Pasireotide versus continued treatment with octreotide or lanreotide in patients with inadequately controlled acromegaly (PAOLA): a randomised, phase 3 trial

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Summary
Background Many patients with acromegaly do not achieve biochemical control despite receiving high doses of the first-generation somatostatin analogues octreotide or lanreotide. In the PAOLA trial, we aimed to assess the efficacy and safety of two different doses of the somatostatin analogue pasireotide long-acting release compared with active control (octreotide or lanreotide) in patients with inadequately controlled acromegaly.

Methods In a multicentre, randomised, phase 3 trial, we enrolled eligible patients aged 18 years or older with acromegaly who were inadequately controlled (5-point, 2h mean growth hormone concentration >2.5 μg/L and insulin-like growth factor 1 [IGF-1] concentration >1.3 times the upper normal limit) and had received 30 mg octreotide long-acting repeatable or 120 mg lanreotide (Somatuline Autogel; Ipsen, UK) as monotherapy for 6 months or longer. We randomly assigned patients in a 1:1:1 ratio with an interactive voice-web response system to receive 40 mg pasireotide long-acting release once every 28 days for 24 weeks, 60 mg pasireotide long-acting release once every 28 days for 24 weeks, or continued treatment with octreotide or lanreotide (active control). Patients were stratified according to previous treatment (octreotide or lanreotide) and growth hormone concentrations at screening (2.5–10 μg/L and >10 μg/L). Patients and study investigators were not masked to study drug assignment but were masked to pasireotide dose allocation. The primary endpoint was number of patients achieving biochemical control defined as mean growth hormone concentration less than 2.5 μg/L and normalised IGF-1 concentration. Efficacy analyses were based on intention to treat. This trial is registered with ClinicalTrials.gov, number NCT01137682.

Findings Between Dec 17, 2010, and Aug 6, 2012, 198 patients were enrolled and randomly assigned to pasireotide 40 mg (n=65), pasireotide 60 mg (n=65), or active control (n=68) groups. At 24 weeks, ten (15%) patients in the pasireotide 40 mg group and 13 (20%) patients in the pasireotide 60 mg group achieved biochemical control, compared with no patients in the active control group (absolute difference from control group 15.4%, 95% CI 7.6–26.5, p=0.0006 for pasireotide 40 mg group and 13 (20%) patients in the pasireotide 60 mg group achieved biochemical control, compared with no patients in the active control group (absolute difference from control group 15.4%, 95% CI 7.6–26.5, p=0.0006 for pasireotide 40 mg group but 13 (20%) patients in the pasireotide 60 mg group achieved biochemical control, compared with no patients in the active control group (absolute difference from control group 15.4%, 95% CI 7.6–26.5, p=0.0006 for pasireotide 40 mg group). The most common adverse events were hyperglycaemia (21 [33%] for treatment with 40 mg pasireotide, 19 [31%] with 60 mg pasireotide, and nine [14%] with active control), diabetes (13 [21%], 16 [26%], and five [8%]), and diarrhoea (ten [16%], 12 [19%], and three [5%]); most were grade 1 or 2 in severity. Serious adverse events were reported in six (10%) patients in the pasireotide 40 mg group, two (3%) in the pasireotide 60 mg group, and three (5%) in the active control group.

Interpretation Pasireotide provides superior efficacy compared with continued treatment with octreotide or lanreotide, and could become the new standard pituitary-directed treatment in patients with acromegaly who are inadequately controlled using first-generation somatostatin analogues.

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Introduction Acromegaly is a rare, serious disorder that if uncontrolled is associated with substantial morbidity and mortality. To reduce morbidity and normalise life expectancy to that of the general population, the key treatment goals are to achieve and maintain control of concentrations of growth hormone and insulin-like growth factor 1 [IGF-1], reduce or stabilise tumour size, preserve pituitary function, and prevent recurrence. The standard medical management of acromegaly is somatostatin analogues octreotide long-acting repeatable or lanreotide Autogel (Ipsen, UK). However, study findings have shown that 20–70% of patients do not achieve adequate biochemical control with these somatostatin analogues, dependent on the patient population and study design. The growth hormone receptor antagonist pegvisomant is used to treat patients with inadequately controlled acromegaly and can normalise IGF-1 concentrations in roughly 60–97% of patients; however, it does not reduce growth hormone concentrations or tumour volume. As such, new treatment options are still needed for patients inadequately controlled with currently available therapies.


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Pasireotide is a multireceptor-targeted somatostatin analogue, which has higher affinity for somatostatin receptor subtype 5 (SST5) and slightly lower affinity for somatostatin receptor subtype 2 (SST2) than have octreotide and lanreotide. These two somatostatin receptors are the most prevalent on somatotroph adenomas. In a randomised, double-blind, phase 3 study in 358 patients with acromegaly who had not previously received pharmaceutical treatment, pasireotide long-acting release (pasireotide-LAR) provided improved biochemical control (mean growth hormone concentration <2.5 μg/L and normalised IGF-1 concentration) compared with octreotide long-acting repeatable (55 of 176 patients <2.5 μg/L and normalised IGF-1 concentration) compared with continued therapy with octreotide long-acting release (pasireotide-LAR) vs active control (continued treatment with either octreotide or lanreotide). These two somatostatin receptor subtype 5 (SST5) and slightly lower affinity for somatostatin receptor subtype 2 (SST2) than have octreotide and lanreotide. These two somatostatin receptors are the most prevalent on somatotroph adenomas.14 In this phase 3 randomised controlled trial, we aimed to assess the efficacy and safety of pasireotide-LAR compared with continued therapy with octreotide long-acting repeatable and lanreotide Autogel in patients with inadequately controlled acromegaly despite previous therapy with first-generation somatostatin analogues.

Methods
Participants
In a prospective, multicentre, randomised, parallel-group, phase 3 study, we enrolled male and female patients aged 18 years or older with inadequately controlled acromegaly (defined as five-point, 2 h mean growth hormone concentration >2.5 μg/L and IGF-1 concentration >1.3 times the sex-adjusted and age-adjusted upper normal limit). Eligible patients had received either 30 mg octreotide long-acting repeatable or 120 mg lanreotide Autogel as monotherapy (ie, the maximum-approved doses at the time of study start in all participating countries except the USA) continuously for 6 months or longer before screening. Patients who had received combination therapy with a growth hormone receptor antagonist or dopamine agonist were eligible, but we required these drugs to have been discontinued at least 8 weeks before screening. Patients could have received previous pituitary surgery. Key exclusion criteria are listed in the appendix. The study was done in accordance with the Declaration of Helsinki, and an independent ethics committee or institutional review board for each study site approved the study protocol. All patients provided written informed consent to participate.

Randomisation and masking
We randomly assigned patients in a 1:1:1 ratio using an interactive voice-web response system to receive one of two doses of pasireotide-LAR (40 mg or 60 mg) or an active control (continued treatment with either octreotide or lanreotide). Randomisation was stratified according to previous treatment (octreotide or lanreotide) and growth hormone concentration at screening (2.5–10 μg/L and >10 μg/L). After signing the informed consent form, each patient was assigned a unique nine-digit patient number by the investigator or their designee. The investigator or staff member then contacted the interactive voice-web response system and provided the requested identifying information to register the patient in the system. The system then assigned a randomisation number to the patient, which was used to link them to a treatment group. If the patient was randomised to one of the two pasireotide-LAR groups, the system specified a unique medication number for the first package of study drug to be dispensed to the patient. Patients, investigators, site staff, monitors, data analysts, and data managers were not masked to study drug allocation (pasireotide-LAR vs active control) but were masked to pasireotide-LAR dose allocation (40 mg vs 60 mg).

Procedures
After a 4-week screening period, patients received 40 mg pasireotide-LAR once every 28 days for 24 weeks, 60 mg pasireotide-LAR once every 28 days for 24 weeks, or continued treatment with 30 mg octreotide long-acting repeatable or 120 mg lanreotide Autogel (active control group). Dose decreases of 20 mg were permitted for tolerability issues in the pasireotide-LAR treatment groups. If a patient receiving octreotide or lanreotide had a severe drug-related adverse event, dose decreases to the next-available lower dose were permitted. Previous dosing was resumed after the tolerability issue had resolved. Further details about data collection are provided in the appendix.

Outcomes
All endpoints were comparisons between each dose of pasireotide-LAR and active control. The two pasireotide-LAR doses were not compared because this was not the objective of the study. The primary endpoint was the proportion of patients achieving biochemical control (mean growth hormone concentration <2.5 μg/L and normalised IGF-1 concentration between the upper and lower limits of normal) at 24 weeks. The key secondary endpoint was the proportion of patients achieving normalised IGF-1 concentration at 24 weeks. Other secondary endpoints were the proportion of patients achieving 5-point, 2 h mean growth hormone concentration >2.5 μg/L, tumour volume reduction of more than 25%, change from baseline in symptoms of acromegaly, and health-related quality of life (assessed with the acromegaly quality of life questionnaire [AcroQoL]). Safety and tolerability were also assessed in each treatment group.

Five-point, 2 h mean growth hormone and IGF-1 concentrations before drug injection were assessed by a central laboratory (Covance, Princeton, NJ, USA and Quest Diagnostics, Madison, NJ, USA) at baseline and at weeks 12 and 24. We present IGF-1 concentrations based on the upper limit of normal (the IGF-1 value divided by the age-specific and sex-specific upper normal limit). The

See Online for appendix
appendix details the growth hormone and IGF-1 assays used, and further details about assessments of tumour volume, acromegaly symptoms, health-related quality of life, safety, and tolerability.

**Statistical analyses**

We calculated the sample size based on the primary endpoint. We postulated that the response rates at week 24 for pasireotide-LAR (40 mg and 60 mg separately) would be 25%, and the response rate at week 24 for the active control group would be 5%. A sample size (calculated using simulation) of 62 patients per treatment group would achieve 90% power to detect a difference of 20% in response rate between active control (5%) and pasireotide-LAR groups (25%), with a family-wise error rate of 2.5% (one-sided). We did efficacy analyses on the full analysis set, which comprised all randomly assigned patients; participants were analysed by intention to treat according to the study drug they were assigned at randomisation and randomisation stratum. The safety analysis set included all patients who received at least one dose of study drug and had a valid post-baseline safety assessment.

We tested the null hypotheses for the primary endpoint and for the key secondary endpoint using an exact logistic regression model that adjusted for the randomisation stratification factors. We tested the four null hypotheses using the gatekeeping procedure based on the graphical approach proposed by Bretz and colleagues. Additionally, we applied the trimmed version of the weighted Simes test to relax the condition of positive-regression-dependent test statistics. For the statistical analyses we used SAS software, version 9.3. Additional statistical methods are described in the appendix.

This study is registered with ClinicalTrials.gov, number NCT01137682.

**Role of the funding source**

The study sponsor designed the trial in collaboration with several investigators, provided funding and organisational support, collected data, did the analyses, had a role in data interpretation, and had a role in writing of the report. The first draft was prepared by a medical writer funded by Novartis Pharmaceuticals. All authors had access to study data, made the decision to submit the manuscript for publication, and vouch for
the accuracy and completeness of the data and for the fidelity of the study to the protocol. The corresponding author had unrestricted access to raw study data and had final responsibility for the decision to submit for publication.

**Results**

Between Dec 17, 2010, and Aug 6, 2012, we enrolled 198 patients from 51 centres in 18 countries and randomly assigned them to receive 40 mg pasireotide-LAR (n=65) once every 28 days, 60 mg pasireotide-LAR (n=65) once every 28 days, or active control (n=68); these patients comprised the full analysis set (figure 1). Table 1 shows patient demographics, characteristics, and disease history at baseline. Two-thirds of patients (132 of 198) had previously received surgery, 27 patients had previously received pegvisomant (seven [11%] in the pasireotide-LAR 40 mg group, ten [15%] in the pasireotide-LAR 60 mg group, and ten [15%] in the active control group), and 64 had previously received cabergoline (21 [32%] in the pasireotide-LAR 40 mg group, 21 [32%] in the pasireotide-LAR 60 mg group, and 22 [32%] in the active control group), either alone or in combination with a somatostatin analogue. 47 (72%) patients in the pasireotide-LAR 40 mg group, 39 (60%) in the pasireotide-LAR 60 mg group, and 47 (69%) in the active control group had diabetes at baseline, and ten (15%), 13 (20%), and 18 (27%) had prediabetes at baseline (definitions of diabetes and prediabetes are provided in the appendix).

Biochemical control (5-point, 2 h mean growth hormone concentration less than 2·5 μg/L and normalised IGF-1 concentrations at 24 weeks) was achieved by ten (15%) patients in the pasireotide-LAR 40 mg group and 13 (20%) patients in the pasireotide-LAR 60 mg group; no patients receiving active control achieved biochemical control (absolute difference between 40 mg group and active control group 15·4%, 95% CI 7·6 to 26·5, p=0·0006; absolute difference between 60 mg group and active control group 20·0%, 11·1 to 31·8, p<0·0001). One additional patient in the pasireotide-LAR 60 mg group had mean growth hormone concentration less than 2·5 μg/L but IGF-1 concentration below the lower limit of normal, so was not recorded as a responder for the primary efficacy endpoint. Biochemical control rates according to baseline growth hormone concentrations are provided in the appendix.

IGF-1 normalisation was achieved by 16 (25%) patients receiving pasireotide-LAR 40 mg and 17 (26%) patients receiving pasireotide-LAR 60 mg at 24 weeks; no patients receiving active control achieved normal IGF-1 concentrations (pasireotide-LAR 40 mg group absolute difference 24·6%, 95% CI 14·8 to 36·9, p=0·0006; pasireotide-LAR 60 mg group absolute difference 26·2%, 16·0 to 38·5, p<0·0001). Mean IGF-1 values (times upper limit of normal) decreased from baseline to week 12 and then remained stable until week 24 in both pasireotide-LAR treatment groups; values remained close to baseline in the active control group (figure 2). Mean percentage change in IGF-1 values at week 24 was −28·0% (95% CI −37·1 to −18·9) in the pasireotide-LAR 40 mg group, −38·6% (−47·3 to −29·9) in the pasireotide-LAR 60 mg group, and −7·2% (−14·2 to −0·2) in the active control group.

23 (35%) patients in the pasireotide-LAR 40 mg group, 28 (43%) patients in the pasireotide-LAR 60 mg group, and nine (13%) patients in the active control group had mean growth hormone concentrations less than 2·5 μg/L at week 24 (absolute difference between 40 mg group and active control group 22·1%, 95% CI 6·3 to 36·6, p=0·0024 [p value given for exploratory purposes]; absolute difference between 60 mg group and active control group 30·9%, 95% CI 14·8 to 47·1, p<0·0001). One additional patient in the pasireotide-LAR 60 mg group had mean growth hormone concentration less than 2·5 μg/L but IGF-1 concentration below the lower limit of normal, so was not recorded as a responder for the primary efficacy endpoint.
control group 29·8%, 95% CI 12·9 to 44·2, p=0·0001 [exploratory]; figure 3). Mean growth hormone concentrations decreased from baseline to week 12 and remained stable until week 24 in both pasireotide-LAR groups; mean concentrations slightly decreased in the active control group (figure 2). Mean percentage change in growth hormone concentrations between baseline and week 24 was –23·1% in the pasireotide-LAR 40 mg group (95% CI –47·7 to 1·5), –50·9% in the pasireotide-LAR 60 mg group (–61·8 to –39·9), and –3·2% in the active control group (–22·5 to 16·2).

More patients receiving 40 mg pasireotide-LAR (12 patients [18·5%]) and 60 mg pasireotide-LAR (seven patients [10·8%]) had tumour volume reduction of more than 25% than did those in the active control group (one patient [1·5%]; figure 3).

We noted more improvements in acromegaly symptom scores in patients given pasireotide-LAR than in patients given active control, and patients in all treatment groups had improvements in AcroQoL score (appendix).

Seven patients were excluded from the safety analysis set (figure 1). 58 (92%) patients receiving 40 mg pasireotide-LAR, 53 (85%) patients receiving 60 mg pasireotide-LAR, and 49 (74%) patients receiving active control had at least one adverse event. The most common adverse events were hyperglycaemia, diabetes, and diarrhoea, which we noted more often with pasireotide-LAR treatment than with active control; most were of mild-to-moderate severity (table 2). The most common adverse events judged to be related to study drug and adverse events of special interest are provided in the appendix. Serious adverse events were reported in six patients (10%) in the pasireotide-LAR 40 mg group, two patients (3%) in the pasireotide-LAR 60 mg group, and three patients (5%) in the active control group. Two patients receiving 40 mg pasireotide-LAR (anaemia and hyperglycaemia in one patient, increased blood glucose in the other) and one patient receiving 60 mg pasireotide-LAR (hyperglycaemia) had serious adverse events that were suspected to be drug related. Six patients discontinued treatment because of an adverse event: four in the pasireotide-LAR 60 mg group (one case of diabetes and three cases of hyperglycaemia) and two in the pasireotide-LAR 40 mg group (one case of hyperglycaemia and one case of colon cancer). All adverse events leading to discontinuation of study drug were suspected to be related to study treatment except the case of colon cancer. One adverse event (liver injury in the pasireotide-LAR 40 mg group) required dose interruption or reduction. No deaths occurred during the study.

We noted hyperglycaemia-related adverse events in 42 (67%) patients in the pasireotide-LAR 40 mg group (one case of diabetes and three cases of hyperglycaemia) and two in the pasireotide-LAR 40 mg group (one case of hyperglycaemia and one case of colon cancer). All adverse events leading to discontinuation of study drug were suspected to be related to study treatment except the case of colon cancer. One adverse event (liver injury in the pasireotide-LAR 40 mg group) required dose interruption or reduction. No deaths occurred during the study.

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active control group remained similar to baseline throughout the study (figure 4). Antidiabetic medication was initiated in 24 (38%) patients in the pasireotide-LAR 40 mg group, 24 (39%) patients in the pasireotide-LAR 60 mg group, and four (6%) patients in the active control group after study start. The most common drugs were metformin (given to ten patients receiving 40 mg pasireotide, 12 receiving 60 mg pasireotide, and two receiving active control), insulin (four, four, and no patients, respectively), and glimepiride (five, three, and no patients, respectively).

Discussion

Findings from the phase 3 PAOLA study showed that pasireotide-LAR 40 mg and pasireotide-LAR 60 mg provide superior efficacy compared with continued treatment with first-generation somatostatin analogues in patients with inadequately controlled acromegaly (panel). No patients in the active control group achieved biochemical control or normalised IGF-1 concentrations; however, this finding is perhaps not surprising because these patients were inadequately controlled on these somatostatin analogues before study entry. Biochemical response rates with 40 mg pasireotide-LAR (15%) and 60 mg pasireotide-LAR (20%) are clinically relevant, because all enrolled patients had long-standing acromegaly (at baseline, median time since diagnosis was 50·0 months in the pasireotide-LAR 40 mg group, 54-5 months in the 60 mg group, and 53-8 months in the active control group) and remained inadequately controlled despite receiving various treatment options for a lengthy period. Indeed, some patients achieved biochemical control for the first time during treatment with pasireotide. However, because the inclusion criteria preselected patients who may have been refractory to somatostatin analogue treatment, the data might underestimate the true efficacy of pasireotide-LAR and of active control in the general population of patients with acromegaly. These findings are in line with those from a previous phase 3 study,15 in which pasireotide-LAR had superior efficacy compared with octreotide long-acting repeatable in patients who had not previously received pharmaceutical treatment for acromegaly.

At present, pegvisomant is used to treat patients with acromegaly who are inadequately controlled by first-generation somatostatin analogues, but unlike pasireotide its effects are not specifically directed towards the pituitary tumour and it does not reduce growth hormone concentrations. Although not approved for use in acromegaly, the dopamine agonist cabergoline is sometimes used off-label in patients with this disorder, especially in those with mildly elevated IGF-1 concentrations. A recent consensus statement has proposed the use of cabergoline or pegvisomant in combination with first-generation somatostatin analogues in patients not fully controlled with monotherapy.17 In the present study, roughly 14% of patients had previously received pegvisomant and about 31% had received cabergoline, either alone or in combination with a somatostatin analogue, and needed alternative treatment. In comparison with first-generation somatostatin analogues, pasireotide-LAR allowed more patients to achieve normalisation of IGF-1, decreased growth hormone concentrations to less than 2·5 μg/L, and reduced tumour volume by more than 25%. The increased effect on IGF-1 by pasireotide-LAR compared with active control is in line with findings from the previous phase 3 study;16 however, this study is the first to show greater

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**Table 2: Most common adverse events (≥5% in any treatment group) in safety analysis set**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>40 mg pasireotide (n=63)</th>
<th>60 mg pasireotide (n=62)</th>
<th>Active control (n=66)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
<td>Grade 3</td>
<td>All grades</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>21 (33%)</td>
<td>7 (11%)</td>
<td>19 (31%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>13 (21%)</td>
<td>0</td>
<td>16 (26%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>10 (16%)</td>
<td>0</td>
<td>12 (19%)</td>
</tr>
<tr>
<td>Cholelithiasis</td>
<td>6 (10%)</td>
<td>0</td>
<td>8 (13%)</td>
</tr>
<tr>
<td>Headache</td>
<td>9 (14%)</td>
<td>0</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>4 (6%)</td>
<td>0</td>
<td>7 (11%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>5 (8%)</td>
<td>2 (3%)</td>
<td>5 (8%)</td>
</tr>
<tr>
<td>Impaired glucose tolerance*</td>
<td>2 (3%)</td>
<td>0</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (3%)</td>
<td>0</td>
<td>4 (6%)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>4 (6%)</td>
<td>0</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>5 (8%)</td>
<td>0</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Increased blood glucose</td>
<td>3 (5%)</td>
<td>0</td>
<td>4 (6%)</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>2 (3%)</td>
<td>0</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>1 (2%)</td>
<td>0</td>
<td>4 (6%)</td>
</tr>
<tr>
<td>First degree atrioventricular block</td>
<td>4 (6%)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table shows all adverse events, irrespective of study drug relationship. Adverse events presented in order of overall frequency and are reported with the preferred terms recorded by the investigators; as such, a single patient might appear in more than one row for hyperglycaemia-related terms. *As measured during an oral glucose tolerance test.

**Table 3: Hyperglycaemia-related adverse events according to baseline diabetic status in the safety analysis set**

<table>
<thead>
<tr>
<th>Event</th>
<th>40 mg pasireotide (n=63)</th>
<th>60 mg pasireotide (n=62)</th>
<th>Active control (n=66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic</td>
<td>32/45 (71%)</td>
<td>26/37 (70%)</td>
<td>30/46 (22%)</td>
</tr>
<tr>
<td>Pre-diabetic</td>
<td>7/10 (70%)</td>
<td>6/12 (50%)</td>
<td>10/18 (56%)</td>
</tr>
<tr>
<td>Normal glucose tolerance</td>
<td>3/8 (38%)</td>
<td>6/13 (46%)</td>
<td>0/2</td>
</tr>
</tbody>
</table>

Data are n/N (%). Definitions of hyperglycaemia-related adverse events and diabetic categories are provided in the appendix.

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Figure 3: Change in growth hormone concentration (A), IGF-1 concentration (B), and tumour volume (C) from baseline to week 24

Data are individually shown for patients with available data at baseline and week 24. The dashed line represents 2.5 μg/L, for growth hormone concentration, the upper limit of normal for IGF-1 concentration, and 25% reduction for tumour volume. Figure shows absolute change for growth hormone and IGF-1 concentration and relative change for tumour volume. IGF-1=insulin-like growth factor 1.
reduction in growth hormone concentrations and tumour volume with pasireotide-LAR than with active control. We speculate that the superior efficacy of pasireotide-LAR in this study is related to the different somatostatin receptor expression profiles of the tumours. Low SST₂ expression in the pituitary tumour, or a low SST₂/SST₅ ratio, predicts resistance to octreotide and lanreotide therapy.7,20 Findings from a study in patients with acromegaly showed that pasireotide was more effective than octreotide in tumours with relatively high SST, expression compared with those with high SST₅, expression. However, tumour somatostatin receptor expression profiles could not be assessed in our study; tumour samples were collected when possible, but an insufficient number were available for analysis.

Pasireotide-LAR was well tolerated; the safety profile was generally similar to that in the active control group, except for the higher frequency and degree of hyperglycaemia and increased frequency of diarrhoea. The rate of hyperglycaemia-related adverse events with 40 mg pasireotide-LAR was slightly higher (67%) than reported previously at the same dose (57%).15 Patients enrolled in this study might have already developed either glucose intolerance or diabetes at baseline, because they had already been exposed to high-dose somatostatin analogue treatment for a lengthy period and were also inadequately controlled. This suggestion is supported by the high prevalence of diabetes (82 [66%] of 125 patients in safety analysis set) and pre-diabetes (22 [18%] of 125) at baseline in patients receiving pasireotide. Enrolled patients might also have been prone to developing pasireotide-induced hyperglycaemia; findings from a mechanistic study in healthy volunteers suggested that pasireotide inhibits insulin and incretin secretion,22 and as such hyperglycaemia might have been further exacerbated during pasireotide treatment in patients who were diabetic or prediabetic at baseline. About a third of patients did not have any hyperglycaemia-related adverse events, and antidiabetic medication was initiated in only about 40% of patients; the discontinuation rate was low (roughly 10%) and we noted improvements in AcroQoL and symptom severity scores. Nevertheless, blood glucose concentrations should be closely monitored in patients treated with pasireotide and antidiabetic treatment should be promptly initiated if levels increase. On the basis of the results of two mechanistic studies in healthy volunteers, a recent paper recommended initiation of treatment with metformin as early as possible after occurrence of hyperglycaemia in patients with Cushings disease treated with pasireotide;23 if not controlled on metformin, a dipeptidyl peptidase 4 inhibitor should be added and, if still not controlled, switching to a glucagon-like peptide 1 (GLP-1) receptor agonist should be considered. If the GLP-1 receptor agonist fails, treatment with insulin should be initiated. On the basis of the association between pasireotide and hyperglycaemia, these recommendations could also be applicable to patients with acromegaly. The rates of other commonly reported adverse events for this drug class, such as diarrhoea (16% and 40%, respectively), cholelithiasis (10% and 26%, respectively), and abdominal pain (8% and 18%, respectively), were lower in the current study than in the previous study.15 This difference might be because patients in the present study had already been
exposed to somatostatin analogues for at least 6 months before enrolment; these adverse events are common when patients start taking any somatostatin analogue, and patients might have become tolerant to the drug class.

We selected the pasireotide-LAR doses used in this study on the basis of previous data suggesting that the steady-state trough concentrations of 40 mg pasireotide-LAR and 60 mg pasireotide-LAR were above the median effective concentration needed to achieve growth hormone concentrations of 2·5 μg/L or less (established in responders to subcutaneous pasireotide treatment). These doses were also shown to be well tolerated. In this study, we selected two separate pasireotide-LAR doses to account for interpatient variability in pharmacokinetic exposure and possible differences in tolerability between doses. Both doses were effective in this patient population; initiation of pasireotide-LAR treatment at a dose of 40 mg would allow up-titration to 60 mg if necessary, because some patients might need higher doses of pasireotide-LAR to achieve biochemical control.

Octreotide long-acting repeatable and lanreotide Autogel are the standard medical treatments for acromegaly; combination therapy with an additional drug is often used as a next-step treatment option in patients unable to achieve control. Although one criticism of this study design could be that patients in the active control group received continued treatment with baseline somatostatin analogue therapy despite inadequate control, we did not know before the study whether pasireotide-LAR could provide better biochemical control than octreotide or lanreotide. Additionally, continued treatment with somatostatin analogues could have led to biochemical control because some patients do not respond to treatment immediately. Furthermore, in clinical practice, many patients receiving somatostatin analogues can remain biochemically uncontrolled but still have lower growth hormone and IGF-1 concentrations than before treatment and remain on their current therapeutic regimen. Of note, all patients in the active control group who remained uncontrolled at week 24 had the opportunity to switch to pasireotide-LAR in an extension study (NCT01137682).

In conclusion, treatment with pasireotide-LAR was associated with a clinically meaningful and statistically significant reduction in IGF-1 and growth hormone concentrations in patients inadequately controlled on octreotide long-acting repeatable or lanreotide Autogel, and was well tolerated except for an increased frequency and degree of hyperglycaemia-related adverse events and an increased frequency of diarrhoea. Pasireotide-LAR could become the new standard pituitary-directed treatment in patients with acromegaly who are inadequately controlled with first-generation somatostatin analogues.

**Contributors**

The study was designed by the sponsor, Novartis Pharma AG, in discussion with the academic investigators, who also endorsed the study design. JF and AMP wrote the study protocol; MA wrote the statistical section of the protocol. MRG, MDB, TB, MC, MF, MG, VP, GR, IS, and AC enrolled patients into the study and collected data using Novartis’ data management systems. MA contributed to the statistical analysis. KKL, JF, MA, and AMP contributed to enhancement of data quality. MRG, MDB, TB, MC, MF, MG, VP, GR, IS, MA, AMP, and AC contributed to interpretation of the data. MRG, MDB, TB, MC, MF, MG, VP, GR, IS, KKL, JF, MA, AMP, and AC contributed to the development of the report. MA wrote the section on statistical analyses. MRG, MDB, TB, MC, MF, MG, VP, GR, IS, KKL, JF, MA, AMP, and AC critically reviewed and amended the report.

**Declaration of interests**

MRG has received research grants from Novartis and Pfizer and served as a principal investigator for clinical trials and speaker for Novartis and Ipsen. MDB has received grants and personal fees as a principal investigator for clinical trials, speaker and steering committee member from Ipsen; grants, personal fees, and non-financial support as a principal investigator for clinical trials, speaker and steering committee member, and for the use of drugs on a compassionate basis from Novartis; grants and personal fees as a principal investigator for clinical trials, speaker and advisory board member from Pfizer; and personal

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**Panel: Research in context**

**Systematic review**

The somatostatin analogues octreotide and lanreotide are the standard of medical management in acromegaly, after surgery or as first-line therapy when surgery is inappropriate, and have demonstrated the effectiveness of this drug class. However, 20–70% of patients can remain inadequately controlled with these first-generation somatostatin analogues. We searched PubMed in June, 2014, with the terms “somatostatin analogue” and “acromegaly” and found no suitable systematic reviews or meta-analyses reporting on the efficacy and safety of somatostatin analogues exclusively in patients with inadequately controlled acromegaly. No systematic review was done during the planning of this study. However, to our knowledge, no studies assessing a novel somatostatin analogue in patients inadequately controlled on currently available somatostatin analogues have been reported; no results were returned fitting these search criteria.

**Interpretation**

Findings from our study show that, in patients who were inadequately controlled during treatment with octreotide and lanreotide, a greater proportion achieved biochemical control (insulin-like growth factor 1 normalisation, growth hormone concentrations less than 2·5 μg/L, insulin-like growth factor 1 normalisation, growth hormone concentrations less than 2·5 μg/L, and tumour volume reduction of more than 25% at 24 weeks with 40 mg or 60 mg pasireotide-LAR than did patients who received continued treatment with octreotide or lanreotide. Pasireotide had a similar safety profile to that of active control, except for a greater frequency and degree of hyperglycaemia-related adverse events and increased frequency of diarrhoea. These results support the notion that pasireotide could become the new standard pituitary-directed treatment in patients with acromegaly who are inadequately controlled with first-generation somatostatin analogues.
fees as an advisory board member from Chiasma. TB has received funding as a co-investigator in clinical trials and advisory board member from Novartis. MC has received non-financial support for the conduct of this clinical trial from Novartis, and personal fees from Novartis. MF has received grants for research support to her institution from Ipsen and personal fees for scientific consulting from Novartis, Ipsen, Pfizer, and Genentech. MG has received honoraria as a principal researcher on this clinical trial from Novartis. GR has received grants and personal fees as a speaker and to his institution for data monitoring from Novartis, and grants and personal fees as a speaker from Ipsen. IS has received grants from Novartis and Pfizer; personal fees from Novartis, Pfizer, Novo Nordisk, Teva, and Neopharm; and non-financial support from Novartis. AC has received grants and honoraria as a speaker and for research in neuroendocrinology from Novartis. KKL, JF, MA, and AMP are employees of Novartis. VP declares no competing interests.

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