2. Single-dose lanreotide PK parameters – PRF versus autogel.

	LAN PRF[a]180 mg		LAN PRF[a]270 mg		LAN PRF[a]360 mg		LAN autogel[b]60 mg		LAN autogel[b]90 mg		LAN autogel[b]120 mg	
	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n
C_{max}, ng/mL	19.0 (15.7)	9	14.0 (10.3)	7	20.5 (5.86)	6	1.65 (0.62)	6	3.54 (2.55)	5	3.05 (0.93)	5
T_{max}, days[c]	0.25 (0.17–1.00)	9	0.25 (0.17–1.00)	7	0.25 (0.17–0.33)	6	0.25 (0.17–0.98)	6	0.25 (0.25–1.00)	5	0.98 (0.24–0.99)	5
C_{trough}, ng/mL	1.00 (0.56)	7	1.01 (0.30)	7	1.73 (0.52)	6	0.73 (0.19)	6	0.97 (0.20)	5	1.41 (0.30)	6
AUC_{0-85}, ng[a]day/mL	161 (97.6)	9	179 (54.2)	7	265 (87.1)	6	-		-		-	
$t_{1/2}$, days	54.2 (17.0)	7	61.7 (13.9)	5	63.1 (13.3)	4	-		-		-	

[a]PK valid population, lanreotide subgroup. Patients who had been treated previously with a stable dose of lanreotide autogel were not included in the lanreotide PK analyses population. Statistical analysis indicated that the following pharmacokinetic parameters were not dose proportional: C_{max}, AUC_{0-85} and $t_{1/2}$. The slope estimation and the corresponding 90% CI suggest that C_{max} and $t_{1/2}$ are independent of the tested dose

[b]Data reported by Bronstein et al [18]; intent-to-treat population; no statistically significant differences were observed by dose

[c]Median (range). AUC_{0-85}, area under the serum concentration–time curve from time 0 to 85 days

C_{max}, maximum observed serum concentration; C_{trough}, concentration at the end of the dosing interval; LAN, lanreotide; PK, pharmacokinetic; PRF, prolonged-release formulation; SD, standard deviation; $t_{1/2}$, apparent terminal elimination half-life; T_{max}, time to maximum serum concentration.

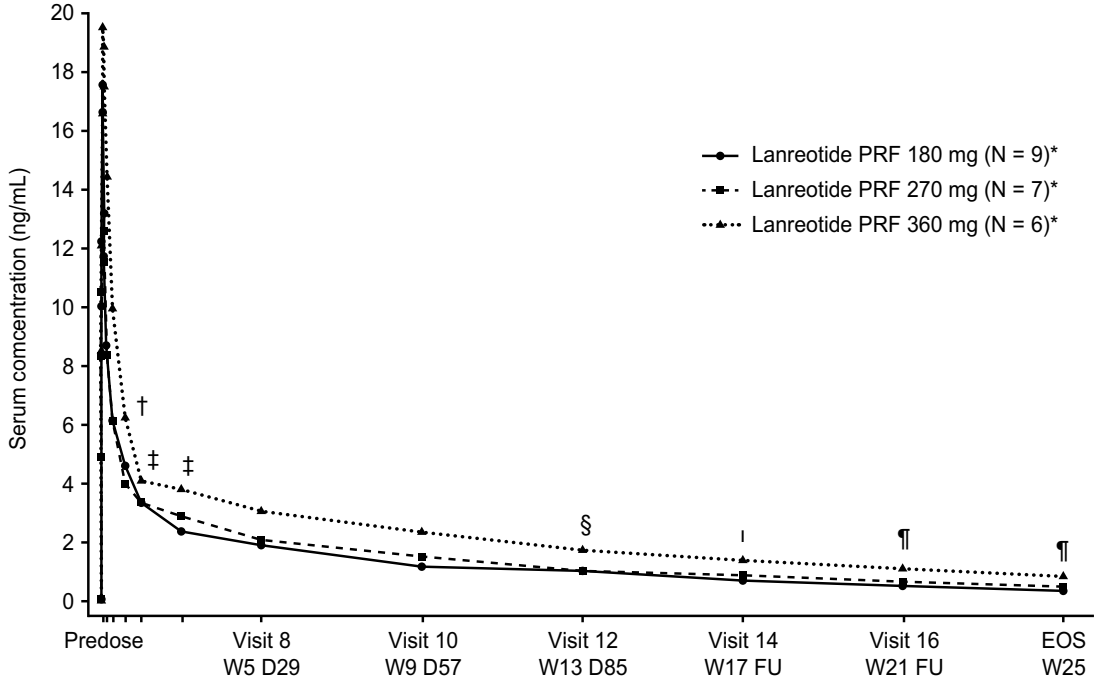

Figure 2. Mean lanreotide serum concentration (PK valid population, lanreotide subgroup). Patients treated previously with a stable dose of lanreotide autogel were not included in this population. D, day; EOS, end of study; FU, follow-up; PRF, prolonged-release formulation; W, week. *Patient numbers are at each visit are n = 9 for lanreotide PRF 180 mg, n = 7 for lanreotide PRF 270 mg and n = 6 for lanreotide PRF 360 mg respectively, except: †n = 8, n = 7, n = 6; ‡n = 9, n = 6, n = 6; §n = 7, n = 7, n = 6; ‖n = 7, n = 5, n = 4; and n = 7, n = 4, n = 4.

normal range for most patients, and remained stable throughout the study, in all cohorts (shown in Supplementary Figure S1).

3.4. Safety/tolerability

All patients were included in the safety population. Overall, 17 TEAEs were reported by six patients in the 180 mg cohort, 25 TEAEs were reported by seven patients in the 270 mg cohort and 27 TEAEs were reported by seven patients in the 360 mg cohort (Supplementary Table S1). The most frequently reported TEAEs were diarrhea (n = 5), cholelithiasis (n = 4), fatigue (n = 3), and headache (n = 3). No patients were withdrawn due to TEAEs and no TEAEs were associated with a fatal outcome.

TEAEs were predominantly Grade 1 or Grade 2 in intensity. Three Grade 3 TEAEs were reported: arthralgia, neutropenia, and osteonecrosis. There were no Grade 4 or Grade 5 events. Treatment-related TEAEs were reported in two, three, and four patients in the 180 mg, 270 mg, and 360 mg cohorts, respectively, with the highest intensity being Grade 2. Overall, the most frequently reported treatment-related TEAEs were cholelithiasis (n = 3), diarrhea (n = 2), and injection-site pain (n = 2) (Supplementary Table S2). Two serious adverse events were reported in two patients but both were considered unrelated to lanreotide PRF: arthralgia (180 mg Cohort) and osteonecrosis with arthralgia (360 mg Cohort).

There were no clinically important changes in laboratory parameters, vital signs, body weight, body mass index, acromegaly symptoms, ECG, or gallbladder echography.

Putative anti-lanreotide antibodies were reported in one patient in the 180 mg cohort and in one patient in the 270 mg cohort; one patient was positive at both baseline and post-dosing so this was not considered treatment-

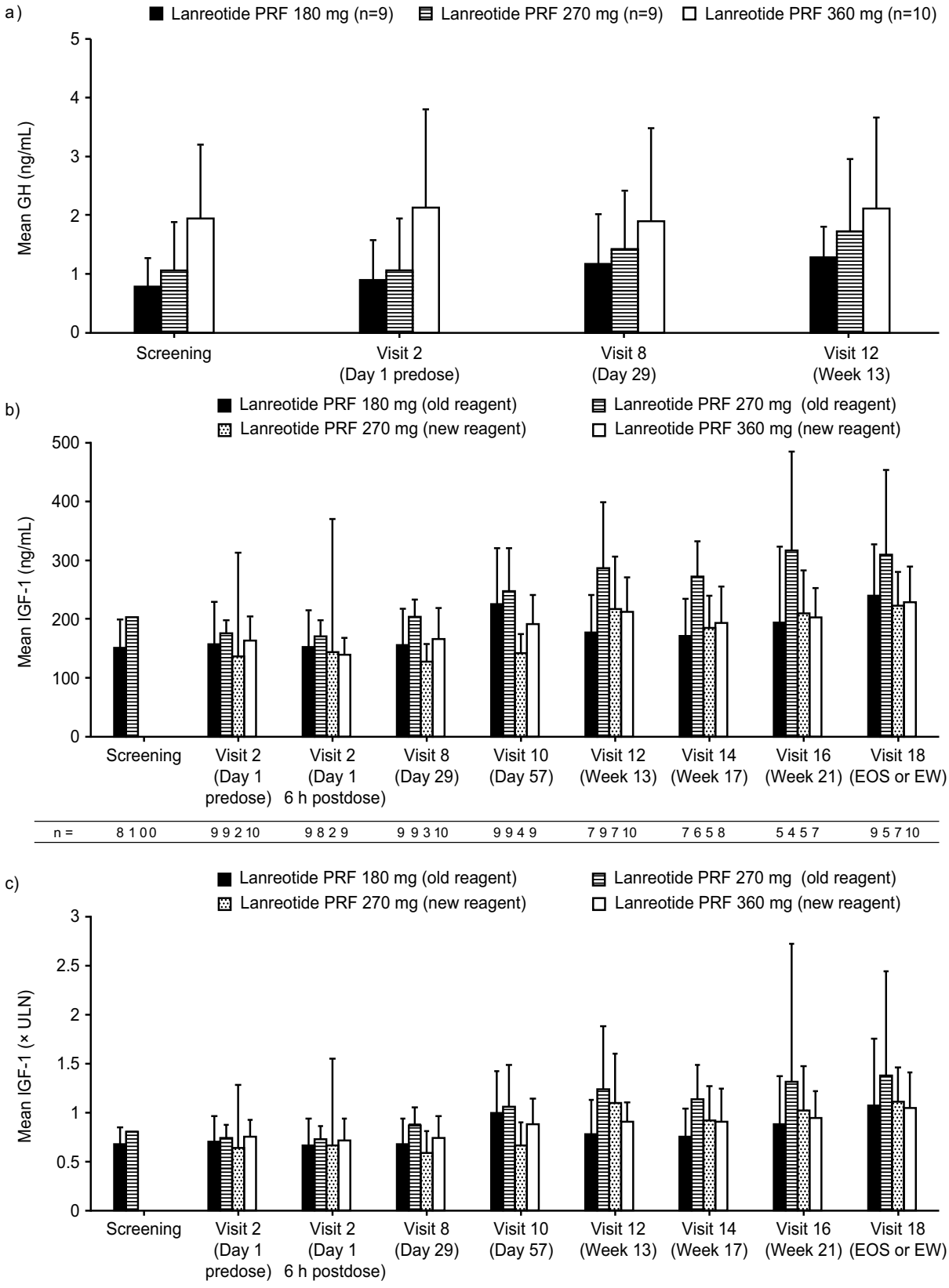

Figure 3. Serum GH a, and IGF-1 b, levels at all sampling time points (safety population). Data are mean, 95% CI. (a) Serum GH was sampled five times (every 30 minutes for 2 hours) at each visit. Normal GH range: <3 ng/mL for males over 18 years old and <8 ng/mL for females >18 years old. IGF-1 levels analyzed with the IMMULITE 2000 platform in ng/mL (b) and × ULN (c). Concordance between IGF-1 values obtained using the old (before February 2017) and new (after February 2017) reagents was analyzed using Pearson's correlation coefficient. CI, confidence interval; EOS, end of study; EW, early withdrawal; GH, growth hormone; IGF-1, insulin-like growth factor-1; PRF, prolonged-release formulation; ULN, upper limit of normal.

related. The other patient (270 mg cohort) had a positive finding at the end of the study that was considered treatment-related. In both patients, IGF-1 levels were not maintained below the age-adjusted ULN up to end of study.

4. Discussion

This study demonstrated that with lanreotide PRF, higher doses of lanreotide can be tolerated in patients with acromegaly compared with the currently available lanreotide formulations. The C_{max} values of the tested lanreotide PRF doses were higher than those observed with 120 mg lanreotide autogel or 30 mg lanreotide LA (steady-state levels of 7.7 ng/mL and 10.9 ng/mL, respectively), and reached in a similar timeframe as observed with lanreotide autogel [6,7]. Furthermore, consistent with the PK for lanreotide autogel, concentrations of lanreotide PRF decreased slowly over time following first-order kinetics. Owing to the flip-flop PK of lanreotide autogel and PRF (sustained rate of drug release, vs. immediate release), $t_{½}$ is driven by the rate of release of lanreotide from the depot. The $t_{½}$ of lanreotide PRF is prolonged compared to lanreotide autogel, which indicates a slower release rate for PRF formulation. Although not demonstrated, we believe that the lanreotide rate of release depends on the properties of the depot, which was modified by the excipient. Previous PK/PD modeling of lanreotide suggests that its efficacy in acromegaly is associated with maintaining serum concentrations above a threshold rather than overall exposure [21]. The longer $t_{½}$ and higher C_{max} observed with lanreotide PRF indicate that lanreotide serum concentrations will stay above the efficacy threshold longer for than 4 weeks and therefore allow longer dosing intervals compared with lanreotide autogel. However, simulation of steady state based on single-dose data suggested that administration of lanreotide PRF 360 mg every 12 weeks would result in lower C_{trough} than that of lanreotide autogel 120 mg.

A similar C_{max} was observed across all the tested doses of lanreotide PRF; however, it is possible that this finding could be artificial, as the PK analysis group was not balanced according to sex and weight. If C_{max} does not change with dose, it is unlikely that a higher dose will yield additional benefits in extending the dosing interval. However, if C_{max} does increase with the dose, administration of higher doses could result in lanreotide serum concentrations above the effective C_{trough} over 12 weeks, but the increase in C_{max} may impair the safety profile.

This study indicates a promising efficacy profile for lanreotide PRF. All patients were expected to be withdrawn prior to the end of the 25-week study due to elevated IGF-1 levels, as the target duration of control was up to 12 weeks. Indeed, IGF-1 increases were observed in some patients when lanreotide serum concentrations fell to ≤1.03 ng/mL. However, prior to Week 12, only two patients were withdrawn from the study owing to increases in serum IGF-1 above the ULN. Both patients were treated with the lowest dose of lanreotide PRF and had previously been treated with high doses of octreotide LAR (30 and 40 mg, respectively). These data suggest that the single-dose lanreotide PRF 180 mg could be too low to control IGF-1 over 12 weeks in patients previously on a high dose of somatostatin analogues. However, at steady state, lanreotide serum from PRF 180 mg would be higher and IGF-1 control duration expected to be improved. The inclusion of patients who had received radiotherapy more than 2 years previously did not appear to impact results as similar levels of serum hormones were detected throughout the study across cohorts, and none of the patients in Cohort 3 had received radiotherapy.

Limitations of this study include the relatively small sample size; thus compromising the statistical power. Another limitation was that the MTD was not reached; therefore, further studies would be required to determine this. Additionally, due to manufacturing factors, the IMMULITE 2000 kit and reagent changed during the study. However, it is unlikely that this would impact the reproducibility of the results as concordance between the reagents was demonstrated. It should also be noted that lanreotide PRF PK calculations were based on single-dose rather than steady-state data. However, the steady-state data for lanreotide autogel were aligned with simulation based on single-dose data; therefore, PK calculations for single-dose lanreotide PRF are believed to provide sufficient characterization.

Although the MTD of lanreotide PRF is still unknown, this study demonstrated that it is greater than 360 mg as no dose-limiting toxicities were reported. The safety profile of lanreotide PRF observed in this study is consistent with the known safety profile of lanreotide autogel. Few TEAEs were considered treatment-related, no patients were withdrawn due to TEAEs, and none of the serious TEAEs were treatment-related. No new safety concerns were identified in this study.

Levels of serum GH were generally stable in all patients and immunogenicity was limited to two patients, one of whom had previously received octreotide but not lanreotide. We hypothesize that this was due to octreotide antibody cross-reaction.

4.1. Conclusions

This study showed that, with a new formulation, it is feasible to maintain concentrations of lanreotide above the efficacy threshold for longer after a single injection. The increase in lanreotide C_{max} is approximately twice that seen for lanreotide autogel but did not affect the safety profile of the product. The PK profile of lanreotide PRF suggests that a dosing interval of 12 weeks is achievable, but that further development would be required to match the C_{trough} of lanreotide autogel 120 mg. The MTD was not reached as no dose-limiting toxicities were recorded, indicating that doses >360 mg may be tolerated, although this may not be clinically beneficial. Furthermore, the safety and tolerability profile of lanreotide PRF were in line with that of existing lanreotide formulations. Taken together, these data demonstrate the potential impact of an excipient on release kinetics from a depot that could

be used to optimize the release properties of any formulation.

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Data sharing

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

Author contributions

SN: Substantial contributions to study conception, design, operational completion, analysis and interpretation of data. Drafting of the publication, revising it critically for important intellectual content and final approval of the publication.

CB: Substantial contribution to the operational completion of the study, data analysis and interpretation, critical review and final approval of the publication.

BB: Substantial contribution to the operational completion of the study, data analysis and interpretation, critical review and final approval of the publication.

LDG: Substantial contribution to PK analysis within the study and interpretation of the data. Drafting of the publication, revising it critically on pharmacokinetic content and final approval of the publication.

AP: Development of lanreotide PRF formulation (including co-solvent selection) and manufacturing process to support clinical studies. Reviewing the publication critically for important intellectual content and final approval of the publication.

PP: Substantial contributions to study operational completion, analysis and interpretation of data. Drafting of the publication, revising it critically for important intellectual content and final approval of the publication.

BR: Substantial contributions to study operational completion, analysis and interpretation of data. Drafting of the publication, revising it critically for important intellectual content and final approval of the publication.

DR: Substantial contributions to study conception, design, operational completion, analysis and interpretation of data. Drafting of the publication, revising it critically for important intellectual content and final approval of the publication.

ZS: Substantial contribution to the operational completion of the study, data analysis and interpretation, critical review and final approval of the publication.

SS: Substantial contributions to acquisition of data. Reviewing the publication critically for important intellectual content and final approval of the publication.

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ORCID

Betina Biagetti http://orcid.org/0000-0002-8837-4343

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Buchfelder M, Schlaffer SM. The surgical treatment of acromegaly. Pituitary. 2017;20(1):76–83.
2. Melmed S, Bronstein MD, Chanson P, et al. A Consensus Statement on acromegaly therapeutic outcomes. Nat Rev Endocrinol. 2018;14(9):552–561.
3. Caron PJ, Bevan JS, Petersenn S, et al. Tumor shrinkage with lanreotide autogel 120 mg as primary therapy in acromegaly: results of a prospective multicenter clinical trial. J Clin Endocrinol Metab. 2014;99(4):1282–1290.
4. Katznelson L, Atkinson JL, Cook DM, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of acromegaly–2011 update. Endocr Pract. 2011;17(Suppl 4):1–44.
5. Carmichael JD. Lanreotide depot deep subcutaneous injection: a new method of delivery and its associated benefits. Patient Prefer Adherence. 2012;6:73–82.
6. Somatuline® LA 30 mg. Summary of product characteristics. 2019 Dec 17 [cited 2021 Jun 25]. Available from: https://www.medicines.org.uk/emc/product/965/smpc
• **The prescribing information is a key source of information on lanreotide and its use in clinical practice.**
7. Somatuline® autogel®. Summary of product characteristics. 2021 Jul 6 [cited 2021 Oct 11]. Available from: https://www.medicines.org.uk/emc/medicine/25104
• **The prescribing information is a key source of information on lanreotide autogel and its use in clinical practice.**
8. Yedinak P, Pulaski-Liebert KJ, Adelman DT, et al. Acromegaly: current therapies benefits and burdens. Clin Pract (Therapy). 2018;15(2):499–511.
•• **This review article cites 126 papers and is of considerable interest because it describes the need for reduced treatment burden in acromegaly.**
9. Strasburger CJ, Karavitaki N, Stormann S, et al. Patient-reported outcomes of parenteral somatostatin analogue injections in 195 patients with acromegaly. Eur J Endocrinol. 2016;174(3):355–362.
•• **This paper is of considerable interest because it reports treatment burden in patients with acromegaly and highlights the need for sustained symptom control, demonstrating the**

importance of considering the patient perspective when evaluating treatment outcomes.

10. Gomez-Panzani E, Chang RJ, Ramis J, et al. Sustained biochemical control in patients with acromegaly treated with lanreotide depot 120 mg administered every 4 weeks, or an extended dosing interval of 6 or 8 weeks: a pharmacokinetic approach. Res Rep Endocr Disord. 2012;2012:79.

•• **This paper is of considerable interest as it shows sustained control of hormone levels in patients with acromegaly who received lanreotide autogel 120 mg at 4, 6 or 8 week dosing intervals.**

11. Neggers SJ, Pronin V, Balcere I, et al. Lanreotide autogel 120 mg at extended dosing intervals in patients with acromegaly biochemically controlled with octreotide LAR: the LEAD study. Eur J Endocrinol. 2015;173(3):313–323.

•• **This paper is of considerable interest as it reports patient preference for lanreotide autogel 120 mg treatment using an extended dosing interval of 6 or 8 weeks, and highlights the need for sustained symptom control, demonstrating the importance of considering the patient perspective when evaluating treatment outcomes.**

12. Schopohl J, Strasburger CJ, Caird D, et al. Efficacy and acceptability of lanreotide autogel(R) 120 mg at different dose intervals in patients with acromegaly previously treated with octreotide LAR. Exp Clin Endocrinol Diabetes. 2011;119(3):156–162.
13. Bernabéu I, Fajardo C, Marazuela M, et al. Effectiveness of lanreotide autogel 120 mg at extended dosing intervals for acromegaly. Endocrine. 2020;70(3):575–583.
14. Störmann S, Schopohl J, Bullmann C, et al. Multicenter, observational study of lanreotide autogel for the treatment of patients with acromegaly in routine clinical practice in Germany, Austria and Switzerland. Exp Clin Endocrinol Diabetes. 2021;129 (3):224–233.
15. Giustina A, Barkhoudarian G, Beckers A, et al. Multidisciplinary management of acromegaly: a consensus. Rev Endocr Metab Disord. 2020;21(4):667–678.
16. Garrido MJ, Cendros JM, Ramis J, et al. Pharmacodynamic modeling of the effects of lanreotide autogel on growth hormone and insulin-like growth factor 1. J Clin Pharmacol. 2012;52(4):487–498.
17. Troconiz IF, Cendros JM, Peraire C, et al. Population pharmacokinetic analysis of lanreotide autogel in healthy subjects: evidence for injection interval of up to 2 months. Clin Pharmacokinet. 2009;48(1):51–62.
18. Bronstein M, Musolino N, Jallad R, et al. Pharmacokinetic profile of lanreotide autogel in patients with acromegaly after four deep subcutaneous injections of 60, 90 or 120 mg every 28 days. Clin Endocrinol (Oxf). 2005;63(5):514–519.
19. Gancel A, Vuillermel P, Legrand A, et al. Effects of a slow-release formulation of the new somatostatin analogue lanreotide in TSH-secreting pituitary adenomas. Clin Endocrinol (Oxf). 1994;40 (3):421–428.
20. Kuhn JM, Legrand A, Ruiz JM, et al. Pharmacokinetic and pharmacodynamic properties of a long-acting formulation of the new somatostatin analogue, lanreotide, in normal healthy volunteers. Br J Clin Pharmacol. 1994;38(3):213–219.
21. Cendros JM, Peraire C, Troconiz IF, et al. Pharmacokinetics and population pharmacodynamic analysis of lanreotide autogel. Metabolism. 2005;54(10):1276–1281.