

Novartis drug Signifor® LAR shows superior efficacy in acromegaly patients not controlled on first generation somatostatin analogues

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- Acromegaly, an endocrine disorder resulting from elevated growth hormone (GH) and insulin-like growth factor-1 (IGF-1) levels, is associated with high mortality^(1,2)
- Phase III data show patients on pasireotide LAR achieved greater biochemical control, as measured by both GH and IGF-1 levels, versus control group⁽³⁾
- These data, supported by a previously published Phase III study, are the basis for worldwide regulatory filings for pasireotide LAR in the treatment of acromegaly

EAST HANOVER, N.J., May 5, 2014 /PRNewswire/ -- Novartis today presented results from a pivotal Phase III trial of investigational therapy Signifor® LAR (pasireotide LAR; SOM230) in patients with acromegaly for whom current standard of care provides inadequate disease control. The study findings showed that patients taking pasireotide long-acting release (LAR) achieved greater disease control when compared to continued treatment with the standard somatostatin analogue therapies, octreotide LAR or lanreotide Autogel*. These data were presented at the 16th European Congress of Endocrinology³.

Acromegaly is caused by a benign (non-cancerous) tumor within the pituitary gland that secretes excess growth hormone (GH), leading to elevated levels of insulin-like growth factor-1 (IGF-1)¹. This combined effect of elevated GH and IGF-1 levels causes the enlargement of body parts, including the hands, feet and facial features, along with serious morbidities such as cardiovascular, metabolic and respiratory diseases^{1,4}. If exposed to long-term elevated levels of GH and IGF-1, acromegaly patients face a two- to three-fold increased risk of death^{2,5}. Biochemical control of the disease, as measured by both GH and IGF-1 levels, is the primary goal of treatment. Other disease management objectives include tumor shrinkage and improvement in clinical signs and symptoms¹.

"Historically, we have evaluated somatostatin analogues for the treatment of acromegaly by the decrease in either growth hormone or insulin-like growth factor levels. With more sensitive assays and more stringent evaluation criteria, a recent meta-analysis indicates that up to 45% of patients can have either GH or IGF-I still elevated," said Dr. Monica Gadelha, professor, Federal University of Rio de Janeiro and study author. "As the health risks associated with acromegaly may persist until both GH and IGF-1 levels are normalized, this study further supports the importance of monitoring for and achieving full biochemical control."

This study evaluated pasireotide LAR 40 mg and 60 mg against continued therapy with octreotide LAR or lanreotide Autogel in patients who did not achieve GH and IGF-1 biochemical control despite receiving the maximum approved doses of these currently available somatostatin analogues (SSAs). In the trial, significantly more patients achieved biochemical control with each dose of pasireotide LAR compared to the octreotide LAR and lanreotide Autogel control arm. Specifically, 15.4% and 20.0% of those with inadequately controlled acromegaly taking pasireotide LAR 40 mg and 60 mg, respectively (95% confidence interval [CI], 7.6–26.5; P=0.0006; 95% CI, 11.1–31.8; P<0.0001), achieved biochemical control versus 0% achieving biochemical

control on continued treatment with octreotide LAR or lanreotide Autogel (95% CI, 0–5.3). 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 arm³.

"These results strengthen our understanding of this rare endocrine disorder and suggest pasireotide LAR may offer benefit for acromegaly patients whose disease is not fully controlled on their current therapy," said Alessandro Riva, president, Novartis Oncology ad interim and Global Head, Oncology Development and Medical Affairs. "As part of our long-standing commitment to transforming the care of rare pituitary diseases, we are working to bring this potentially meaningful solution to the acromegaly community."

Worldwide regulatory filings for pasireotide LAR in acromegaly are currently underway based on these results and separate previously published robust Phase III data.

About the study

The multicenter Phase III study was a randomized, double-blind trial examining pasireotide LAR 40 mg or pasireotide LAR 60 mg versus continued open-label treatment with octreotide LAR 30 mg or lanreotide Autogel 120 mg (the control group) for 24 weeks. The trial included 198 patients with inadequately controlled acromegaly on maximum approved doses of octreotide LAR or lanreotide Autogel for at least 6 months, regardless of prior surgical status. The primary endpoint of this study was the proportion of patients achieving biochemical control as measured by the mean GH levels of $<2.5\mu\text{g/L}$ and normalized IGF-1 at 24 weeks³.

The key secondary endpoint was the percentage of patients achieving normalized IGF-1; other secondary endpoints included the percentage of patients achieving normalized GH levels, tumor reduction and safety. Notably, in this study, IGF-1 normalization was achieved by 24.6% and 26.2% of patients taking pasireotide LAR 40 mg and 60 mg, respectively (95% CI, 14.8–36.9; $P<0.001$; 95% CI, 16.0–38.5; $P<0.001$), and was not achieved by any patients in the control arm (95% CI, 0–5.3). Additionally, 35.4% and 43.1% of patients in the pasireotide LAR 40 mg and 60 mg arms, respectively (95% CI, 23.9–48.2; 95% CI, 30.8–56.0), had mean GH levels of $<2.5\mu\text{g/L}$ compared to 13.2% in the control arm (95% CI, 6.2–23.6)³.

Tumor size was also evaluated and the study found a greater proportion of patients receiving pasireotide LAR 40 mg and 60 mg achieved a greater than 25% decrease compared with those receiving octreotide LAR and lanreotide Autogel (18.5% [95% CI, 9.9–30.0] and 10.8% [95% CI, 4.4–20.9] versus 1.5% [95% CI, 0–7.9], respectively)³.

The most common AEs associated with pasireotide LAR 40 mg, 60 mg and the 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%), respectively³.

About acromegaly

Worldwide, the estimated prevalence of acromegaly is between 115 and 295 people per million and the estimated incidence is three to four people per million^{6,7}. Acromegaly most commonly presents in middle-aged men and women. This debilitating disease can be difficult to detect because it can develop gradually and/or individual symptoms may be mistaken for another medical condition¹. In fact, the average delay from disease onset to diagnosis has been estimated to be 6 to 10 years⁸. Acromegaly is also associated with serious health risks including heart disease, hypertension, diabetes, arthritis and an increased risk of colon cancer¹. Heart disease is responsible for approximately 60% of deaths among people with acromegaly⁹.

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.

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 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 (AEs) (greater than or equal to 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.

Disclaimer

The foregoing release contains forward-looking statements that can be identified by words such as "investigational therapy," "goal," "suggests," "may," "supports," "suggest," "commitment," "to bring," "potentially," "underway," "being evaluated," "investigational agent," or similar terms, or by express or implied discussions regarding potential regulatory approvals for SOM230, or regarding potential future revenues from SOM230, Signifor and octreotide LAR. You should not place undue reliance on these statements. Such forward-looking statements are based on the current beliefs and expectations of management regarding future events, and are subject to significant known and unknown risks and uncertainties. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those set forth in the forward-looking statements. There can be no guarantee that SOM230 will be approved for sale in any market for any indication for which it has been submitted, or at any particular time. Neither can there be any guarantee that SOM230 will be submitted or approved for any additional indications or labeling in any market, or at any particular time. Nor can there be any guarantee that SOM230, Signifor or octreotide LAR will be commercially successful in the future. In particular, management's expectations regarding such products could be affected by, among other things, the uncertainties inherent in research and development, including unexpected clinical trial results and additional analysis of existing clinical

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Novartis Pharmaceuticals Corporation researches, develops, manufactures and markets innovative prescription drugs used to treat a number of diseases and conditions, including cardiovascular, dermatological, central nervous system, bone disease, cancer, organ transplantation, psychiatry, infectious disease and respiratory. The company's mission is to improve people's lives by pioneering novel healthcare solutions.

Located in East Hanover, New Jersey, Novartis Pharmaceuticals Corporation is an affiliate of Novartis AG, which provides innovative healthcare solutions that address the evolving needs of patients and societies. Headquartered in Basel, Switzerland, Novartis offers a diversified portfolio to best meet these needs: innovative medicines, eye care, cost-saving generic pharmaceuticals, preventive vaccines, over-the-counter and animal health products. Novartis is the only global company with leading positions in these areas. In 2013, the Group achieved net sales of USD 57.9 billion, while R&D throughout the Group amounted to approximately USD 9.9 billion (USD 9.6 billion excluding impairment and amortization charges). Novartis Group companies employ approximately 135,000 full-time-equivalent associates and sell products in more than 150 countries around the world. For more information, please visit <http://www.novartis.com>.

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