Efficacy and safety of switching to pasireotide in acromegaly patients controlled with pegvisomant and somatostatin analogues: PAPE extension study.

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ABSTRACT

Objective: to assess the efficacy and safety after 48 weeks of treatment with pasireotide long-acting-release (PAS-LAR) alone or in combination with pegvisomant in patients with acromegaly. In addition, we assessed the relation between insulin secretion and pasireotide-induced hyperglycemia.

Design: The PAPE extension study is a prospective follow-up study until 48 weeks after the core study of 24 weeks.

Methods: 59 out of 61 patients entered the extension study. Efficacy was defined as the percentage of patients achieving IGF-I normalization (≤ 1.2 x the Upper Limit of Normal (ULN)) at 48-weeks through protocol-based adjustment of pegvisomant and PAS-LAR doses. At baseline, insulin secretion was assessed by an oral glucose tolerance test (OGTT).

Results: At the end of the study median IGF-I was 0.98 x ULN, and 77% of patients achieved normal IGF-I levels with a mean pegvisomant dose of 64 mg/week, and an overall cumulative pegvisomant dose reduction of 52%. Frequency of diabetes mellitus increased from 68% at 24 weeks to 77% at 48 weeks, and 9 patients discontinued PAS-LAR treatment, mainly because of severe hyperglycemia. Pasireotide-induced hyperglycemia was inversely correlated with baseline insulin secretion ($r = -0.37$, $P < 0.005$).

Conclusions: PAS-LAR normalizes IGF-I levels in most acromegaly patients, with a fifty percent pegvisomant-sparing effect. However, PAS-LAR treatment coincided with a high incidence of diabetes mellitus. The risk for developing diabetes during PAS-LAR treatment seems inversely related to insulin secretion at baseline.

INTRODUCTION

Acromegaly is a systemic condition most commonly caused by pituitary adenomas secreting excess growth hormone (GH) and insulin-like growth factor I (IGF-I) levels, leading to increased mortality and morbidity (1). The main goals of the present treatment for acromegaly are to normalize GH and IGF-I levels, reduce or control tumor size, and to improve quality of life (QoL) and multisystem comorbidities (2, 3).

First-generation long-acting somatostatin analogues (LA-SSAs) are considered the mainstay medical treatment of acromegaly. LA-SSAs suppress GH secretion by preferential binding to somatostatin receptor subtype 2a (SST_{2a}). LA-SSAs have favorable safety profiles and a clinically neutral impact on glucose homeostasis (4, 5).
In clinical practice only about 40% of patients treated with monotherapy LA-SSAs achieve biochemical normalization of GH and IGF-I. Therefore, most patients are refractory to treatment with LA-SSAs, and require additional therapies (6-8).

The competitive GH receptor antagonist pegvisomant (PEGV) is currently the most effective treatment to normalize circulating IGF-I levels in acromegaly, as monotherapy or in combination with LA-SSA (9-14). PEGV has as advantage that it improves insulin sensitivity (15-18). In combination with LA-SSA a lower necessary PEGV dose is required to normalize IGF-I levels in acromegaly than compared with PEGV monotherapy (19, 20).

Pasireotide long-acting release (PAS-LAR) is a second-generation multi-receptor somatostatin analogue designed with a broader binding somatostatin receptor profile than first-generation LA-SSAs (21). PAS-LAR has been shown to provide superior clinical efficacy over LA-SSA in treatment-naïve acromegaly patients and in patients inadequately controlled with LA-SSAs (22, 23). PAS-LAR has a similar safety profile to LA-SSAs, with the exception of a higher incidence of hyperglycemia, and this incidence has been reported to occur in about 60-88% of patients during treatment with PAS-LAR (22-24). Recently, we have reported the efficacy and safety of PAS-LAR alone or in combination with PEGV in acromegaly patients up to 24 weeks treatment (PAPE core study) (24). Switching to PAS-LAR treatment resulted in a 66% reduction in PEGV dose, but was simultaneously associated with a higher incidence of diabetes mellitus. Here, we present the long-term 48 weeks results of the efficacy and safety of PAS-LAR alone or in combination with PEGV treatment in acromegaly.

SUBJECTS AND METHODS

Study design

The PAPE study is a prospective, open-label, single-centre study in acromegaly patients, designed to assess the efficacy and safety of PAS-LAR alone, or in combination with PEGV (24) (ClinicalTrials.gov, number NCT02668172). The primary endpoint was to assess efficacy at 24 weeks. Here, we report the secondary endpoints: efficacy and safety from 24 up to 48 weeks. During this follow-up, the goal was to achieve IGF-I normalization (IGF-I ≤ 1.2 x ULN) through protocol-based dose titration of PEGV and PAS-LAR (Figure 1). In the core study two groups of patients continued in the extension phase: the PAS-LAR 60 mg monotherapy group and the PAS-LAR/PEGV combination group (24).

Patients in the PAS-LAR 60 mg monotherapy group continued with the 60 mg dose until 48 weeks, unless their IGF-I levels decreased below the median sex- and age adjusted IGF-I normal limits. In that case, the PAS-LAR dose was decreased to 40 mg every 4 weeks. Subsequently, if after at least two PAS-LAR 40 mg injections, IGF-I levels remained suppressed (below the median IGF-I), the PAS-LAR dose was further

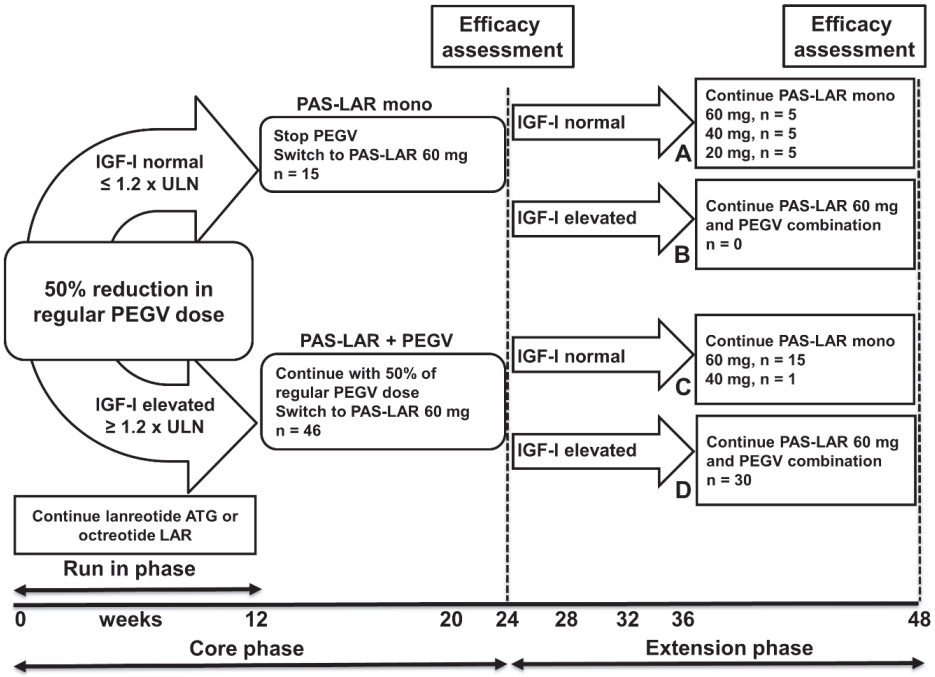

Figure 1. PAPE study design. The number of participants in each study arm were based on the intention-to-treat population (n = 61).

decreased to 20 mg (ARM A). However, if IGF-I became elevated (≥ 1.2 x ULN) during PAS-LAR monotherapy, PEGV treatment was restarted in the same dose of the run-in phase (ARM B).

Patients in the PAS-LAR/PEGV combination group who achieved IGF-I normalization at 24 weeks using PEGV doses ≤ 80 mg/week, were after 24 weeks instructed to discontinue PEGV treatment and to continue with PAS-LAR 60 mg monotherapy during follow-up (ARM C) (Figure 1). In patients using PEGV doses higher than 80 mg/week, the dose was reduced by 50% every 4 weeks until their IGF-I was normalized (≤ 1.2 x ULN). If IGF-I levels became elevated above 1.2 x ULN during combination treatment, the PEGV dose was further increased every 4 weeks depending on the measured IGF-I levels after adjusting treatment (ARM D):

- IGF-I between 1.2–1.5× ULN, the PEGV dose was increased by 20%.
- IGF-I between 1.5–1.7× ULN, the PEGV dose was increased by 30%.
- IGF-I between 1.7–2.0× ULN, the PEGV dose was increased by 40%.
- IGF-I ≥ 2.0 x ULN, the PEGV dose was increased by 50%.

If monitoring revealed glucose levels in the diabetic range according to the American Diabetes Association (ADA) criteria (25), metformin was initiated as first-line treatment option. If glycemic control was not achieved after metformin treatment, a DPP-4 inhibitor was added as second choice. When patients still did not achieve normoglycemia they were switched to a treatment with sulfonylureas or GLP-1 receptor analogues. Finally, insulin was started in patients intolerant to GLP-I analogues or when glycemic control was not achievable with GLP-1 analogues. All patients received intensive blood glucose monitoring after start of treatment. Patients who developed rapid hyperglycemia received insulin treatment. The PAPE study was approved by the medical ethics committee of the Erasmus University Medical Centre, and all patients provided written informed consent.

Patients

After 24 weeks, 59 out of 61 patients entered the extension phase (supplemental figure 1). The in- and exclusion criteria have been reported previously (24). Briefly, key inclusion criteria were patients with good metabolic control of acromegaly (IGF-I ≤ 1.2 x ULN) for at least 6 months combination treatment of weekly PEGV and maximum doses of first-generation LA-SSAs. Key exclusion criteria were pituitary surgery or radiotherapy within the 6 months prior to study entry and poorly controlled diabetes mellitus, defined as HbA1c ≥ 9.0%.

Study assessments

Laboratory measurements were described previously in the core study (24). Safety assessments included: assessment of heart function by electrocardiogram at baseline, 24 weeks, and 48 weeks. The severity of adverse events (AEs) was evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) (26). At baseline after an overnight fast, a standardized oral glucose tolerance test (OGTT) was performed with 1.75 g glucose per kg body weight (maximum 75 g while simultaneously glucose and insulin levels were measured at t = −15 minutes, t = 0 min., t = 30 min., t = 60 min., t = 90 min., and t = 120 min. (27). We used published indexes of ß-cell function to estimate the first phase and second phase insulin secretion during the OGTT (28).

Outcomes

The secondary efficacy endpoints were descriptive in nature and were based on the intention-to-treat population. For patients who discontinued the study before 48 weeks imputation based on the principle of last observation carried forward (LOCF) was used. Main efficacy endpoint was defined as the percentage of responders at 48 weeks in the intention-to-treat population, and in each treatment arm (PAS-LAR monotherapy and PAS-LAR/PEGV combination treatment), with an exact 95% confidence interval (95% CI). Response was defined as IGF-I ≤ 1.2 x ULN. Other descriptive endpoints for efficacy included the percentage of patients who could stop PEGV treatment after 48 weeks, and the percentage cumulative PEGV dose reduction, which was calculated as the sum of all administered PEGV doses of all patients at 48 weeks compared with baseline. As reported previously (24), secondary endpoints for safety included the incidence of hyperglycemia and diabetes mellitus, vital signs, and electrocardiogram.

Statistical analyses were performed using SPSS software (version 24 for Windows; SPSS Inc., Chicago, Illinois) and GraphPad Prism® Version 6.04 (GraphPad Software, San Diego, USA). Categorical data were represented as observed frequencies and percentages. Continuous data were represented as mean and 95% CI or median and range. The Kolmogorov-Smirnov and the Shapiro-Wilk test were used to test normality of variables. If assumption of normality was met, the paired t-test was used. For non-normally distributed variables the Wilcoxon signed-rank test was used. For data that did not meet the criteria for normality, logarithmic transformation was applied. Correlation analyses were performed using the Pearson correlation test. *P*-values of < 0.05 were considered statistically significant.

RESULTS

Efficacy

The baseline characteristics of the study population have been published before in the core study (24). The percentage of patients achieving IGF-I and GH normalization are shown in table 1.

Table 1. Percentage of patients achieving normal IGF-I and GH levels during the study

	Baseline	12 weeks	24 weeks	48 weeks
IGF-I ≤ 1.2 x ULN				
Overall	53/61 (86.9%)	15/61 (24.6%)	45/61 (73.8%)*	47/61 (77.0%)*
PAS-LAR monotherapy	14/15 (93.3%)	15/15 (100%)	14/15 (93.3%)	14/15 (93.3%)*
PAS-LAR/PEGV combination	39/46 (84.8%)	0/46 (0%)	31/46 (67.4%)	33/46 (71.7%)*
GH ≤ 2.5 µg/l				
Overall	23/61 (37.7%)	29/61 (47.5%)	41/61 (67.2%)*	41/61 (67.2%)*
PAS-LAR monotherapy	10/15 (66.7%)	11/15 (73.3%)	15/15 (100%)*	14/15 (93.3%)*

*Data based on last observation carried forward (LOCF).

At 48 weeks, 77.0% of patients had IGF-I levels within the reference range with a mean IGF-I of 0.98 x ULN (95% CI 0.90 – 1.06) (table 1 and figure 2A). Stratified by treatment group; 93.3% of patients using PAS-LAR monotherapy achieved IGF-I normalization at 24 weeks, which was sustained at 48 weeks. While 67.4% of patients using PAS-LAR and PEGV combination therapy achieved IGF-I normalization at 24 weeks, which increased to 71.7% at 48 weeks. Overall after 48 weeks, 12 of the 14 non-controlled patients had IGF-I levels between 1.2–1.4× ULN. During the extension phase the mean PEGV dose had to be increased from 47 mg/week (95% CI 21–73) to 64 mg/week (95% CI 33–95). At 48 weeks the cumulative reduction in PEGV dose decreased to 52.0% after 48 weeks compared with baseline, and 50.8% (31/61) of patients were off PEGV treatment at the end of study.

In figure 2B GH serum levels are shown stratified by treatment group. Patients in the PAS-LAR monotherapy group had significantly lower baseline GH levels (GH 2.5 µg/l (95% CI 0.8 – 4.2)) than patients in the PAS-LAR/PEGV combination group (GH 11.5 µg/l (95% CI 5.5 – 17.4)). Both groups showed a significant decrease in GH serum levels after initiation of PAS-LAR treatment, with subsequently stable suppressed GH levels in the PAS-LAR monotherapy group until 48 weeks.

The 15 patients in the PAS-LAR monotherapy group remained controlled throughout the study (Figure 1). In fact, in 10 patients (66.7%) a dose reduction was possible to PAS-LAR 40 mg and 20 mg (ARM A). No patients had to restart PEGV treatment

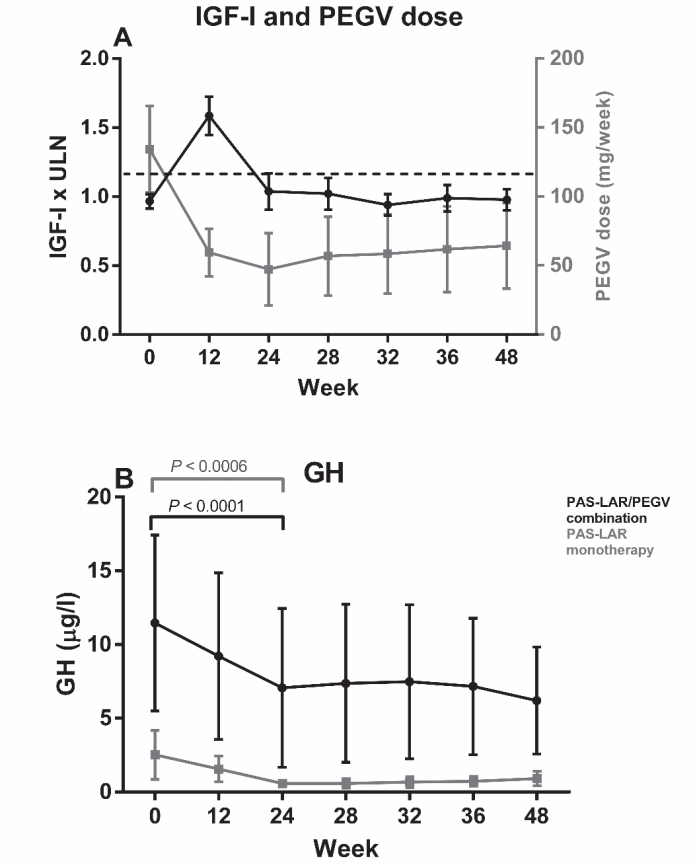

Figure 2. IGF-I serum levels and the weekly PEGV dose (2A). Dotted straight black line reflects the IGF-I 1.2 x ULN cut-off. GH serum levels (2B) are depicted in the PAS-LAR monotherapy group in grey and in the combination PAS-LAR/PEGV group in black. Data are expressed as mean (95% CI).

in this group (ARM B). In patients using PAS-LAR and PEGV combination therapy, 16 (34.8%) patients switched to PAS-LAR monotherapy during the extension phase, and in one patient a further dose reduction was possible to PAS-LAR 40 mg (ARM C). The remaining 30 patients required PAS-LAR and PEGV combination treatment, of which 13 patients (21.3%) achieved less than 25% PEGV dose reduction (ARM D). In 12 patients (19.7%) between 25 to 50% PEGV dose reduction was achieved, and in 5 patients (8.2%) a reduction of more than 50% could be attained.

Pasireotide LAR monotherapy

Among the 15 patients that were switched to PAS-LAR 60 mg monotherapy at 12 weeks, 10 patients had a progressive decline in IGF-I during follow-up, with levels dropping below the median IGF-I reference range. In these patients, the PAS-LAR dose

was therefore reduced to 40 mg every 4 weeks. Subsequently, in five of those patients the dose was further decreased to 20 mg. At baseline, these patients used a relatively low median PEGV dose of 60 mg/week. In one additional patient who could stop PEGV after 24 weeks, the PAS-LAR could be further reduced to 40 mg during the follow-up.

Partial and non-responders

We observed that 10 patients on combination treatment who achieved IGF-I normalization after 24 weeks and therefore could stop PEGV, had to restart PEGV treatment during follow-up because their IGF-I levels again increased above 1.2 x ULN (arm D). One patient required a higher dose of PEGV after 48 weeks (100 mg/week) than at baseline (80 mg/week). In three patients using very high doses of PEGV (at baseline (mean baseline PEGV dose 580 mg/week), we could not attain a significant PEGV dose reduction (mean PEGV dose was remained 560 mg/week after 48 weeks).

Safety

Hyperglycemia and diabetes mellitus

The most common AE related to PAS-LAR treatment was hyperglycemia, and mainly recorded during the core study (24). In total 60 out of 61 patients had a hyperglycemia-related AE, of which 47 (77.0%) were grade 1 and 2 (table 2). During the extension study grade 3 hyperglycemia was recorded in two patients, while no patients had a grade 4 hyperglycemia-related AE.

Table 2. Adverse events regardless of study-drug relationship (>5%) until 48 weeks

Adverse events	Grade 1/2	Grades 3/4
Hyperglycemia	48 (78.7%)	14 (23.0%)
Diarrhoea	21 (34.4%)	0
Fatigue	19 (31.1%)	0
Arthralgia	16 (26.2%)	0
Myalgia	16 (26.2%)	0
Headache	13 (21.3%)	0
Pain injection site	12 (19.7%)	0
Dizziness	11 (18.0%)	0
Hypoglycemia	9 (14.8%)	0
Arthralgia	16 (26.2%)	0
Nausea	7 (11.5%)	0
Alopecia	5 (8.2%)	0
Abdominal pain	4 (6.6%)	0

At 48 weeks, diabetes of most patients was managed with a combination of metformin and a DPP-4 inhibitor. 73.8% patients required at least one antidiabetic medication. Between 24 and 48 weeks, five patients developed mild diabetes which required additional treatment with metformin alone or combined with a DPP-4 inhibitor. Due to hypoglycemic symptoms related to sulfonylurea treatment, four patients were switched to a GLP-I analogue (supplementary table 1).

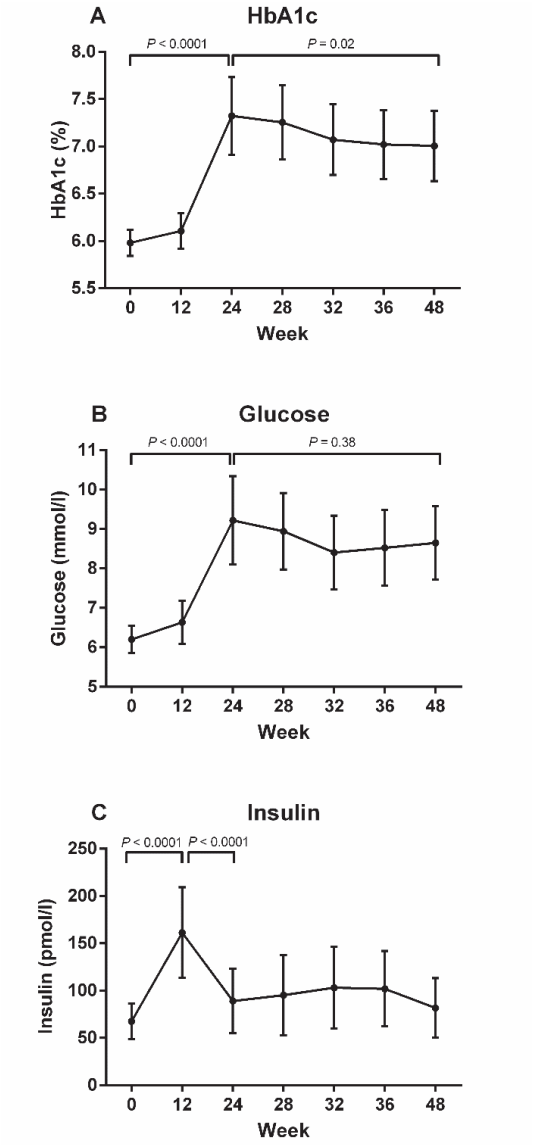

Figure 3. HbA1c (3A), fasting plasma glucose (3B), fasting plasma insulin (3C) concentrations are expressed as mean (95% CI).

During the extension phase the incidence of diabetes mellitus increased slightly from 68.9% to 77.0%. Mean HbA1c and fasting plasma glucose levels increased significantly after PAS-LAR treatment, but decreased slightly after initiation of antidiabetic treatment during follow-up (Figure 3A and 3B).

Mean HbA1c concentrations increased from 6.0% (5.8 – 6.1) at baseline to 7.3% (6.9 – 7.7) after 24 weeks, but decreased slightly to 7.0% (6.6 – 7.4) after 48 weeks. Stratified by treatment group; in the PAS-LAR monotherapy group, mean HbA1c increased from 6.0% (95% CI 5.5– 6.5%) at baseline to 7.1% (95% CI 6.3 – 7.9%) at 24 weeks, and decreased to 6.8% (95% CI 6.0 – 7.7%) at 48 weeks. In the combination treatment group, HbA1c levels showed a similar pattern, increasing from 6.0% (95% CI 5.9 – 6.1%) at baseline to 7.4% (95% CI 6.9 – 7.9%) at 24 weeks, and decreasing to 7.1% (95% CI 6.6 – 7.5%) after 48 weeks. No significant difference was observed in HbA1c levels between patients using PAS-LAR monotherapy and combination treatment at baseline (P = 0.36), 24 weeks (P = 0.72), and after 48 weeks (P = 0.26).

Fasting plasma glucose levels followed a similar profile with 6.2 mmol/l (5.8 – 6.5) at baseline to 9.2 mmol/l (8.1 – 10.3) at 24 weeks, and 8.7 mmol/l (95% CI 7.7 – 9.6) after 48 weeks.

Excluding patients that were receiving insulin therapy at baseline (n = 3), fasting insulin levels rose from 67.5 mmol/l (95% CI 48.8 – 86.2) at baseline to 161.4 mmol/l (95% CI 113.5 – 209.3) after 12 weeks. Insulin levels dropped significantly after initiation of PAS-LAR treatment. After 24 weeks, fasting insulin levels decreased significantly to 89.0 mmol/l (95% CI 54.9 – 123.1). We observed a significant inverse relationship between the insulin area under the curve (AUC) during OGTT at baseline and the increase in HbA1c levels between baseline and 24 weeks (r = −0.30, P = 0.03). The estimates for ß-cell function showed a stronger correlation with the increase in HbA1c; first phase insulin secretion (Stumvoll index, r = −0.37, P = 0.005) and second phase insulin secretion (r = −0.38, P = 0.004).

Non-hyperglycemia related adverse events

After hyperglycemia, diarrhea (34.4%), and fatigue (31.1%) were the most common AEs (table 2). Headache was reported by 13 (21.3%) patients and most frequently experienced in the first week after initiation of PAS-LAR treatment, but resolved later after consecutive injections. One patient was diagnosed with sick sinus syndrome during PAS-LAR treatment. After discontinuation of PAS-LAR this AE resolved and she was successfully switched to PEGV monotherapy. Slightly more patients developed diarrhea during the extension phase (n = 21) compared to core phase of the study (n = 18).

DISCUSSION

The results of this clinical study suggest that the efficacy of PAS-LAR was long-term sustained, as after 48 weeks, 77% of patients achieved IGF-I normalization while a cumulative PEGV dose reduction of 54.2% could be achieved, reconfirming the PEGV sparing effect of PAS-LAR. Hyperglycemia was the most important and most common adverse event during the follow-up until 48 weeks. The incidence of diabetes mellitus increased from 68.9% at 24 weeks to 77% at 48 weeks.

It is important to note that the extension phase of our study was not designed to detect a statistically significant difference between the treatment groups after 48 weeks, but it was undertaken to optimally titrate the PEGV and PAS-LAR dose to achieve control of IGF-I within the reference ranges. To achieve IGF-I normalization, we used a systematic PEGV and PAS-LAR dose titration protocol.

We observed that PAS-LAR elicited a wide range of clinical response in this study, ranging from patients that were very sensitive to very resistant. On one hand of the spectrum, patients could stop PEGV treatment and switch to a lower PAS-LAR dose of 40 mg and even 20 mg/month. This IGF-I over-suppression to below median range during PAS-LAR treatment has also recently been described in two patients with acromegaly that were uncontrolled with octreotide LAR 20-30 mg/month and, after crossover to PAS-LAR 40 mg/month, achieved suppressed IGF-I levels below the normal range (29). Conversely, on the other end of the spectrum, a number of patients achieved less than 25% PEGV dose reduction. This heterogeneous clinical response to PAS-LAR may be explained by the inclusion of a heterogeneous acromegaly population with a large variation in baseline PEGV dose.

It is unlikely that a carry-over effect of first-generation LA-SSAs had a large impact in our study on the ultimately achieved PEGV dose reduction after 48 weeks. Nevertheless, it is possible that the initial response in IGF-I normalization of the 10 patients who had to restart PEGV treatment during the extension phase was related to a disappearing carry-over effect of the first-generation LA-SSAs.

It is not clear why the three patients using the highest doses of PEGV could not reduce their PEGV dose after switching to PAS-LAR. Theoretically, one could hypothesize that patients using combination treatment of LA-SSA and high doses PEGV have relatively low SST_2 and high SST_5 expression compared to patients using LA-SSA monotherapy, and that therefore these patients would be good responders to PAS-LAR treatment. It remains to be determined whether SST_2 or SST_5 protein expression is responsible

for driving the response to PAS-LAR treatment in our study. Furthermore, it is still unknown how PEGV is metabolized in humans, and a wide inter-individual variation in PEGV serum levels have been observed when the same doses were administered (17, 30-32). PEGV serum levels are increased during combination treatment of LA-SSA and PEGV, but it is unknown whether this also occurs during combination treatment with PAS-LAR. Therefore, theoretically patients using high doses of PEGV may benefit less from switching to PAS-LAR.

The insulin-suppressive effect of PAS-LAR may be related to the degree of pasireotide-induced hyperglycemia, as insulin AUC and (more pronounced) baseline ß-cell function were inversely correlated with the observed increase in HbA1c between baseline and 24 weeks. These findings indicate that the lower the insulin secretion is at baseline, the greater will be the risk of pasireotide-induced hyperglycemia during follow-up, even in patients with well-controlled diabetes at baseline. Therefore, besides pre-treatment baseline glucose and HbA1c levels (33), pancreatic ß-cell function is probably an additional and independent risk factor of pasireotide-induced hyperglycemia. Patients using PAS-LAR and PEGV combination treatment did not have a lower HBA1c level than patients using PAS-LAR monotherapy. This observation suggests that the PEGV insulin sensitizing effect does not work in pasireotide-induced hyperglycemia (33).

Our results show that PAS-LAR treatment reduces IGF-I and GH levels after two injections which parallels the reduction in insulin levels which also occurs after two injections, suggesting that the early onset effect of PAS-LAR on IGF-I reduction may be (partly) mediated by suppressing insulin secretion. This is further supported by the observation that although the effects of PAS-LAR on GH suppression were superimposable compared with octreotide LAR, PAS-LAR treatment induced a greater suppression of IGF-I (22).

CONCLUSIONS

PAS-LAR monotherapy or in combination with PEGV normalizes IGF-I levels in most acromegaly patients despite an about fifty percent reduction in cumulative PEGV doses. However PAS-LAR therapy coincides with a high incidence of diabetes mellitus, and the risk for developing diabetes during PAS-LAR therapy seems inversely related to insulin secretion at baseline.

Declaration of interests

AM received a speaker fee from Novartis Pharma. AVDL is a consultant for Novartis Pharma, Pfizer International, and received grants from Novartis Pharma, Ipsen Pharma International and Pfizer International. SN received research and speakers' fee grants from Ipsen Pharma International, Novartis Pharma, Pfizer International and consulting fee from Ipsen Pharma International. The other authors have nothing to declare.

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Author contributions

AM, AVDL, and SN conceived and designed the study. AM was responsible for data management and statistical analyses after discussion with all authors. All authors participated in data interpretation and in writing of the report.

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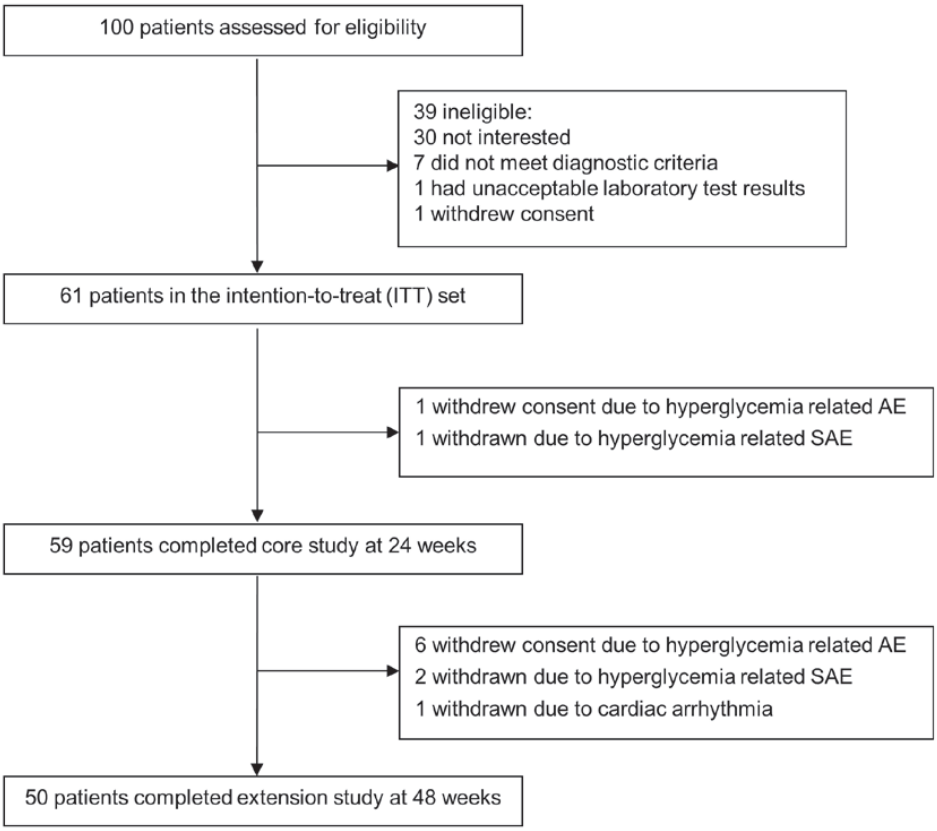
APPENDIX



Supplemental figure 1. Trial profile. AE = Adverse Event, SAE = Serious Adverse Events

Supplemental table 1. Antidiabetic medications initiated after pasireotide LAR initiation.

Antidiabetic medication	Baseline	24 weeks	48 weeks
None	46 (75.4%)	19 (31.1%)	16 (26.3%)
Metformin	15 (24.6%)	19 (31.1%)	25 (41.0%)
DPP4 inhibitors	0	14 (23.0%)	17 (27.9%)
Sulfonylureas	3 (4.9%)	12 (19.7%)	8 (13.1%)
Insulin	3 (4.9%)	6 (9.8%)	6 (9.8%)
GLP-I analogues	2 (3.3%)	3 (4.9%)	7 (11.5%)
Thiazolidinediones	1 (1.6%)	1 (1.6%)	1 (1.6%)

Patients may have taken more than one antidiabetic medication. Data based on last observation carried forward (LOCF).