Multicenter, Observational Study of Lanreotide Autogel for the Treatment of Patients with Acromegaly in Routine Clinical Practice in Germany, Austria and Switzerland

Authors

Sylvère Störmann[1], Jochen Schopohl[1], Catharina Bullmann[2], Christoph Terkamp[3], Mirjam Christ-Crain[4], Reinhard Finke[5], Jörg Flitsch[6], Ilonka Kreitschmann-Andermahr[7], Anton Luger[8], Günter Stalla[1, 9], Aude Houchard[10], Dorit Helbig[11], Stephan Petersenn[12]

Affiliations

1 Medizinische Klinik und Poliklinik IV, Klinikum der Universität München, München, Germany
2 Amedes VZ, Hamburg
3 Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover
4 Clinic of Endocrinology, Diabetology and Metabolism, University Hospital Basel, Basel
5 Medical practice at the Kaisereiche (üBAG), Berlin
6 Department of Neurosurgery, University Hospital Hamburg-Eppendorf, Hamburg
7 Department of Neurosurgery and Spine Surgery, University Medicine Essen, University of Duisburg-Essen, Essen, Germany
8 Division of Endocrinology and Metabolism, Medical University of Vienna, Vienna
9 MEDICOVER Neuroendocrinology MVZ, Munich
10 Ipsen, Boulogne-Billancourt Cedex
11 Ipsen Pharma GmbH, Ettlingen
12 ENDOC Center for Endocrine Tumors, Hamburg

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Georg Thieme Verlag KG, Rüdigerstraße 14,
70469 Stuttgart, Germany

Correspondence

Prof. Dr. med. Stephan Petersenn
ENDOC Center for Endocrine Tumors
Erik-Blumenfeld-Platz 27A
22587 Hamburg
Deutchland
Tel.: +49 40 401 87985
stephan.petersenn@endoc-med.de

ABSTRACT

Background Evidence from controlled trials has shown that lanreotide autogel is effective in achieving biochemical and symptom control in patients with acromegaly. However, it is important to better understand the real-world patient population receiving lanreotide autogel treatment.

Methods In this non-interventional study the long-term treatment response to lanreotide autogel in adult patients with acromegaly from office-based centers or clinics in Germany, Austria and Switzerland was studied. Assessments included growth hormone and insulin-like growth factor-I levels, symptoms, quality of life, lanreotide plasma levels and tumor somatostatin receptor subtype expression. The primary endpoint was achievement of full biochemical control, defined as growth hormone ≤ 2.5 µg/L and insulin-like growth factor I normalization at month 12.

Results 76 patients were enrolled from 21 sites. 7/51 (13.7 %) patients of the efficacy population had full biochemical control at baseline, 15/33 (45.5 %) at month 12 and 10/26 (38.5 %) at month 24 of treatment. At 12 months of treatment higher rates of biochemical control were observed in the following subgroups: older patients (> 53 years [median]), females, treatment-naïve patients, and patients with a time since diagnosis of longer than 1.4 years (median). No clinically relevant differences in acromegaly symptoms or quality of life scores were observed. Median fasting blood glucose and glycated hemoglobin levels remained unchanged throughout the study. No new safety signals were observed. Overall tolerability of treatment with lanreotide autogel was judged by 80.8 % of the enrolled patients at month 12 as 'very good' or 'good'.

Conclusion Treatment with lanreotide autogel in a real-world setting showed long-term effectiveness and good tolerability in patients with acromegaly.

Introduction

Acromegaly is a disorder caused by excessive secretion of growth hormone (GH) usually associated with a GH-secreting pituitary adenoma. It is a rare disease with an annual incidence of approximately 3 per million people [1, 2]. Adenomas can present either as microadenoma with a diameter ≤ 10 mm or as macroadenoma > 10 mm in diameter. Acromegaly has both an insidious onset and slow progression and therefore diagnosis is often delayed up to ten years [3, 4]. Clinical manifestations are due to excess GH and an associated increase of insulin-like growth factor-I (IGF-I), and include a slowly progressive somatic changes caused by skeletal and soft tissue growth, severe perspiration, headaches, osteoarthritis, and impaired cardiac and respiratory functions, hypertension as well as glucose intolerance or diabetes mellitus [5, 6].

The conventional first-line treatment of acromegaly is transsphenoidal resection of the adenoma [5]. Despite surgery, acromegaly remains active in less than 15 % of patients with microadenomas and in 50–60 % of patients with macroadenomas, as defined by increased levels of GH and IGF-I, and by persistence of clinical symptoms [5, 6]. Somatostatin analogs allow control of GH and IGF-I levels, reduce tumor size and improve clinical symptoms in a relevant proportion of these patients [7–10]. The guidelines for acromegaly management recommend first generation somatostatin analogs as first-line therapy if surgery is contraindicated or if a poor likelihood of success is expected owing to patient-specific and/or tumor-specific factors [6], or as second-line treatment if no biochemical control is achieved by surgery, and complementary to radiation therapy until onset of benefit from radiation [6, 11]. If biochemical control cannot be achieved despite increasing dose and/or dosing frequency of first-generation somatostatin analogs, other medical treatment options include dopamine agonists, the second-generation somatostatin analogue pasireotide and/or the GH antagonist pegvisomant. If second-line therapy has proven to be unsuccessful, stereotactic radiosurgery or surgical (re-)intervention should be reconsidered [6].

First generation somatostatin analogs include octreotide and lanreotide. Compared with endogenous somatostatin, which binds to all somatostatin receptors (SSTR) similar affinity, lanreotide shows a high binding affinity to SSTR2, 3 and 5 [12]. The long-acting somatostatin analog lanreotide autogel in doses of 60–120 mg is given once every 28 days [13] via deep subcutaneous injection. The dosing interval for lanreotide autogel may be extended to 56 days when given at 120 mg. There is a substantial body of evidence from controlled trials that lanreotide autogel is effective in controlling GH and IGF-I levels in a large proportion of patients with acromegaly [13–20].

The aim of this non-interventional study was to evaluate the long-term treatment response in patients with acromegaly treated with lanreotide autogel in real-life clinical practice. In addition, the study was designed to better understand the patient population receiving treatment in this setting.

Methods

Patients

Adult patients aged 18 years and older diagnosed with acromegaly to be treated de novo with lanreotide autogel or who had previously been receiving treatment with lanreotide autogel for a maximum of 6 months could be included. Retrospective documentation was allowed for a maximum of 1/3 of the planned total patient number. In patients pre-treated with lanreotide autogel, baseline and all other available data since baseline were documented retrospectively. Prospective documentation followed from the timepoint of inclusion. Patients were recruited from 21 medical practices or clinics in Germany, Austria and Switzerland specialized in endocrinology and treatment of patients with pituitary diseases.

The enrolled population consisted of all enrolled patients, the efficacy population consisted of all patients who received lanreotide autogel at least once during the study and for whom the GH/IGF-I level was available for both the baseline visit and at least one post-baseline visit.

Study design

This was an international, multicenter, non-interventional, observational study. Both, prospective and retrospective documentation was allowed. Patients received treatment as prescribed by the investigator and in accordance with the current recommendations, routine practice and local regulations. Administration of lanreotide autogel was in accordance with the local label. All diagnostic and therapeutic decisions were made by treating physician and completely independent of the decision to include the patient in this non-interventional study. Physicians were therefore allowed to include other treatments such as surgery or radiotherapy in addition to lanreotide treatment, when indicated. Visits were scheduled at baseline and at approximately 1, 3, 6, 12, 18 and 24 months.

Assessments included basal GH and IGF-I levels as well as clinical markers such as ring size, risk for sleep apnea as assessed by the Epworth Sleepiness Scale (ESS) [21], glucose metabolism (fasting blood glucose, HbA_{1c}, antidiabetic co-medication as a surrogate for diagnosed diabetes mellitus), hyperhidrosis, headache and arthralgia, each assessed by a visual analogue scale (VAS, rated from 0 = no symptoms to 10 = maximum symptoms). Vital signs, i. e., systolic and diastolic blood pressure, heart rate and body weight, were assessed at all study visits. GH and IGF-I were measured as collected in daily routine in local laboratories using either of the following assays: For GH measurements Mediagnost human GH ELISA, Reutlingen, Germany; Immulite 2000, Siemens Healthcare Diagnostics, Erlangen, Germany, iSYS human GH, IDS, Tyne & Wear, UK; Liaison, Sorin, Saluggia, Italy, and others; for IGF-I measurements Immulite 2000, Siemens Healthcare Diagnostics, Erlangen, Germany; IGF-1 ELISA E20, Mediagnost, Reutlingen, Germany, CLIA, Genova Diagnostics, Asheville, USA; Liaison, Sorin, Saluggia, Italy, iSYS IGF-1, IDS, Tyne & Wear or others.

The primary endpoint was full biochemical response, i. e. the long-term response to lanreotide autogel treatment, defined as the control rate after 1 year with a GH level ≤ 2.5 µg/L and a normalized IGF-I concentration according to site-specific age-dependent reference ranges. Secondary endpoints included prediction of treatment efficacy according to baseline biochemical parameters and early changes of GH and IGF-I levels, the proportion of patients with normalized IGF-I or a GH ≤ 2.5 µg/L at each visit, and the proportion of patients with a global evaluation of effectiveness by the physician at 24 months. Other secondary endpoints included changes of clinical parameters and QoL as well as global evaluation

of tolerability as assessed by the patient by categories (very poor, poor, moderate, good, and very good).

Quality of life (QoL) was assessed by the German validated version of the Acromegaly Quality of Life Questionnaire (AcroQoL) [22], which was standardized to a score range between 0 (worst QoL) and 100 (best QoL). The 22 items are divided into a physical and psychological function scale, the latter being further subdivided into areas addressing appearance and personal relationships. If tumor tissue was available from previous surgery, tissue samples could be submitted optionally for analysis of SSTR status by immunohistochemistry using polyclonal rabbit anti-SSTR2A, rabbit anti-SSTR5 (both Zytomed Systems, Bargteheide, Germany) and rabbit anti-SSTR3 (Thermo Fisher, Rockford, USA) antibodies. SSTR analyses were all performed at the Department of Neuropathology, University Hospital Eppendorf, Hamburg, Germany.

Adverse events reporting followed regulations related to non-interventional post-authorization studies. Any related non-serious or serious adverse event as well as any unrelated serious adverse event independent of the circumstances or suspected cause, was reported immediately (within 24 h of the investigator's knowledge of the event) to the pharmacovigilance contact. The routine collection of unrelated non-serious adverse events was not required as such events are considered unlikely to contribute significant relevant new information regarding the safety of the medicinal product. The presence of gall bladder stones was assessed by ultrasound at baseline and during lanreotide autogel treatment.

This study was conducted in compliance with independent ethics committees/institutional review boards, informed consent regulations, the Declaration of Helsinki (Version 2013) and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines. Written informed consent was obtained from all patients prior to inclusion.

Statistical analysis

All effectiveness endpoints were analyzed by means of descriptive statistical analyses. Data are presented as mean (95 % CI). The primary analysis based on the primary endpoint was performed in patients with documented core variables (age, gender, diagnosis of acromegaly, baseline date, date and dose of lanreotide autogel administration at baseline), who had not started lanreotide autogel treatment more than 30 days prior to baseline and had a baseline and an on-treatment assessment of biochemical parameters (i. e., GH and IGF-I available at the same visit) (efficacy population). The primary endpoint of long-term treatment response was evaluated by frequency distributions with corresponding 95 % Clopper–Pearson confidence intervals.

Results

Patient characteristics

76 patients with acromegaly were enrolled from 21 medical practices and clinics. 25 patients were excluded from the efficacy population due to lack of core variable documentation, lack of baseline and on-treatment assessments of biochemical control or start of lanreotide autogel treatment > 30 days prior to baseline. 50 (65.8 %) patients discontinued the study prematurely. Of these, 22 (28.9 %) patients were lost to follow-up, 5 (6.5 %) patients discontinued treatment due to adverse events, 2 (2.6 %) patients withdrew consent, 1 (1.3 %) patient discontinued due to inefficacy of treatment, and 20 patients discontinued due to other reasons.

▶ **Table 1** shows the baseline characteristics of the enrolled patients. In this population, 51.3 % were males. Most patients had macroadenomas (82 %), and acromegaly had been diagnosed a median of 1.2 years (95 % CI, 0.6–2.0) before study entry, median time since onset of symptoms was 10.0 years (95 % CI, (6.2–19.1). Mean tumor size at the time of diagnosis was 20.9 mm (95 % CI, 17.1–24.8) in patients prior to pituitary surgery and 14.9 mm (95 % CI, 10.6–19.1) in patients without subsequent pituitary surgery.

Baseline mean GH of the patients was 13.5 ng/mL (95 % CI, 3.3–23.6). 59.4 % of patients had a GH value ≤ 2.5 ng/mL at baseline, 96.7 % had a nadir GH of ≥ 1 ng/mL in the oral glucose tolerance test. At baseline, mean IGF-I of all enrolled patients (n = 66) was 2.12 × ULN (95 % CI, 1.81–2.43), of treatment-naïve patients (n = 43) 2.22 × ULN (95 % CI, 1.83–2.61), and of pre-treated patients (n = 23) 1.94 × ULN (95 % CI, 1.37–2.51).

23/42 (54.8 %) of patients with pituitary dysfunction had gonadotrophic deficiency, 50.0 % thyrotrophic and 38.1 % corticotrophic dysfunction. 9.5 % patients had diabetes insipidus. 75.0 % patients had previous treatment of acromegaly. 72.4 % of patients had previously received surgery, 42.1 % medical treatment, and 10.5 % radiosurgery. Previous medical treatment consisted of dopamine agonists (27.6 %), octreotide LAR (19.7 %) or a GH receptor antagonist (5.2 %) (▶ **Table 1**). The most frequently administered octreotide LAR dose was 30 mg in 9/15 (60.0 %) patients, followed by 20 mg and 10 mg for 3 patients each (20.0 %). At the start of the study, 18/63 (28.6 %) patients were on combination treatment with either a dopamine agonist or pegvisomant.

In 85.5 % of patients, comorbidities were reported. Most frequent comorbid conditions were hypertension (56.6 %), pituitary dysfunction (55.3 %) and diabetes mellitus (28.9). 51 (67.1 %) enrolled patients received concomitant medication for conditions other than acromegaly, of these 88.2 % had antihypertensives, 33.3 % antidiabetics, and 9.8 % oral anticoagulants. Five patients with diabetes and one patient with hypertension did not receive medication for these conditions. At baseline mean glycated hemoglobin (HbA_{1c}) was 5.9 % (95 % CI, 5.8–6.1), mean fasting glucose 105.3 mg/dL (95 % CI, 97.6–113.1).

Expression of somatostatin receptor (SSTR) 2 and SSTR5 was documented in somatotroph tumors of 16 of 76 enrolled patients. Of these, 93.8 % tumors expressed SSTR2 or SSTR2a and 75.0 % expressed SSTR5. All tumors that expressed SSTR5 also expressed SSTR2. None from 8 tumors studied expressed SSTR3 (▶ **Fig. 1**). SSTR2/2a-positive tumors mainly showed intermediate (+ + , 50.0 %) or high (+ + + , 31.3 %) levels of receptor expression, whereas in SSTR5-positive tumors high (+ + + , 43.8 %) receptor expression predominated.

Treatment of acromegaly

On the enrolled population, the starting dose was 60 mg lanreotide autogel in 40/76 (52.6 %), 90 mg in 24 (31.6 %) patients and 120 mg in 12 (15.8 %) patients (▶ **Fig. 2**). At month 12, 36.4 % of

▶ **Table 1** Baseline patient characteristics of the enrolled and efficacy populations.

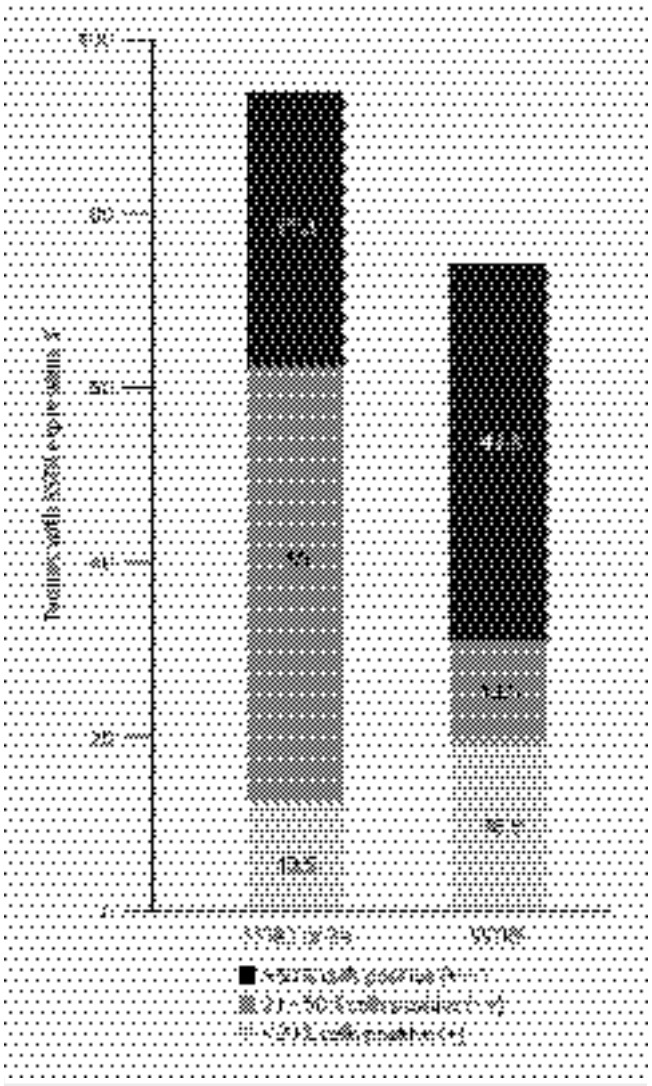
Variable	Enrolled population		Efficacy population	
	N		N	
Age, mean years (95 % CI)	76	52.2 (49.0–55.3)	51	52.8 (48.9–56.7)
Gender, n (%)				
Female	76	37 (48.7)	51	27 (52.9)
Male	76	39 (51.3)	51	24 (47.1)
BMI, mean (95 % CI)	68	30.3 (28.7–31.8)	47	30.5 (28.6–32.4)
Duration since diagnosis of acromegaly, mean years (95 % CI)	74	6.7 (4.4–8.9)	51	8.1 (5.0–11.1)
Duration since onset of symptoms, mean years (95 % CI)	32	13.8 (9.4–18.3)	25	15.7 (10.5–21.0)
Time since most recent pituitary surgery Mean years (95 % CI)	52	8.9 (6.0–11.9)	36	9.7 (5.8–13.5)
Median tumor size at the time of diagnosis, mm (95 % CI)				
With prior pituitary surgery	35	20.9 (17.1–24.8)	26	21.3 (16.2–26.3)
Without prior surgery	16	14.9 (10.6–19.1)	9	14.7 (8.5–20.8)
Tumor size, n (%)				
Macroadenoma	61	50 (82.0)	43	36 (83.7)
Microadenoma	61	11 (18.0)	43	7 (16.3)
Baseline GH, mean (95 % CI)	64	13.5 (3.3–23.6)	51	14.7 (2.2–27.3)
≤ 2.5 ng/mL, n (%)	64	38 (59.4)	51	31 (60.8)
> 2.5 ng/mL, n (%)	64	26 (40.6)	51	20 (39.2)
GH in OGTT, mean (95 % CI), ng/mL				
Basal	30	22.3 (4.8–39.9)	18	23.6 (0.0–53.4)
Nadir	30	11.3 (6.8–15.8)	18	7.6 (5.0–10.2)
Nadir ≥ 1 ng/mL, n (%)	30	29 (96.7)	18	17 (94.4)
Baseline IGF-I				
Mean IGF-I × ULN (95 % CI)	66	2.12 (1.81–2.43)	51	2.20 (1.83–2.57)
≤ 1 × ULN, n (%)	66	12 (18.2)	51	8 (15.7)
> 1 to ≤ 3 × ULN, n (%)	66	36 (54.5)	51	28 (54.9)
> 3 × ULN, n (%)	66	18 (27.3)	51	15 (29.4)
Concomitant disease, n (%)				
Hypertension	76	43 (56.6)	51	30 (58.8)
Pituitary dysfunction	76	42 (55.3)	51	28 (54.9)
Diabetes mellitus	76	22 (28.9)	51	16 (31.4)
Impaired glucose tolerance	76	10 (13.2)	51	8 (15.7)
Coronary heart disease	76	8 (10.5)	51	5 (9.8)
Adenomatous colon polyps	76	7 (9.2)	51	1 (2.0)
Previous treatment of acromegaly, n (%)				
Surgery	76	55 (72.4)	51	38 (74,5)
Medication	76	32 (42.1)	51	26 (51.0)
Dopamine agonist	76	21 (27.6)	51	16 (31.4)
Octreotide LAR	76	15 (19.7)	51	12 (23.5)
GH receptor antagonist	76	4 (5.3)	51	3 (5.9)
Radiotherapy	76	8 (10.5)	51	6 (11,8)
No previous treatment	76	19 (25.0)	51	11 (21.6)

BMI: body mass index, GH: growth hormone, IGF: insulin-like growth factor, IQR: interquartile range (first and third quartile), LAN: lanreotide autogel, LAR: long-acting release, OGTT: oral glucose tolerance test, SD: standard deviation, ULN: upper limit of normal.

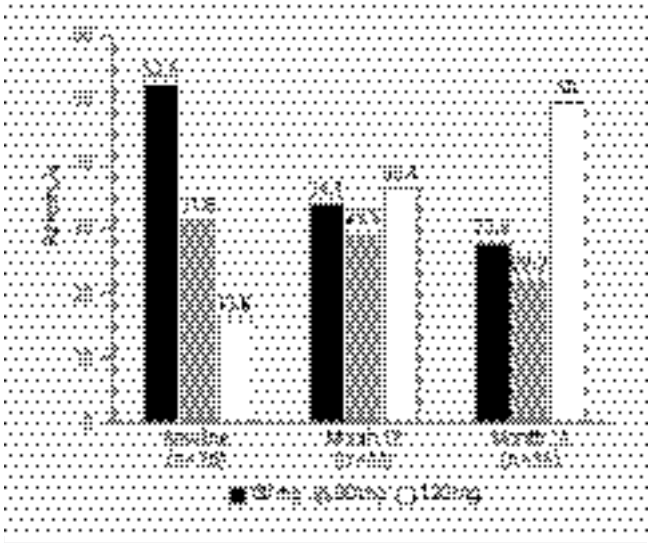
the patients received 120 mg lanreotide autogel and 50.0 % received 120 mg at month 24 (▶ **Fig. 2**).

At month 24, lanreotide autogel was administered by 19.4 % of the patients themselves or by their partners compared with 5.3 % at baseline.

During the course of the study, 28.6 % of patients received concomitant medical treatment for acromegaly consisting either of a dopamine agonist in 17.1 % patients or of a GH receptor antagonist in 6.6 % patients, respectively.



▶ **Fig. 1** Expression of SSTR subtypes at baseline (n = 16).



▶ **Fig. 2** Lanreotide autogel doses at baseline, month 12 and month 24 as proportions of patients receiving lanreotide autogel 60 mg, 90 mg or 120 mg every 4 weeks (enrolled population).

Biochemical control

Mean GH concentration in the efficacy population was 14.7 ng/mL (95 % CI, 2.2–27.3) at baseline, 3.1 ng/mL (95 % CI, 0.0–6.3) at month 12 and 4.7 ng/mL (95 % CI, 0.0–10.2) at month 24. The proportion of patients with GH ≤ 2.5 ng/mL was 60.8 % at baseline, 87.9 % at month 12 and 74.1 % at month 24. Mean change of GH from baseline was − 6.7 ng/mL (95 % CI, − 13.9–0.5) at month 12, and − 0.7 ng/mL (95 % CI, − 2.8–1.3) at month 24 (▶ **Fig. 3a**). Mean IGF-I concentrations were 2.20 × ULN (95 % CI, 1.83–2.57) at baseline, 1.18 × ULN (95 % CI, 0.96–1.41) at month 12 and 1.11 × ULN (95 % CI, 0.86–1.36) at month 24. Mean change of IGF-I from baseline was − 1.06 × ULN (95 % CI, − 1.44– − 0.79) at month 12 and − 0.98 × ULN (95 % CI, − 1.46– − 0.51) at month 24 (▶ **Fig. 3b**). At baseline, IGF-I values were within the normal range in 8 (15.7 %) patients of the efficacy population; 45.5 % patients achieved IGF-I normalization at month 12 and 55.6 % patients at month 24 of the study.

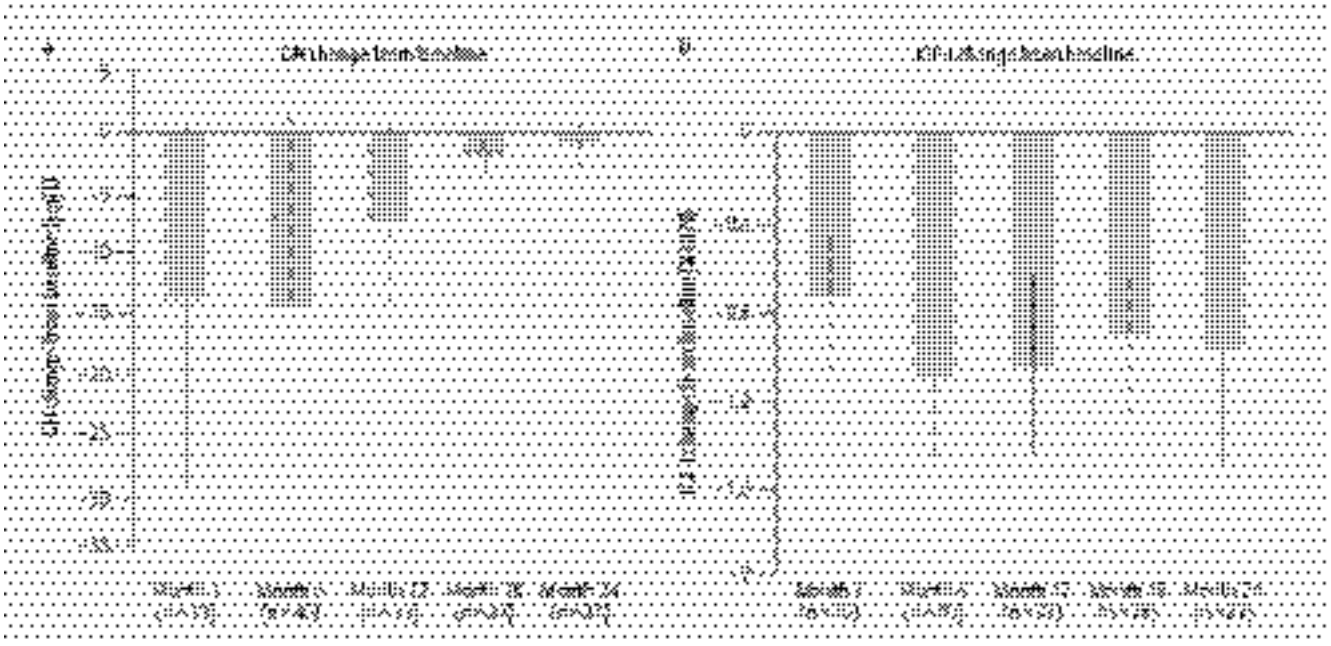
At baseline, 7/51 (13.7 %) patients of the efficacy population had full biochemical control. After 1 year of lanreotide treatment, 15/33 (45.5 %) patients achieved full biochemical control (= primary endpoint) and 10/26 (38.5 %) at month 24. At month 12, 14 (42,4 %) patients had GH ≤ 2.5 and elevated IGF-I, no patient had GH > 2.5 ng/ml and IGF-I normalized, and 4 (12.1 %) patients had GH > 2.5 and elevated IGF-I.

Biochemical control rates were additionally analyzed according to the following variables at baseline and categories: age (≤ median vs > median [= 53 years]), treatment-naïve vs pretreated patients, duration of acromegaly (≤ median vs > median [= 1.4 years]), and body mass index (BMI) (≤ median vs > median [= 30.1 kg/m^2]). At 12 months of treatment higher rates of biochemical control were observed in the following subgroups: older patients (> 53 years of age), females, treatment-naïve patients (no medical pre-treatment), patients who had been diagnosed with acromegaly for > 1.4 years, and patients with a BMI ≤ 30.1 kg/m^2 (▶ **Fig. 4**). 50.0 % initially treatment-naïve patients had full biochemical control at month 12 and 7/15 (46.7 %) at month 24, whereas 5/13 (38.5 %) pre-treated patients were fully biochemically controlled at month 12 and 3/11 (27.3 %) at month 24 (pegvisomant n = 4, radiotherapy n = 8, treatment-naïve n = 11).

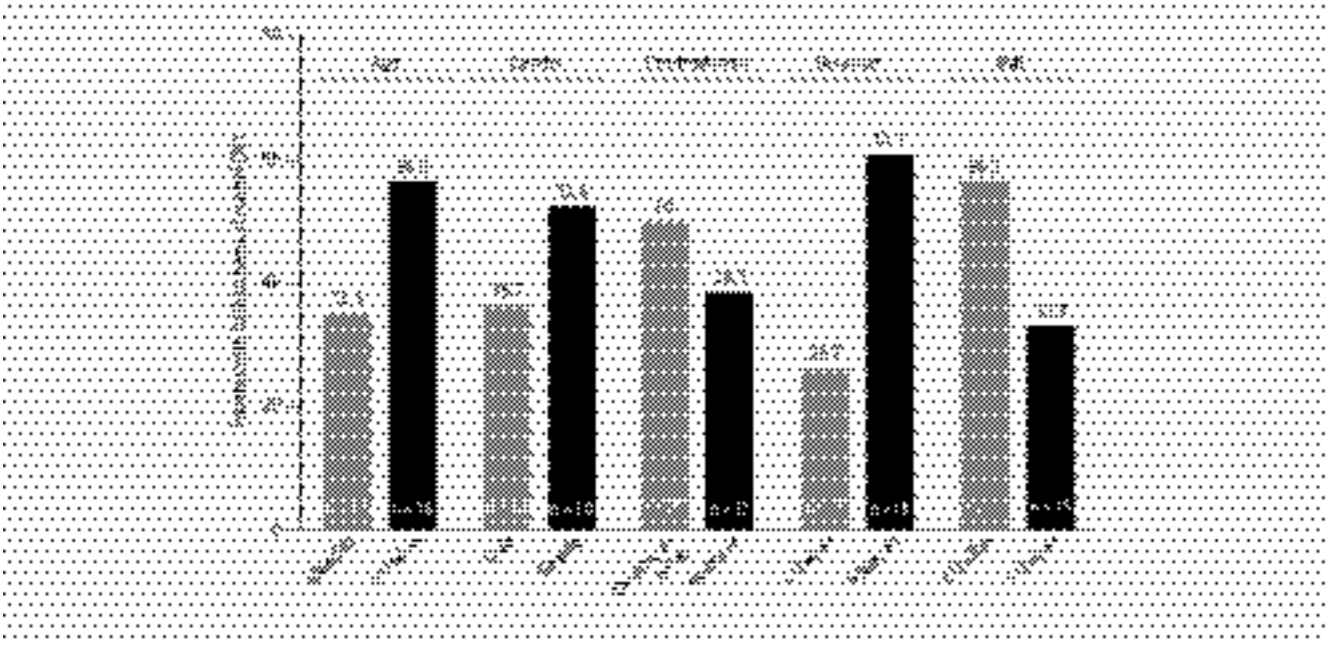
Symptoms and QoL

Clinical activity of acromegaly was evaluated on the efficacy population by assessing ring size, hyperhidrosis, sleepiness (ESS scale), headache and arthralgia in addition to assessing the use of antihypertensives as surrogate parameter of hypertension. Mean ring size was 72.8 mm (95 % CI, 69.5–76.0) at baseline (n = 21). Mean change from baseline was − 2.0 mm (95 % CI, − 4.5–0.5) at month 12 (n = 10) and − 0.2 mm (95 % CI, − 3.3–3.0) at month 24 (n = 6). Mean VAS for hyperhidrosis was 4.5 (95 % CI, 3.3–5.8) at baseline (n = 24); mean change from baseline was − 0.3 (95 % CI, − 2.2–1.7) at month 12 (n = 14) and 0.5 (95 % CI, − 1.5–2.6) at month 24 (n = 11). For headache and arthralgia, the mean VAS showed little variation during the course of the study, as did the mean ESS (range, 6.3–7.5) (not shown). 25 (49 %) patients received antihypertensive treatment at baseline, 21 (63.6 %) at month 12 and 16 (57.1 %) patients at month 24.

No major changes of the mean standardized AcroQoL global score and subscores were observed during the study period. At

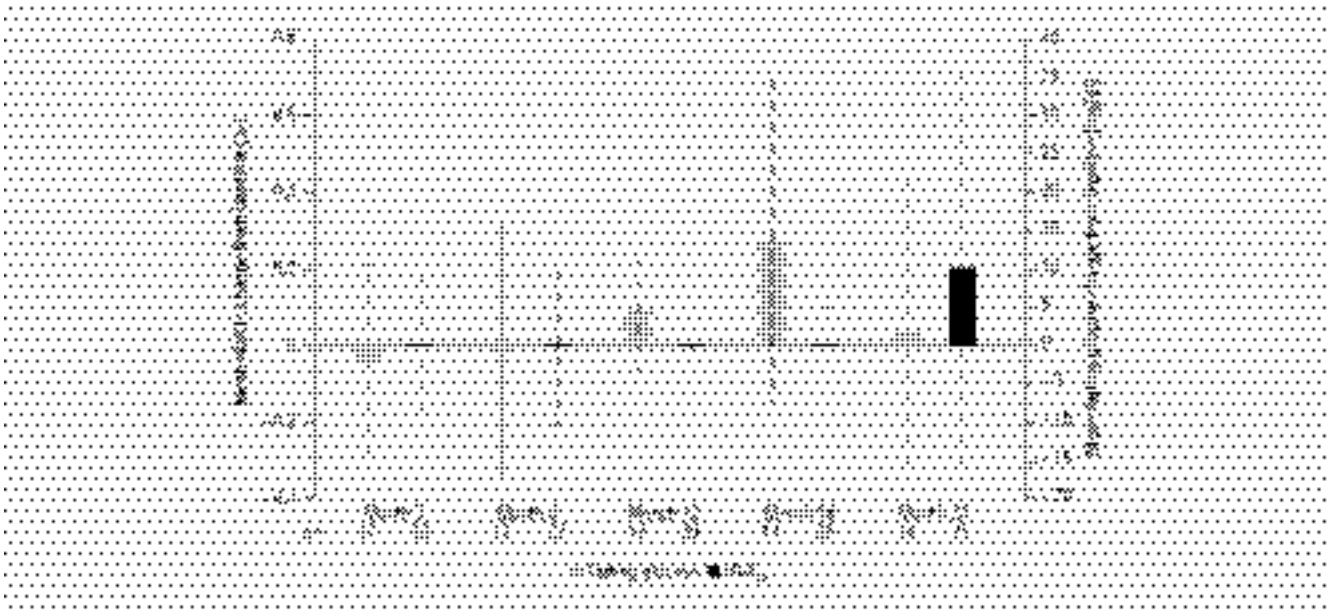


▶ **Fig. 3** Change from baseline with lanreotide autogel in months 3 to 24 (efficacy population) of **a**. mean GH concentrations (95 % CI), and **b**. mean IGF-I concentrations (95 % CI). Baseline GH concentration was 14.7 ng/mL (95 % CI, 2.2–27.3); baseline IGF-I value was 2.19 × ULN (95 % CI, 1,83–2.57); GH: growth hormone; IGF-I: insulin-like growth factor-1; ULN: upper limit of normal.



▶ **Fig. 4** Subgroup analysis of percentage of patients who achieved full biochemical control at 12 months according to median age (53 years), gender, pre-treatment (n = 33), median duration of acromegaly (1.4 years) and median BMI (30.1 kg/m^2) (n = 33, efficacy population); treatment-naïve: no medical pre-treatment of acromegaly, i. e. octreotide LAR, GH receptor antagonists or dopamine agonists within 6 months prior to baseline. BMI: body mass index; F: female; M: male; dotted line: proportion of full biochemical control in all evaluable patients (efficacy population) at month 12 (15/33 [45.5 %] patients).

baseline, mean standardized global AcroQoL score was 62.6 (95 % CI, 56.3–68.9) (n = 40). Mean changes from baseline for the mean standardized global AcroQoL were − 6.7 (95 % CI, − 14.8–1.5) at month 12 (n = 14) and − 3.7 (− 13.8–6.4) at month 24 (n = 16). Baseline mean AcroQoL scores was lowest for the dimensions appearance (55.7 [95 % CI, 48.6–62.7]) and physical (59.1 [95 % CI, 51.7–66.6]) and highest for personal relationship (72.9 [95 % CI, 66.0–79.7]).



▶ **Fig. 5** Changes from baseline (95 % CI) of mean HBA1C and mean fasting blood glucose during the study (efficacy population). Mean baseline HbA1c value: 6.0 % (95 % CI, 5.8–6.2). Mean baseline fasting glucose value: 109.2 mg/dL (95 % CI, 99.3–119.1).

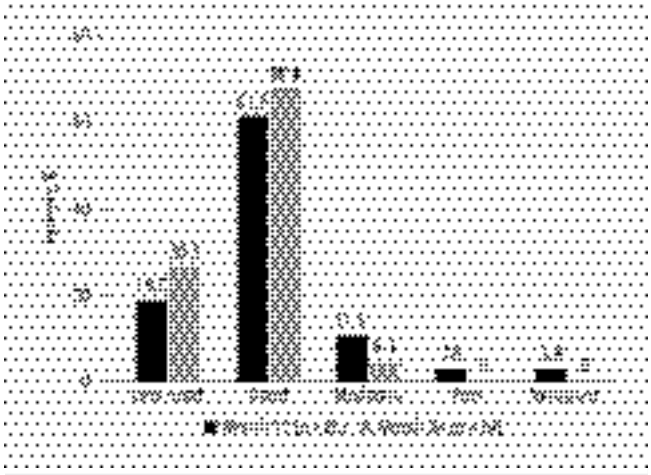
Overall effectiveness of the treatment with lanreotide autogel was judged by the participating physicians as 'very good' or 'good' for 19 (90.5 %) patients at month 12 and for 14 patients (87.5 %) at month 24.

Tolerability

Vital signs were unremarkable throughout the study for all patients. In one patient, who had no gall bladder stones at baseline, gall bladder stones were detected during treatment with lanreotide autogel. No new safety issues arose from this study and/or required further investigation and no related serious adverse events were reported during the study.

There was only little variation of mean fasting glucose levels and HbA_{1c} levels throughout the course of the study. The mean fasting glucose value was 109.2 mg/dL (95 % CI, 99.3–119.1) at baseline (n = 38), mean changes from baseline were 4.7 mg/dL (95 % CI, − 3.9–13.4) at month 12 (n = 17), and 1.8 mg/dL (95 % CI, − 17.5–21.2) at month 24 (n = 14) (▶ **Fig. 5**). More than 80 % of patients had fasting glucose levels < 126 mg/dL at all study visits (not shown). 11 (21.6 %) of the patients of the efficacy population received antidiabetic co-medication at baseline, 6 (18.2 %) of the patients at month 12, and 6 (23.1 %) patients at month 24. Mean HbA_{1c} levels generally remained constant over the 24-months treatment phase. The mean baseline HbA_{1c} value was 6.0 % (95 % CI, 5.8–6.2) at baseline (n = 45), mean changes from baseline were 0.0 % (95 % CI, − 0.2–0.2) at month 12 (n = 25), and 0.2 % (95 % CI, − 0.3–0.6) at month 24 (n = 25). More than 70 % of patients had HbA_{1c} levels < 6.5 % and less than 30 % had levels ≥ 6.5 % at all study visits (not shown).

Overall, tolerability of treatment with lanreotide autogel was judged by 80.8 % of the enrolled patients at month 12 and by 94.7 % at month 24 as 'very good' or 'good' (▶ **Fig. 6**).



▶ **Fig. 6** Global evaluation of lanreotide autogel tolerability by enrolled patients at month 12 and month 24 of treatment.

Discussion

This study presents the data of a 24-month observational study of lanreotide autogel therapy for acromegaly in Germany, Austria and Switzerland. It provides insights into patient characteristics, treatment effectiveness and disease control in various patient subgroups in a clinical 'real-world' setting within the limitations of a non-interventional study design.

Our results show that in routine medical practice lanreotide autogel treatment was associated with a decrease of IGF-I and GH concentrations to long-term full biochemical control, defined as GH ≤ 2.5 ng/mL plus IGF-I normalization, in 40–50 % of the patients of the efficacy population within 24 months. We are aware that

nowadays biochemical disease control of acromegaly is generally defined as a random GH level < 1.0 ng/mL using an ultrasensitive assay in addition to a IGF-I level in the age-adjusted normal range [23]. However, an upper limit of ≤ 2.5 ng/mL was chosen, since this was the cut-off for a controlled random GH value when designing this study [24–27]. There is a large body of evidence from controlled trials that lanreotide autogel is effective in controlling GH and IGF-I levels in patients with acromegaly [13–20]. Lanreotide autogel shows rapid onset of action and sustained efficacy over time [28]. Our observational study confirms the effectiveness of lanreotide autogel in routine clinical practice in Germany, Austria and Switzerland, in particular IGF-I normalization rates being in agreement with results from other open-label studies [7, 28]. A higher rate of treatment-naïve than medically pre-treated patients showed biochemical control at 12 and 24 months of lanreotide treatment. Moreover, higher rates of biochemical control at one year of treatment were observed in patients with a longer duration of disease, in older patients, in female patients, and in patients with a lower BMI. Besides initial GH and IGF-I levels, tumor mass and expression of SSTR2 and 5, younger age at diagnosis and male gender have previously been shown to be associated with higher biochemical activity of acromegaly and predict response to somatostatin analogs [29, 30]. The differences in biochemical control achieved according to age and gender may be attributed to the well-known decline of GH secretion with age as well as to different age- and gender-dependent patterns of GH secretion and rhythmicity in patients with acromegaly [31]. However, in other studies associations between age and gender and biochemical outcome were not observed [32–34]. Although associations between body weight and both, GH and IGF-1 levels have been described [35, 36], BMI has previously not been identified as a predictor of response to somatostatin analogs. Our findings showing worse outcomes for pre-treated (surgery and medical treatment) compared with somatostatin analog-naïve patients are not completely in line with results from other studies [10, 37]. These discrepancies may result from a different study design, patient population, pre-treatment and treatment discontinuation rates and, in particular, from lower sample sizes in our study.

Immunohistochemistry results confirm previous studies showing variable expression of SSTR in GH secreting pituitary tumors with most tumors expressing both, SSTR2 and SSTR5, at higher levels, and lower or absent expression of SSTR1, SSTR3 and SSTR4 [38–41]. In particular, expression of SSTR2 has been associated with response to first-line somatostatin analog therapy [41–44].

During the 24 months of follow-up, changes in acromegaly symptoms and QoL were modest or absent. It is known that comorbidities such as osteoarthritis or sleep apnea and associated symptoms of acromegaly often persist even after biochemical cure [45, 46]. Furthermore, symptoms are associated with persistent impairment of QoL in patients with acromegaly, even in patients with biochemically stable disease [47]. Accordingly, our AcroQoL results confirm a marked impairment of the patients' QoL, notably in relation to appearance and the physical dimension [48].

Our findings emphasize the need for initiation and optimization of adequate acromegaly management in a real-world setting. Although almost three-quarters of the patients had previous pituitary surgery and nearly half were medically pre-treated, less than 15 % were biochemically controlled at baseline. This is in line with data from the German Acromegaly Registry showing that almost one fifth of patients had elevated IGF-I concentrations and GH ≥ 1 ng/mL irrespective of the type of treatment [49]. In addition, in our observational study, only 50 % of patients received the maximal dose of lanreotide autogel of 120 mg every 4 weeks at month 24. It has been shown, though, that up-titration of lanreotide autogel doses can contribute to an effective control of GH and IGF-I [26, 50]. In fact, the 2018 consensus statement on acromegaly therapeutic outcomes recommends that an increase of dose and/or dose frequency of first-generation somatostatin analog or the addition of cabergoline may be considered in patients having a partial response [6]. Other options for treatment optimization include switching to pasireotide LAR or pegvisomant or combination with pegvisomant [6, 51]. In our study, physicians opted for combination of lanreotide autogel with dopamine agonists in 17.1 % and with pegvisomant in 6.6 % of patients. Therefore, making more frequently use of the approved lanreotide autogel dose range of up to 120 mg every 4 weeks or of combined treatments might have further improved biochemical control rate in our patients. Indeed, according to a survey of the German Acromegaly Registry, apart from non-compliance with medical treatment recommendations, one main reason for the failure to achieve disease control in acromegaly is disregard of therapy escalation [52].

Tolerability of lanreotide autogel was rated as good or very good by more than 80 % of patients [13–20, 53]. 5 (10.0 %) patients discontinued lanreotide autogel treatment during the 24-month study period due to adverse events. Our study does not provide evidence for a significant sustained glycemic effect of lanreotide autogel in patients with acromegaly either in terms of fasting plasma glucose, HbA_{1c} or the proportion of patients with antidiabetic-co-medications. Therefore our results provide further real-world support for the tolerability of lanreotide autogel.

There are important limitations of this study, which are essentially due to the real-life nature of the study design. It reflects routine clinical practice of the centers included and leaves decision-making on diagnostic and therapeutic matters exclusively in the hands of the treating physician. This most likely explains the variable patient numbers at study visits and comparatively high number of dropouts, resulting in reduced numbers of valid measurements during the course of the study. It also explains the variability in the quality of documentation in the centers. Overall, approximately two-thirds of patients who started treatment with lanreotide autogel discontinued the study prematurely, a number which is comparable with drop-out rates of other non-interventional studies [34, 54]. In addition, GH and IGF-I were assessed according to local clinical routine using various techniques and assays [34, 54].

In conclusion, lanreotide autogel is an effective and well-tolerated treatment option in both pre-treated and treatment-naïve patients with acromegaly in specialized medical practices.

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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.

Conflict of Interest

SS has received personal fees and grants from Novartis, IPSEN, and Pfizer. JP has received research funding and consulting fees by Novartis, IPSEN, and Pfizer, and research funding by Chiasma, OPKO, Aeterna Zentaris, and Crinetics. CB declared no conflict of interest. CT has received conference and/or travel grants and/or consulting fees from IPSEN, Novartis and Pfizer. MC-C has participated in advisory boards by IPSEN. RF has participated in advisory boards by IPSEN. JF has received speaker fees and/or conference travel support from IPSEN, Novartis, Lilly, Pfizer, Olympus, Integra, and has been a member of advisory boards of IPSEN and Novartis. IK-A has received research, conference and/or travel grants and/or consulting fees from IPSEN, Novartis and Pfizer. AL has received speaker fees and/or conference travel support from IPSEN, Novartis, Novo Nordisk, Sandoz and Pfizer, and has been member of advisory boards of IPSEN, Novartis and Pfizer. GS has received consultancy fees from IPSEN, Novo Nordisk, Recordati, Sandoz. AH is an IPSEN employee. DH is an IPSEN employee. SP has served as an advisory board member for IPSEN, Crinetics, Recordati, Takeda, and Novartis, and has received honoraria for speaking at symposia for IPSEN, Novartis, Recordati, Takeda, and Pfizer.

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