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). 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 diseases. Long-term exposure to elevated GH and IGF-1 levels can ultimately increase patients’ risk of death by two- to three-fold. 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 objectives.

Current Standard of Care

Somatostatin analogs, including octreotide LAR or lanreotide Autogel* are traditionally considered to be the primary medical therapeutic options for acromegaly. 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 option. 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 treatment.

<table>
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<th>Trial</th>
<th>Pasireotide LAR versus Octreotide LAR or Lanreotide Autogel in patients with Inadequately Controlled Acromegaly</th>
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<tbody>
<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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<td>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&lt;.0001) achieved biochemical control compared to 0% that were treated with</td>
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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**

Signifor is contraindicated in patients with hypersensitivity to the active substances in Signifor or to any of the excipients and in patients with severe liver impairment.

Alterations in blood glucose levels have been frequently reported in healthy volunteers and patients treated with Signifor. Glycemic status should be assessed prior to starting treatment with Signifor. Patients need to be monitored for hyperglycemia; if hyperglycemia develops, the initiation or adjustment of antidiabetic treatment is recommended. Dose reduction or treatment discontinuation should be considered if
uncontrolled hyperglycemia persists. After treatment discontinuation, glycemic monitoring (e.g. FPG or HbA1c) should be done according to clinical practice.

Monitoring of liver function is recommended prior to starting treatment with Signifor and after one, two, four, eight and twelve weeks during treatment and thereafter as clinically indicated. Therapy should be discontinued if the patient develops jaundice, other clinical signs of significant liver dysfunctions, sustained AST (aminotransferases) or ALT (alanine aminotransferase) increase five times the upper limit of normal (ULN) or greater, or if ALT or AST increase three times ULN with concurrent bilirubin elevation greater than two times ULN.

Patients with cardiac disease and/or risk factors for bradycardia need to be closely monitored. Caution is to be exercised in patients who have or may develop QT prolongation. Hypokalemia or hypomagnesemia must be corrected prior to initiating therapy and monitored thereafter. Electrocardiography should be performed prior to the start of Signifor therapy and as clinically indicated thereafter.

Treatment with Signifor leads to rapid suppression of adrenocorticotropic hormone (ACTH) secretion in Cushing’s disease patients. Patients need to be monitored and instructed how to monitor for signs and symptoms of hypocortisolism. Temporary exogenous steroid (glucocorticoid) replacement therapy and/or dose reduction or interruption of Signifor therapy may be necessary.

Monitoring of gallbladder and pituitary hormones is recommended prior to initiating treatment and periodically thereafter.

Signifor should not be used during pregnancy unless clearly necessary. Breast feeding should be discontinued during treatment with Signifor.

Signifor may affect the way other medicines work, and other medicines can affect how Signifor works. Caution is to be exercised with the concomitant use of drugs with low therapeutic index mainly metabolized by CYP3A4, bromocriptine, cyclosporine, anti-arrhythmic medicines or drugs that may lead to QT prolongation.

The most frequently reported adverse events (AE) (>10%) by investigators for Signifor were diarrhea, nausea, hyperglycemia, cholelithiasis, abdominal pain, diabetes mellitus, injection site reactions, fatigue and increased glycosylated hemoglobin (HbA1c), with most events being Grade 1-2. The tolerability profile of Signifor was similar to that of other somatostatin analogs with the exception of the greater degree of hyperglycemia.

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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*Lanreotide Autogel (Somatuline® Autogel®) is a registered trademark of Ipsen.

References