Overview: Phase III Study of Pasireotide in Patients with Inadequately Controlled Acromegaly

Acromegaly is an endocrine disorder caused by a benign (non-cancerous) tumor on the pituitary gland that secretes excess growth hormone (GH), leading to elevated levels of insulin-like growth factor-1 (IGF-1)1. The combined effect of elevated GH and IGF-1 levels causes the enlargement of body parts along with serious morbidities such as cardiovascular, metabolic and respiratory diseases1. Long-term exposure to elevated GH and IGF-1 levels can ultimately increase patients’ risk of death by two- to three-fold2. Therefore, normalizing and maintaining biochemical control, as measured by both GH and IGF-1 levels, is a primary goal of treatment. Tumor shrinkage and improvement in clinical manifestations are also key treatment objectives1.

Current Standard of Care
Somatostatin analogs, including octreotide LAR or lanreotide Autogel® are traditionally considered to be the primary medical therapeutic options for acromegaly3. Octreotide LAR is approved as a long-term maintenance therapy in acromegalic patients who have had an inadequate response to surgery and/or radiotherapy, or for whom surgery and/or radiotherapy is not an option4. Lanreotide Autogel is approved for the treatment of acromegaly when the circulating levels of growth hormone and/or IGF-1 remain abnormal after surgery and/or radiotherapy or in patients who otherwise require medical treatment5.

Trial Overview

<table>
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<tr>
<th>Trial</th>
<th>Pasireotide LAR versus Octreotide LAR or Lanreotide Autogel in patients with Inadequately Controlled Acromegaly</th>
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<tr>
<td>Overview</td>
<td>Pivotal Phase III trial evaluating the efficacy and safety of pasireotide LAR in patients with inadequately controlled acromegaly versus continued treatment with octreotide LAR or lanreotide Autogel³</td>
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<td>Trial Design</td>
<td>• Prospective, randomized, parallel-group study of patients with inadequately controlled acromegaly, as measured by the mean GH levels of &lt;2.5μg/L and normalized IGF-1 levels, currently receiving the maximum doses of octreotide LAR (30 mg) or lanreotide Autogel (120 mg) monotherapy³</td>
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<td>• Eligible patients included those who had previously received octreotide LAR 30 mg or lanreotide Autogel 120 mg monotherapy (i.e., maximum-approved doses) for ≥6 months prior to screening³</td>
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<td>• Overall, 198 patients were randomized to pasireotide LAR 40 mg (n=65), pasireotide LAR 60 mg (n=65) and continued treatment with octreotide LAR/lanreotide Autogel (active control; n=68)³</td>
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<td>• Total of 63 study locations in 18 countries were involved, including Argentina, Belgium, Brazil, Canada, Colombia, France, Germany, Israel, Italy, Norway, Poland, Romania, Russia, Saudi Arabia, Spain, Turkey, the UK and the US⁵</td>
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<td>Primary Endpoint</td>
<td>• To determine the proportion of patients achieving biochemical control at 24 weeks. Biochemical control was defined as the following:</td>
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<td>o Mean GH levels (&lt;2.5μg/L)</td>
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<td>o Normalized IGF-1 levels³</td>
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<td>Secondary endpoints</td>
<td>• Percentage of patients achieving normalized IGF-1 levels (key secondary endpoint)</td>
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<td>• Percentage of patients achieving normalized GH levels (&lt;2.5μg/L)</td>
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<td>• Tumor volume reduction (&gt;25%)³</td>
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<td>• Safety</td>
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<td>Trial Results</td>
<td>• The primary endpoint, percentage of biochemically controlled patients, was significantly higher among patients taking pasireotide LAR 40 mg and 60 mg versus the octreotide LAR or lanreotide Autogel:</td>
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| | o 15.4% and 20.0% with inadequately controlled acromegaly treated with pasireotide (95% CI, 7.6–26.5; P=.0006; 95% CI, 11.1–31.8; P<.0001) achieved biochemical control compared to 0% that were treated with...
Octreotide LAR or lanreotide Autogel (95% CI, 0–5.3)\(^3\)

- The key secondary endpoint, percentage with normalized IGF-1 levels, was attained by 24.6% and 26.2% of patients treated with pasireotide LAR 40 mg and 60 mg respectively (95% CI, 14.8–36.9; \(P<.001\); 95% CI, 16.0–38.5; \(P<.001\)), versus 0% in the octreotide LAR or lanreotide Autogel arm (95% CI, 0–5.3)\(^3\)

- Another secondary endpoint, percentage with normalized GH levels, was achieved by 35.4% and 43.1% of those treated with pasireotide LAR 40 mg and 60 mg (95% CI, 23.9–48.2; 95% CI, 30.8–56.0) compared with 13.2% of patients in the active control group (95% CI, 6.2–23.6)\(^3\)

- In the secondary endpoint of tumor volume reduction, a greater proportion of those receiving pasireotide LAR 40 mg and 60 mg achieved a greater than 25% decrease versus those receiving octreotide LAR or lanreotide Autogel (18.5% [95% CI, 9.9–30.0] and 10.8% [95% CI, 4.4–20.9] vs. 1.5% [95% CI, 0–7.9], respectively)\(^3\)

### Safety Findings

- The incidence and severity of adverse events (AEs) was similar across all treatment groups, except for a higher frequency and degree of hyperglycemia in the pasireotide LAR arm. The most common AEs associated with pasireotide LAR 40 mg, 60 mg and the active control arm were hyperglycemia (33.3%, 30.6% and 13.6%), diabetes mellitus (20.6%, 25.8% and 7.6%) and diarrhea (15.9%, 19.4% and 4.5%)\(^3\)

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**About pasireotide and pasireotide LAR**

Pasireotide is approved as Signifor in the US for the treatment of adult patients with Cushing’s disease for whom pituitary surgery is not an option or has not been curative and in the EU for the treatment of adult patients with Cushing’s disease for whom surgery is not an option or for whom surgery has failed.

For the treatment of Cushing’s disease, Signifor has been studied as a twice-daily subcutaneous (sc) injection and is currently being evaluated as a long-acting release (LAR), once-monthly intramuscular (IM) injection as part of a global Phase III program in Cushing’s disease and acromegaly. Signifor is a multireceptor targeting somatostatin analog (SSA) that binds with high affinity to four of the five somatostatin receptor subtypes (sst 1, 2, 3 and 5). There is no guarantee that Signifor LAR will become commercially available anywhere in the world for Cushing’s disease or any other indication.

Pasireotide LAR (SOM230) is an investigational multireceptor targeting SSA that binds with high affinity to four of the five somatostatin receptor subtypes (sst 1, 2, 3 and 5). As an investigational agent, the safety and efficacy profile of pasireotide LAR has not been established in acromegaly or any other indication. The formulation and dosage of pasireotide LAR when used for studying the acromegaly patient population are different from that of pasireotide sc in the approved Cushing’s disease indication. Pasireotide LAR is available for patients with acromegaly through carefully controlled and monitored clinical trials which are designed to better understand the potential benefits and risks of the compound. For various reasons, including the uncertainty of clinical trials, there is no guarantee that pasireotide LAR will become commercially available for acromegaly anywhere in the world.

Information about Novartis clinical trials for pasireotide can be obtained by healthcare professionals at [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

**Important safety information about Signifor (pasireotide) injection**

Treatment with Signifor may lead to a decrease in circulating levels of cortisol resulting in biochemical and/or clinical hypocortisolism. Signifor dose of reduction or interruption and/or adding low-dose short-term glucocorticoid therapy may be necessary.

Hyperglycemia and diabetes occurs with initiation of Signifor therapy. Cushing’s disease patients with poor glycemic control (as defined by hemoglobin A1c (HbA1c) values >8% while receiving anti-diabetic therapy) may be at a higher risk of developing severe hyperglycemia and associated complications, e.g.,
ketoacidosis. Intensive glucose monitoring is recommended and may require initiation or adjustment of anti-diabetic treatment.

Treatment with Signifor may lead to bradycardia and QT prolongation. Use with caution in at-risk-patients. ECG testing is recommended prior to dosing and during treatment. Hypokalemia and hypomagnesemia must be corrected prior to Signifor administration and should be monitored periodically during therapy.

Liver test elevations are associated with Signifor use. Elevations of ALT or AST >3X ULN were observed in 5% of patients in the Phase III trial. Liver tests are recommended prior to and after 1 to 2 weeks on treatment, then monthly for 3 months, and every 6 months thereafter.

Cholelithiasis is associated with Signifor use. Perform gallbladder ultrasounds before and at 6- and 12-month intervals.

Inhibition of pituitary hormones may occur with Signifor treatment. Monitoring of pituitary function should occur prior to initiation of therapy and periodically during treatment with Signifor.

Caution is required when co-administering Signifor with anti-arrhythmics and drugs that prolong QT. The following drugs may require monitoring and possible dose adjustments when used with Signifor: cyclosporine, bromocriptine.

The most common adverse events (AE) (≥20%) occurring in patients in clinical trials are diarrhea (59%), nausea (58%), hyperglycemia (43%), cholelithiasis (30%), headache (29%), abdominal pain (25%), fatigue (24%), and diabetes mellitus (20%).

Please see full Prescribing Information at Signifor.com.

**About octreotide LAR**

Octreotide LAR, a long-acting, injectable depot formulation of octreotide acetate is approved in the United States (US) as Sandostatin® LAR® Depot for long-term maintenance therapy in patients with acromegaly who have had an inadequate response to surgery and/or radiotherapy, or for whom surgery and/or radiotherapy is not an option in patients in whom initial treatment with immediate release Sandostatin (octreotide acetate) Injection has been shown to be effective and tolerated. The goal of treatment in acromegaly is to reduce GH and IGF-1 levels to normal. Outside the US, octreotide LAR is available as Sandostatin LAR for the treatment of patients with acromegaly who are adequately controlled on subcutaneous treatment with Sandostatin or in whom surgery or radiotherapy is inappropriate or ineffective; in the interim period until radiotherapy becomes fully effective. Acromegaly indications vary by country.

Octreotide LAR is available from Novartis for different uses and not all indications are available in every country.

**Important safety information about Sandostatin LAR (octreotide/IM injection)**

Treatment with Sandostatin LAR may affect gallbladder function, sugar metabolism, thyroid and heart function, and nutritional absorption, which may require monitoring.

Caution is to be exercised for those with a history of heart disease or taking other medications, including cyclosporine, insulin, oral hypoglycemic agents, beta-blockers, and bromocriptine.

Common side effects include diarrhea, gallstones, abdominal pain and flatulence.

Please see full Prescribing Information at Sandostatin.com.

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References