

Tumor Shrinkage with Lanreotide Autogel 120 mg as Primary Therapy in Acromegaly: Results of a Prospective Multicenter Clinical Trial

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Context Methodological shortcomings often compromise investigations into the effects of primary somatostatin-analog treatment on tumor size in acromegaly. There are also limited data for the long-acting lanreotide formulation.

Objective To better characterize the effects of primary lanreotide Autogel treatment on tumor size in patients with growth hormone (GH)-secreting macroadenomas.

Design PRIMARYS—48-week multicenter open-label single-arm (ClinicalTrials.gov—NCT00690898; EudraCT—2007—000155—34).

Setting Specialist endocrine centers.

Patients Treatment-naïve acromegalic patients with GH-secreting macroadenomas.

Intervention Subcutaneous lanreotide Autogel 120 mg every 28 days (without dose titration).

Outcome measures Primary endpoint: null hypothesis (H_0)—proportion of patients with clinically significant ($\geq 20\%$) tumor volume reduction (TVR) at week 48/last post-baseline value available (LVA) is $\leq 55\%$, using central assessments from three readers. Secondary endpoints included: TVR at other time points; GH and insulin-like growth factor-1 (IGF-1); acromegalic symptoms; quality of life (QoL); safety.

Results 64/90 (71.1%) patients completed the study. Clinically significant TVR at 48 weeks/LVA achieved by 62.9% [95%CI: 52.0, 72.9] of 89 patients in the primary analysis (intention-to-treat population; H_0 not rejected) and 71.9–75.3% in sensitivity ($n = 89$) and secondary analyses ($n = 63$) (H_0 rejected). At 12 weeks, 54.1% had clinically significant TVR. Early and sustained improvements also occurred in GH and IGF-1, acromegalic symptoms, and QoL. No patients withdrew due to gastrointestinal intolerance.

Conclusions Primary treatment with lanreotide Autogel, administered at 120 mg (highest available dose) without dose titration, in patients with GH-secreting macroadenomas provides early and sustained reductions in tumor volume, GH and IGF-1, and acromegalic symptoms, and improves QoL.

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Abbreviations: AE, adverse event; FPG, fasting plasma glucose; GH, growth hormone; H_0 null hypothesis; HbA_{1c}, glycated hemoglobin; IGF-1, insulin-like growth factor-1; ITT, intention to treat; LVA, last post-baseline value available; MRI, magnetic resonance imaging; PP, per protocol; QoL, quality of life; SSR, standardized sensitivity ratio; TVR, tumor volume reduction

Long-acting somatostatin analogs are established treatments for patients with acromegaly following unsuccessful pituitary surgery (1). Primary therapy with these agents, meanwhile, is recommended principally for a subgroup of patients with larger tumors, when a surgical cure is unlikely (2), and additionally if surgery is refused or contraindicated (1, 3, 4). Studies have adequately demonstrated that primary treatment with octreotide LAR and lanreotide Autogel improves symptoms and attenuates or normalizes growth hormone (GH) and insulin-like growth factor-1 (IGF-1) hypersecretion (5, 6). While reducing the tumor burden is also critical to therapeutic success in this setting, the evidence for tumor-shrinkage effects with long-acting somatostatin analogs is less compelling. There are, moreover, indications that biochemical and tumor-shrinkage effects are dissociated in acromegaly (7, 8). Accordingly, it is particularly important to have robust studies specifically designed to investigate the effects of somatostatin analogs on tumor size. Such studies should be undertaken with treatment-naïve patients, using tumor size as the primary endpoint, and with efforts made to reduce variability in tumor measurements. Few studies to date incorporate these features (7, 9–11). Many are also compromised by mixed-treatment settings (eg, variable doses) and patient populations (eg, microand macroadenomas), and by selecting patients responsive to somatostatin analogs. Meta-analyses based on these studies are then additionally hampered by methodological heterogeneity among studies, such as assessment intervals, study durations, treatment formulations, and study populations. Against this background of heterogeneity, authors of a recent meta-analysis concluded that first-line octreotide treatment may produce tumor shrinkage in up to two-thirds of patients (9). It seems likely lanreotide has a comparable effect (10), although, to date, fewer studies have investigated its effects on tumor size.

The aim of the ‘PRIMARY treatment of macroadenomas in acromegaly with Somatuline’ (PRIMARYS) study was to better characterize the effects of primary lanreotide Autogel on tumor size. Accordingly, this was a prospective study with change in tumor volume as the primary endpoint and pituitary magnetic resonance imaging (MRI) scans read centrally using rigorous prespecified methodologies to minimize measurement variability. Treatment was started and continued at the highest available dose to improve dataset homogeneity and investigate the time to onset of effects. Patients were treatment-naïve and all had GH-secreting macroadenomas.

Patients and Methods

Patients

Treatment-naïve adult (18–75 years) men or women with acromegaly were eligible if mean GH levels (mean of five samples

taken at 10–15-minute intervals for patients with diabetes mellitus) or nadir GH (assessed by oral glucose tolerance test (OGTT) for all other patients) was $> 1 \mu\text{g/liter}$ and IGF-1 levels were above age- and sex-matched normal ranges (GH and IGF-1 levels analyzed centrally). All participants had macroadenomas (diameter ≥ 10 mm measured centrally by MRI) and no visual field defects (assessed using Goldmann and automated visual field perimeter examinations). Patients were not selected based on sensitivity to somatostatin analogs.

Patients were excluded if they had undergone/likely to require pituitary surgery or radiotherapy, had been treated with a somatostatin analog, dopamine agonist or GH receptor antagonist (GHRA), or were likely to require these agents (other than lanreotide Autogel 120 mg). They were also excluded if: there was cosecretion of prolactin at $> 100 \mu\text{g/liter}$, optic nerve disease or any visual abnormality with risk of worsening during the study, acute/chronic severe renal insufficiency (glomerular filtration rate (GFR) $< 30 \text{ mL/min/1.73 m}^2$), medical conditions that may have interfered with the study, allergy to gadolinium (MRI contrast agent), or hypersensitivity to lanreotide or drugs with similar chemical structure; they had taken/were scheduled to take an unlicensed drug in the previous 30 days. Women were excluded if they were not using acceptable methods of contraception, or were pregnant or lactating.

Patients were withdrawn at any time if there was evidence of new visual field abnormalities or other safety concerns (withdrawal at investigator’s discretion), insufficient IGF-1 response (IGF-1 level reduction $< 10\%$ at week 24 vs. baseline or investigator’s judgment that the response was inadequate), or post-baseline prolactin $> 100 \mu\text{g/liter}$ (for patients with baseline levels of 20–100 $\mu\text{g/liter}$).

Study design and interventions

This 48-week open-label single-arm phase 3b study was conducted in 27 specialist endocrine centers in nine countries (Belgium, Czech Republic, Finland, France, Germany, Italy, The Netherlands, Turkey, UK) between May 20, 2008 and February 13, 2012. Twelve lanreotide Autogel injections were administered by deep subcutaneous injection, one every 28 days, using at the highest available dose (120 mg) throughout the study (ie, no dose titration). Injections other than those taking place during study visits could be administered in the patient’s home as part of the patient’s normal care. The study is registered with ClinicalTrials.gov (NCT00690898) and EudraCT (2007–000155–34).

Patients provided written informed consent before study start, and the trial was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and all local regulatory requirements. Before trial initiation, the protocol, its amendments, consent form, study questionnaires, and the patient information leaflet were approved by institutional review boards. Protocol amendments occurring during the study are summarized in the Supplementary Appendix.

Assessments and outcome measures after 12, 24, and 48 weeks

Study visits were conducted during the 4-week screening period, weeks 1 (baseline), 12, 24, and 48 (and early withdrawal, if applicable). MRI scans were performed during screening (used as baseline value for tumor volume) and weeks 12, 24, 48 (and early withdrawal, if applicable). Tumor volumes were measured

centrally by three neuroradiologists blind to the chronology of patients' scans using prespecified methods, including computer modeling of tumor volumes, to ensure consistent and unbiased measurements (Figure 1). Assessments did not incorporate measures of tumor extension.

Hormone levels were determined centrally from blood samples taken under fasting conditions and before injections. IGF-1 levels were assessed from a single sample at each visit using a radioimmunoassay (RIA) (Esoterix/LabCorp Endocrine Sciences, Calabasas Hills, CA, USA) with a lower limit of detection (LOD) of 7.7 $\mu\text{g/liter}$, a lower limit of quantitation of 15 $\mu\text{g/liter}$, intra-assay precision of 5.3–14.1%, and interassay precision of 7.2–17.0%. Five consecutive samples taken at 10–15-minute intervals were used to determine a mean GH level for each visit, and prolactin levels were assessed at each postscreening visit if the screening value was $> 20 \mu\text{g/liter}$. GH and prolactin levels were measured with simultaneous one-step immunoenzymatic assays (Access[®] Ultrasensitive GH and prolactin assays; Beckman Coulter Inc., Brea, CA, USA). The GH assay had an LOD of 0.002 $\mu\text{g/liter}$, intra-assay precision of 1.9–3.8%, and inter-assay precision of 2.73–3.85%. For the prolactin assay, corresponding values were 1.0 $\mu\text{g/liter}$, 2.9–4.6%, and 3.04–4.32%, respectively.

Acromegalic symptoms (headache, excessive perspiration, fatigue, soft tissue swelling, arthralgia) were rated by patients at each visit on a scale ranging from 0 to 8 (0, no symptoms; 8, severe incapacitating symptoms). Quality of life (QoL) was determined from patient-reported assessments at each postscreening visit using the AcroQoL questionnaire (except Finland and Turkey, where validated translations were not available).

Safety assessments included adverse events (AEs) collected throughout the study and physical examination and vital signs assessed at all visits. Hematology and biochemistry were assessed from blood samples at screening and week 48/premature withdrawal, with fasting plasma glucose (FPG) and glycated hemoglobin (HbA_{1c}) levels assessed additionally at weeks 12 and 24. Gallbladder ultrasound was performed at screening and week 48/premature withdrawal, with additional examinations at any time in case of possible biliary symptoms.

The null hypothesis (H_0) for the primary endpoint was that the proportion of patients with $\geq 20\%$ reduction in tumor volume at week 48 (or last postbaseline value available [LVA]) was $\leq 55\%$, an arbitrary threshold in line with studies published at the time PRIMARYS was designed (7). Secondary efficacy endpoints included: tumor volume at weeks 12 and 24; GH and IGF-1 levels; proportions of patients achieving GH ≤ 2.5 and $\leq 1.0 \mu\text{g/liter}$ and/or normalized IGF-1 (ie, within age- and sex-matched normal ranges); prolactin (for patients with baseline values of 20–100 $\mu\text{g/liter}$); proportions of patients with improved/unchanged/worsened acromegaly symptoms vs. baseline; change in AcroQoL scores; and safety.

Statistical analyses

The sample size required ($n = 86$) was calculated using A'Hern's exact method for single-stage designs (12) and assuming an H_0 that the proportion of responders is $\leq 55\%$ (with alternative hypothesis that the proportion is $\geq 72\%$), providing an alpha risk of 2% with 90% power. Enrolment of 100 patients was needed to obtain evaluable data for 86 patients.

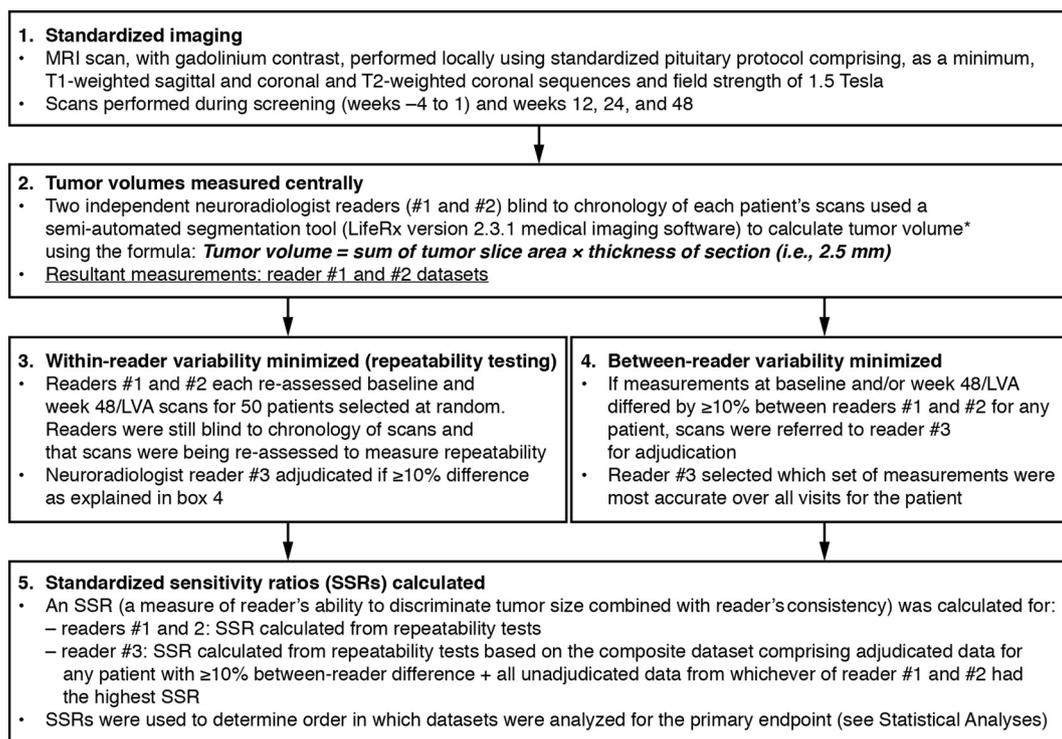


Figure 1. Prespecified methodology used to ensure consistent and unbiased evaluations of tumor volume. *Reader defined the regions of interest on images of the first and final slices of the tumor, with Life Rx software determining regions of interest on images of intervening slices. Details of how the standardized sensitivity ratios were calculated are reported in the Supplementary Appendix. LVA, last postbaseline value available; MRI, MRI.

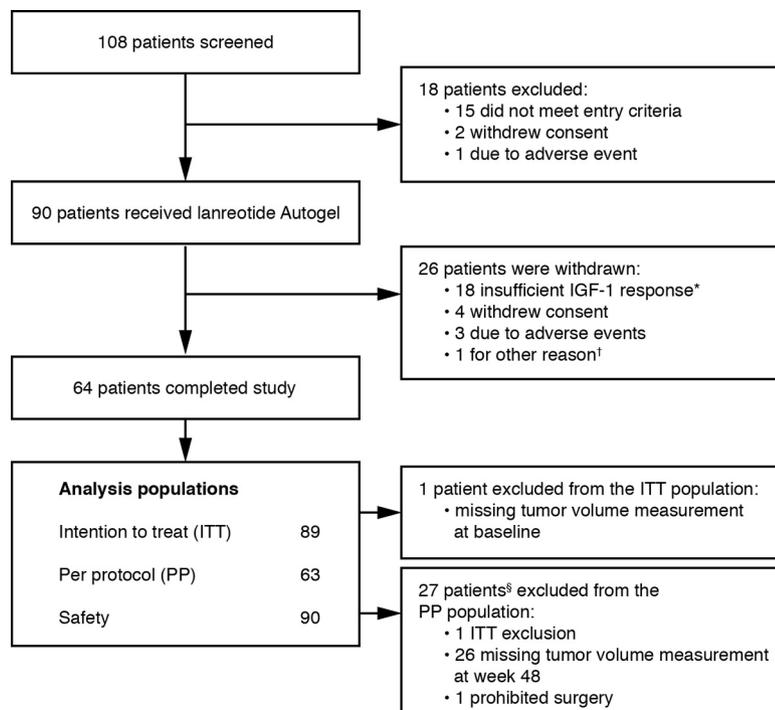


Figure 2. Flow of patients through the study. *IGF-1 levels decreased by $< 10\%$ at week 24 vs. baseline (as defined in the protocol) or investigator's judgment of insufficient response; †patient not able to attend due to mobility issues; §one patient had two major protocol violations. IGF-1, insulin-like growth factor-1.

A standardized sensitivity ratio (SSR) for tumor volume measurements was calculated for each reader (for detailed mathematical rationale and derivation, see Supplementary Appendix). In brief, the SSR measured readers' consistencies (based on standard deviations for each patient in repeatability tests) combined with sensitivities (mean absolute differences between final and baseline measures). The primary analysis for the primary endpoint was then conducted with the reader dataset with the highest SSR, using the intention-to-treat (ITT) population (patients receiving at least one injection of study medication and with at least one baseline efficacy assessment for the primary endpoint). The robustness of the primary analysis was examined by analyzing ITT data from the other two readers (sensitivity analyses). A secondary analysis was also performed using the per-protocol (PP) population (patients from the ITT population without major protocol deviations) for the reader with the highest SSR.

Descriptive statistics were used for secondary efficacy and safety endpoints. Secondary efficacy analyses were based only on the ITT population, except the proportions of patients reaching both GH and IGF-1 targets, which were also analyzed for the PP population. Safety analyses were based on the safety population (patients receiving at least one injection of study medication). Although missing data were not imputed, LVA assessments were compiled for all efficacy endpoints. Statistical analyses were performed using Statistical Analysis System (SAS)[®] software version 9.2.

Results

Patient disposition and baseline characteristics

Ninety patients received treatment, and 64 (71.1%) completed the study (Figure 2). Five patients experienced

a total of five treatment-emergent AEs leading to premature withdrawal: of these, alopecia, intracranial hypotension (cerebral fluid leakage), and hypertension were considered treatment-related (hypophysectomy and increased IGF-1 level were not considered treatment related and were later coded as insufficient IGF-1 response).

Baseline characteristics are shown in Table 1. Nineteen patients (21.1%) had a history of diabetes mellitus at baseline. Of 87 patients undergoing baseline gallbladder ultrasound, four (4.6%) had sludge and six (6.9%) had gallstones. Compared with the ITT population, patients withdrawing because of an insufficient IGF-1 response had similar baseline characteristics, but were slightly younger and a greater proportion had a history of diabetes mellitus (6/18 patients; 33.3%).

Efficacy

Primary endpoint: proportions of patients with $\geq 20\%$ reduction in tumor volume at week 48/LVA

Overall, 76% of tumor volume measurements were adjudicated. Reader #2 dataset had the highest SSR (0.65) and was used for primary ITT and secondary PP analyses; reader #1 and #3 datasets (SSRs, 0.57 and 0.52, respectively) were used for ITT sensitivity analyses.

The proportion of patients achieving $\geq 20\%$ tumor

Table 1. Baseline demographic and disease characteristics.

	Patients (n = 90)
Age, years	49.5 (12.4)
Men: women, n (%)	43 (47.8): 47 (52.2)
Body mass index, kg/m ²	27.7 (4.6)
Time since acromegaly diagnosis, days*	121.2 (149.9)
Maximum tumor diameter, mm	19.0 (7.1)
Median (Q1--Q3)	18.1 (13.9--21.9)
Maximum tumor volume, mm ³	2739 (3263)
Median (Q1--Q3)	1677 (867--3422)
Growth hormone level, $\mu\text{g/liter}$	15.0 (18.8)
Median (Q1--Q3)	8.5 (4.0--16.6)
Insulin-like growth factor-1 level, $\mu\text{g/liter}$	810 (300)
Median (Q1--Q3)	785 (596--994)

Data are mean (sd), unless stated otherwise, from the safety population. *Relative to baseline; n = 71.

Q1--Q3, quartiles 1--3.

volume reduction after 48 weeks/LVA was 62.9% with the primary ITT analysis, 75.3% and 71.9% with ITT sensitivity analyses, and 74.6% with the secondary PP analysis (Figure 3a). H_0 was not rejected for the primary analysis because the lower confidence interval (CI) just included the arbitrary 55% threshold; H_0 was rejected, however, for sensitivity and secondary analyses (Figure 3a). Tumor volume increased from baseline in nine patients; only two of these had increases > 20% (Figure 3b). (Two of the nine patients had IGF-1 changes between baseline and LVA < 10% [7.9% decrease; 9.8% increase]; by contrast, the range of IGF-1 reductions in the remaining seven patients was 20.8–71.4%.)

Secondary endpoints

The proportions of patients with $\geq 20\%$ tumor volume reduction was 54.1% [95% CI: 43.0, 65.0%] at week 12 and 56.3% [44.7, 67.3%] at week 24 (reader #2 dataset). Mean tumor volumes and levels of GH and IGF-1 (and prolactin in patients with baseline levels of 20–100 $\mu\text{g/liter}$) were greatly reduced at week 24 vs. baseline, and reductions maintained until study end (Figure 3c and Table 2). For tumor volume, mean reductions from baseline were 20% by week 12, 25% by week 24, and 27% by study end. Corresponding mean GH reductions were

62.1%, 64.6% and 70.9%, respectively, and mean IGF-1 reductions were 43.8%, 47.4%, and 56.7%, respectively. The proportions of patients achieving GH and/or IGF-1 targets increased over time (Figure 4). Of 18 patients withdrawn because of ‘an insufficient IGF-1 response’ (in investigator’s opinion or because IGF-1 reduction at week 24 was < 10%), the IGF-1 decrease was, in fact, > 10% at week 24 for three patients and at the early withdrawal visit for a further four patients. Tumor volume changes for these seven patients were in the same range as those for the remaining 11 patients.

Of the acromegalic symptoms assessed, headache was the least severe at baseline (mean [sd] score, 2.8 [2.6]), but nonetheless improved during the study (proportion of patients with improvements, 38.7–46.9% across visits). Greater proportions of patients experienced improvements in the other symptoms (55.1–68.5% across symptoms and visits). The global AcroQOL score improved from a mean (sd) baseline of 56.2 (16.1) ($n = 84$) by 7.8 (9.3) ($n = 82$) by the third injection and by 9.5 (12.7) ($n = 59$) at study end (corresponding LVA values, 7.7 [12.2]; $n = 84$).

Safety

A total of 340 treatment-emergent AEs were reported for 73 (81.1%) patients. Most of these patients experi-

Table 2. GH, IGF-1, and prolactin levels at each assessment point.

	Baseline (<i>n</i> = 89)	Week 12 (<i>n</i> = 85)	Week 24 (<i>n</i> = 78)	Week 48 (<i>n</i> = 63*)	LVA (<i>n</i> = 89*)
GH level					
Mean (SE.), $\mu\text{g/liter}$	15.0 (2.0)	3.6 (0.6)	2.9 (0.4)	2.4 (0.5)	3.3 (0.5)
Mean [95% CI] change from baseline, %	–	–62.1 [–70.5, –53.6]	–64.6 [–72.3, –57.0]	–70.9 [–79.2, –62.5]	–61.2 [–69.5, –52.9]
IGF-1 level					
Mean (SE.), $\mu\text{g/liter}$	804 (31)	446 (31)	406 (28)	335 (27)	428 (29)
Mean [95% CI] change from baseline, %	–	–43.8 [–50.1, –37.5]	–47.4 [–53.6, –41.2]	–56.7 [–62.1, –51.3]	–46.0 [–52.0, –40.1]
Prolactin level [†]	(<i>n</i> = 21)	(<i>n</i> = 20)	(<i>n</i> = 20)	(<i>n</i> = 12)	(<i>n</i> = 21)
Mean (SE.), $\mu\text{g/liter}$	48.0 (5.3)	31.0 (4.0)	30.6 (4.4)	27.5 (4.2)	31.3 (4.0)
Mean [95% CI] change from baseline, %	–	–18.0 [–26.9, –9.1]	–18.6 [–28.1, –9.1]	–17.3 [–29.0, –5.6]	–16.7 [–24.3, –9.2]

Data are from the intention-to-treat population.

*Missing IGF-1 data for one patient; [†]for patients with baseline prolactin levels of 20–100 $\mu\text{g/liter}$.

CI, confidence interval; GH, growth hormone; IGF-1, insulin-like growth factor-1; LVA, last post-baseline value available.

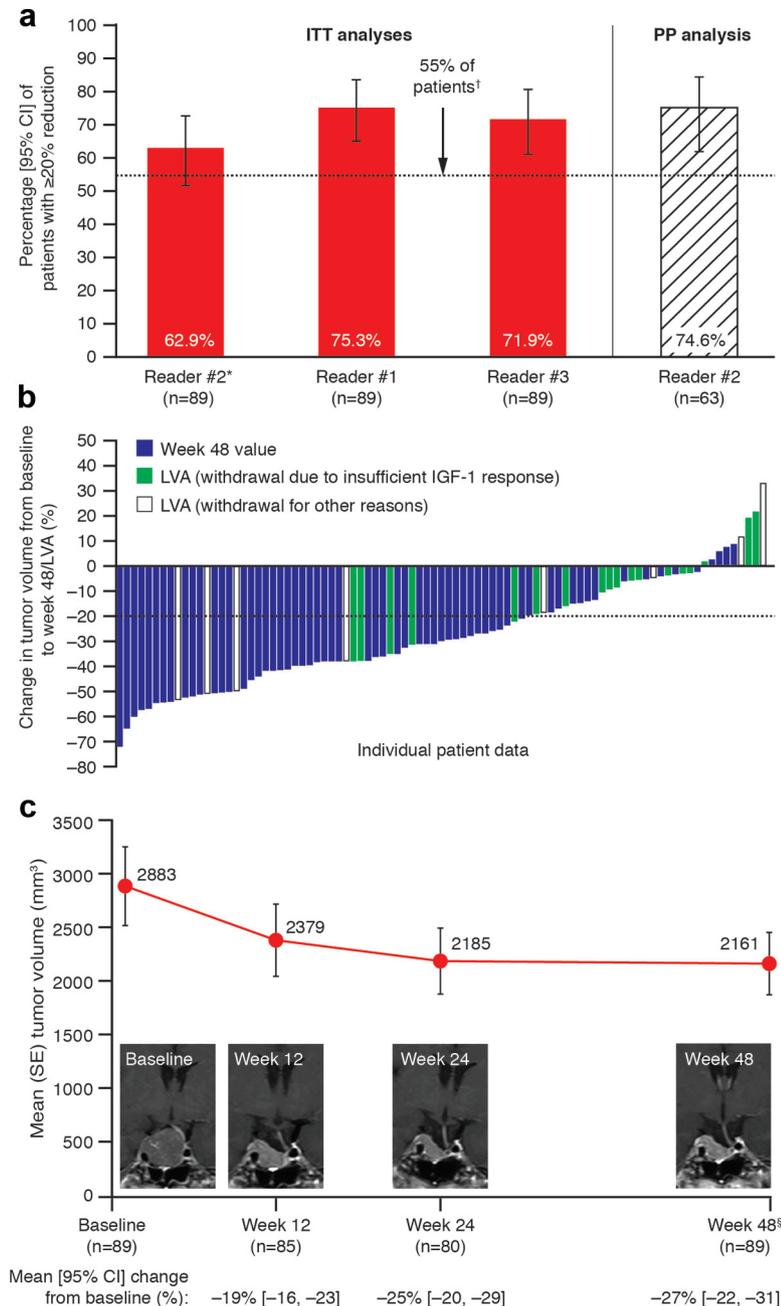


Figure 3. Reductions in tumor volume. Figure a) shows analyses of the proportions of patients with $\geq 20\%$ reduction in tumor volume from baseline to week 48/LVA (primary endpoint; ITT and PP populations), b) shows the tumor volume reductions for individual patients (ITT population), c) shows the time course of changes in tumor volume reductions (ITT population) with an illustrative MRI series from one patient. The four patients with greatest increases in tumor volumes (all based on LVA measurements) in figure b) had IGF-1 changes ranging from +9.8% to -40.9%. The patient with the greatest increase in tumor volume (33.1%) discontinued in the study at week 24 following discussions about the increase with the investigator. *Primary analysis based on highest standardized sensitivity ratio; †proportions and 95% CIs for each reader data set were compared with the predetermined threshold of 55%; ‡data are from week 48 or LVA. IGF-1, insulin-like growth factor-1; ITT, intention to treat (ITT); LVA, last postbaseline value available; MRI, MRI; PP, per protocol.

ders, 63.3%). Three patients experienced AEs leading to withdrawal (see earlier). Of 22 serious AEs, only intracranial hypotension (cerebral fluid leakage) was considered treatment-related and only syncope occurred in more than one patient (Supplementary Appendix).

There was no overall trend for any laboratory parameter. Only four abnormal values were considered clinically significant: decreased hemoglobin, thrombocytopenia, increased serum glutamate pyruvate transaminase, and increased γ -glutamyl transferase levels. FPG and HbA_{1c} levels were compared with American Diabetes Association threshold values for categories of glycemic control (13). Thirty-four patients had normal baseline FPG levels; at week 48, 12 of these had levels classified as impaired fasting glucose (5.6–6.9 mmol/liter) and two as diabetic (≥ 7.0 mmol/liter; week-48 data missing, n = 7). Of 43 patients with impaired fasting glucose at baseline, three had levels classified as diabetic and four as normoglycemic at week 48 (week-48 data missing, n = 14). Similarly, of 25 patients with normal baseline HbA_{1c} levels, nine had HbA_{1c} levels considered ‘at risk for diabetes’ (5.7–6.4%) and none had levels classified as diabetic ($\geq 6.5\%$) at week 48 (week-48 data missing, n = 8). Of 42 patients with ‘at risk’ baseline HbA_{1c} levels, none had levels classified as diabetic and three had levels considered normoglycemic at week 48 (data missing at week 48, n = 12). Gallbladder ultrasound revealed new sludge in 8/60 patients (13.3%) and new cholelithiasis in 15/61 patients (24.6%). No clinically significant changes occurred in vital signs.

enced mild or moderate AEs (Supplementary Appendix). Sixty-two patients (68.9%) experienced treatment-related AEs, the most common of which was diarrhea (38.9%) (most common AE class was gastrointestinal (GI) disor-

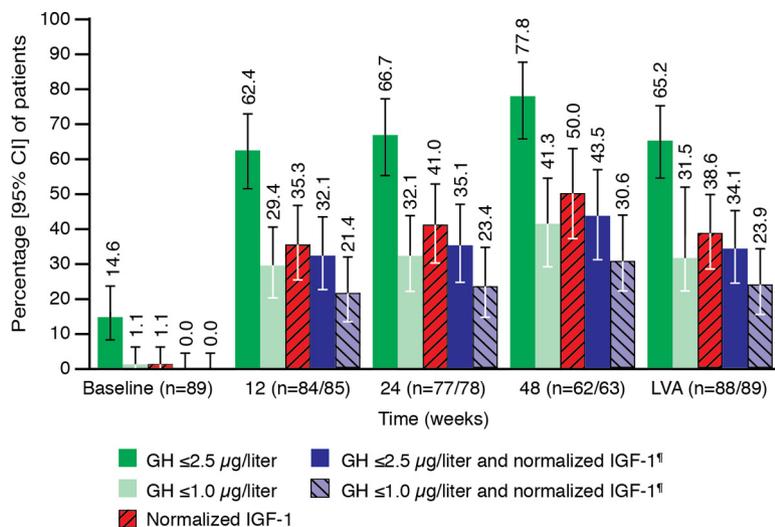


Figure 4. Proportions of patients reaching biochemical targets for GH and IGF-1 levels (secondary endpoints, ITT populations). *The proportions of patients reaching the GH and IGF-1 combined endpoints were the same for the PP population. Normalized IGF-1 defined as IGF-1 levels within age- and sex-matched normal ranges. GH, GH; IGF-1, insulin-like growth factor-1; ITT, ITT; PP, per protocol.

Discussion

Confidence in previous studies examining tumor-shrinkage effects with somatostatin analogs is undermined by significant methodologic shortcomings and study design heterogeneity. In early studies, for example, assessments of tumor size were hindered by poor image resolution (7). More recently, standard formulae (14, 15) or geometric approximations (16) have commonly been used to estimate tumor volume, but these methods lack precision for larger, more irregularly shaped tumors. Generally, little has been done to address the persistent problem of intra- and inter-reader variability in tumor measurements. In contrast, the PRIMARYS methodology was rigorous, particularly regarding efforts to minimize variability in tumor-size measurements (Figure 1). The patient population, moreover, was homogeneous in terms of treatment (starting and continuing with the highest available dose) and disease (GH-secreting macroadenomas). PRIMARYS showed that primary treatment with lanreotide Autogel 120 mg every 28 days provides clinically significant reductions ($\geq 20\%$) in tumor volume in 62.9% of patients at 1 year. These reductions were evident in 54.1% of patients by the first postbaseline visit at 3 months, suggesting the response at 3 months is broadly predictive of the longer-term response. For some individuals, the tumor volume reduction was very marked indeed. Of the few patients with a tumor volume increase, only two had an accompanying IGF-1 nonresponse (that is, an IGF-1 decrease $< 10\%$ between baseline and LVA). Overall, the study also confirmed previous observations in this setting regarding improvements in GH and IGF-1 levels (34% of patients achieved both $\text{GH} \leq 2.5 \mu\text{g/liter}$ and IGF-1 normaliza-

tion) and acromegalic symptoms (5). QoL changes with primary lanreotide Autogel have hitherto received limited attention. PRIMARYS showed QoL improvements occur as early as 3 months and are maintained for up to 1 year. Importantly, despite starting treatment at the highest dose, no patients withdrew because of GI intolerance.

A previous meta-analysis, necessarily based on studies varying greatly in design, suggested that first-line octreotide may produce tumor shrinkage in up to two thirds of patients (9). The data from PRIMARYS for lanreotide Autogel accord well with this estimate. The PRIMARYS data are also broadly consistent with individual studies most closely

approximating PRIMARYS in design. At 1 year, 77% of 26 patients (20 with macroadenomas) receiving lanreotide Autogel 120 mg every 4–8 weeks had tumor volume reductions of $\geq 25\%$ (5) while 72% of 60 patients with macroadenomas receiving octreotide LAR 10–30 mg achieved $\geq 20\%$ reduction (6). Investigations into tumor-shrinkage effects with the newer SSA pasireotide are at an earlier stage. In a phase 2 study with the subcutaneous formulation in a mixed primary and adjunct therapy setting, 7/14 treatment-naïve patients with macroadenomas had $\geq 20\%$ reduction in tumor volume after 3 months (17). Full publication of further studies with the long-acting formulation are awaited to better characterize tumor shrinkage effects.

As anticipated, the beneficial effects of primary lanreotide Autogel treatment on GH and IGF-1 hypersecretion, the cardinal symptoms of acromegaly, and QoL in PRIMARYS resonate with data from previous studies involving either this agent or octreotide LAR (5, 6, 18). The tolerability profile of lanreotide Autogel in PRIMARYS was also as expected. Although impaired glucose tolerance and frank diabetes mellitus are common acromegaly complications (1), there has been speculation that somatostatin analogs may have an additional adverse effect on glucose metabolism. A meta-analysis of lanreotide and octreotide data in acromegaly, however, indicated that modifications of glucose homeostasis induced by these agents may have an overall minor clinical impact (19). Data from PRIMARYS corroborate these findings. There were also no concerns due to using the highest available lanreotide Autogel dose (120 mg) throughout the study, as AEs overall were generally consistent with those from

other studies (20, 21). Initial GH, IGF-1, and safety data for the newer somatostatin analog pasireotide contrast somewhat from data for lanreotide Autogel and octreotide LAR. In a mixed primary and adjunct therapy setting, pasireotide LAR afforded superior biochemical control to octreotide LAR (31 vs. 19% of patients, respectively, achieving GH < 2.5 $\mu\text{g}/\text{liter}$ and normalized IGF-1 levels) (22). However, early reports indicate that hyperglycemia incidence and severity are increased (22).

As with all trials, there are limitations to the PRIMARYYS study. The null hypothesis for the primary endpoint, that the proportion of tumor volume responders was $\leq 55\%$, was not rejected for the primary analysis. However, the 55% threshold was based on studies published at the time PRIMARYYS was designed (7); none of these trials used the same design, and populations were commonly a mixture of patients with micro and macroadenomas, possibly enriching study populations with responders. Tumor volume measurements, moreover, are greatly influenced by inter and intra-reader variabilities (23). While considerable efforts were made to minimize variabilities in PRIMARYYS, with three-quarters of scan measurements for the primary endpoint adjudicated because they differed by $\geq 10\%$, we cannot rule out that residual variability influenced the findings. Confidence that a large proportion of patients will show clinically significant tumor volume reduction with lanreotide Autogel in clinical practice should nonetheless be high: the null hypothesis was rejected for all three sensitivity analyses of the primary endpoint, despite confounding factors affecting tumor volume assessments. While the open-label uncontrolled nature of the study may also have affected outcomes, the case for using such a design is strengthened when, as in PRIMARYYS, the primary endpoint is measured objectively and the probability of no treatment effect (as judged by previous studies) is low. The use of the highest available lanreotide Autogel dose and the absence of dose titration contributed to dataset homogeneity and seemed not to have affected treatment tolerability. It is possible, however, that variation in patients' individual sensitivities, such as occurs with biochemical responses (20), would have allowed some patients to achieve a tumor volume response at lower doses (60 or 90 mg). It bears repetition also that PRIMARYYS elucidates the clinical effects of primary therapy with lanreotide Autogel 120 mg specifically in patients with macroadenomas. The body of evidence from other studies indicates microadenoma volume reduction also occurs with either primary lanreotide Autogel or octreotide LAR (9, 10). However, transsphenoidal surgery affords higher biochemical cure rates for patients with smaller adenomas (2) and is therefore generally the first-line treatment. Nevertheless, the early reductions in

tumor volume in PRIMARYYS, when starting with the highest lanreotide Autogel dose licensed for acromegaly, could be of potential benefit to patients with optic chiasma compression. Such patients were not included in PRIMARYYS; any future study of this patient group would require careful safety monitoring.

In summary, PRIMARYYS underscores the potential of lanreotide Autogel 120 mg as a primary treatment for patients with acromegaly and GH-secreting macroadenoma. The study confirms, using a robust methodology, that clinical benefits include early and sustained reductions in tumor volume. QoL improvements are also apparent, alongside known benefits of improved biochemical control and amelioration of symptoms. A PRIMARYYS extension study is ongoing to characterize the longer-term efficacy and safety of lanreotide Autogel 120 mg as a primary treatment.

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References

- Katznelson L, Atkinson JL, Cook DM, Ezzat SZ, Hamrahian AH, Miller KK. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of acromegaly—2011 update. *Endocr Pract* 17 Suppl. 2011;4:1–44.
- Nomikos P, Buchfelder M, Fahlbusch R. The outcome of surgery in 668 patients with acromegaly using current criteria of biochemical ‘cure’. *Eur J Endocrinol*. 2005;152:379–387.
- Melmed S, Colao A, Barkan A, Molitch M, Grossman AB, Kleinberg D, Clemmons D, Chanson P, Laws E, Schlechte J, Vance ML, Ho K, Giustina A; Acromegaly Consensus Group. Guidelines for acromegaly management: an update. *J Clin Endocrinol Metab*. 2009;94:1509–1517.
- Giustina A, Bronstein MD, Casanueva FF, Chanson P, Ghigo E, Ho KK, Klibanski A, Lamberts S, Trainer P, Melmed S. Current management practices for acromegaly: an international survey. *Pituitary*. 2011;14:125–133.
- Colao A, Auremma RS, Reborra A, Galdiero M, Resmini E, Minuto F, Lombardi G, Pivonello R, Ferone D. Significant tumour shrinkage after 12 months of lanreotide Autogel-120 mg treatment given first-line in acromegaly. *Clin Endocrinol (Oxf)*. 2009;71:237–245.
- Mercado M, Borges F, Bouterfa H, Chang TC, Chervin A, Farrall AJ, Patocs A, Petersenn S, Podoba J, Safari M, Wardlaw J; SMS995B2401 Study Group. A prospective, multicentre study to investigate the efficacy, safety and tolerability of octreotide LAR (long-acting repeatable octreotide) in the primary therapy of patients with acromegaly. *Clin Endocrinol (Oxf)*. 2007;66:859–868.
- Bevan JS. Clinical review: The antitumoral effects of somatostatin analog therapy in acromegaly. *J Clin Endocrinol Metab*. 2005;90:1856–1863.
- Resmini E, Dadati P, Ravetti JL, Zona G, Spaziante R, Saveanu A, Jaquet P, Culler MD, Bianchi F, Reborra A, Minuto F, Ferone D. Rapid pituitary tumor shrinkage with dissociation between antiproliferative and antisecretory effects of a long-acting octreotide in an acromegalic patient. *J Clin Endocrinol Metab*. 2007;92:1592–1599.
- Giustina A, Mazziotti G, Torri V, Spinello M, Floriani I, Melmed S. Meta-analysis on the effects of octreotide on tumor mass in acromegaly. *PLoS One*. 2012;7:e36411.
- Mazziotti G, Giustina A. Effects of lanreotide SR and Autogel on tumor mass in patients with acromegaly: a systematic review. *Pituitary*. 2010;13:60–67.
- Melmed S, Sternberg R, Cook D, Klibanski A, Chanson P, Bonert V, Vance ML, Rhew D, Kleinberg D, Barkan A. A critical analysis of pituitary tumor shrinkage during primary medical therapy in acromegaly. *J Clin Endocrinol Metab*. 2005;90:4405–4410.
- A’Hern RP. Widening eligibility to phase II trials: constant arcsine difference phase II trials. *Control Clin Trials*. 2004;25:251–264.
- American Diabetes Association. Standards of medical care in diabetes—2013. *Diabetes Care*. 2013;36 Suppl 1:S11–S66.
- Colao A, Ferone D, Marzullo P, Cappabianca P, Cirillo S, Boerlin V, Lancranjan I, Lombardi G. Long-term effects of depot long-acting somatostatin analog octreotide on hormone levels and tumor mass in acromegaly. *J Clin Endocrinol Metab*. 2001;86:2779–2786.
- Baldelli R, Colao A, Razzore P, Jaffrain-Rea ML, Marzullo P, Ciccarelli E, Ferretti E, Ferone D, Gaia D, Camanni F, Lombardi G, Tamburrano G. Two-year follow-up of acromegalic patients treated with slow release lanreotide (30 mg). *J Clin Endocrinol Metab*. 2000;85:4099–4103.
- Bevan JS, Atkin SL, Atkinson AB, Bouloux P-M, Hanna F, Harris PE, James RA, McConnell M, Roberts GA, Scanlon MF, Stewart PM, Teasdale E, Turner HE, Wass JAH, Wardlaw JM. Primary medical therapy for acromegaly: an open, prospective, multicenter study of the effects of subcutaneous and intramuscular slow-release octreotide on growth hormone, insulin-like growth factor-I, and tumor size. *J Clin Endocrinol Metab*. 2002;87:4554–4563.
- Petersenn S, Schopohl J, Barkan A, Mohideen P, Colao A, Abs R, Buchelt A, Ho YY, Hu K, Farrall AJ, Melmed S, Biller BM; Pasireotide Acromegaly Study Group. Pasireotide (SOM230) demonstrates efficacy and safety in patients with acromegaly: a randomized, multicenter, phase II trial. *J Clin Endocrinol Metab*. 2010;95:2781–2789.
- Colao A, Cappabianca P, Caron P, De Menis E, Farrall AJ, Gadelha MR, Hmissi A, Rees A, Reincke M, Safari M, T’Sjoen G, Bouterfa H, Cuneo RC. Octreotide LAR vs. surgery in newly diagnosed patients with acromegaly: a randomized, open-label, multicentre study. *Clin Endocrinol (Oxf)*. 2009;70:757–768.
- Mazziotti G, Floriani I, Bonadonna S, Torri V, Chanson P, Giustina A. Effects of somatostatin analogs on glucose homeostasis: a meta-analysis of acromegaly studies. *J Clin Endocrinol Metab*. 2009;94:1500–1508.
- Chanson P, Borson-Chazot F, Kuhn JM, Blumberg J, Maisonobe P, Delemer B. Control of IGF-I levels with titrated dosing of lanreotide Autogel over 48 weeks in patients with acromegaly. *Clin Endocrinol (Oxf)*. 2008;69:299–305.
- Melmed S, Cook D, Schopohl J, Goth MI, Lam KS, Marek J. Rapid and sustained reduction of serum growth hormone and insulin-like growth factor-1 in patients with acromegaly receiving lanreotide Autogel therapy: a randomized, placebo-controlled, multicenter study with a 52 week open extension. *Pituitary*. 2010;13:18–28.
- Bronstein M, Sheppard M, Freda P, Gu F, Shen C-C, Gadelha M, Fleseriu M, Hermosillo Resendiz K, Ruffin M, Chen Y, Colao A. Pasireotide LAR is significantly more effective than octreotide LAR at providing biochemical control in patients with acromegaly: results of a 12-month randomized, double-blind, multicenter, phase III study. *Endocr Rev*. 2012;33:OR49–3.
- Bahurel-Barrera H, Assie G, Silvera S, Bertagna X, Coste J, Legmann P. Inter- and intra-observer variability in detection and progression assessment with MRI of microadenoma in Cushing’s disease patients followed up after bilateral adrenalectomy. *Pituitary*. 2008;11:263–269.