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Novartis drug pasireotide LAR shows superior efficacy compared to Sandostatin® LAR® in Phase III trial of patients with acromegaly

- *Patients on pasireotide (SOM230) LAR were 63% more likely to achieve full biochemical control than those on Sandostatin LAR, the current standard of care*(1)

- *Acromegaly, a rare endocrine disorder caused by excess growth hormone, can result in enlarged hands, feet and internal organs, and increased risk of death(2),(3)*

- *Presently only 20-25% of acromegaly patients naïve to previous somatostatin analog treatment achieve full control with current somatostatin analogs*(1)

Basel, May 7, 2012 Results of the largest Phase III study of acromegaly patients show the novel therapy pasireotide (SOM230) long-acting release (LAR), was significantly more effective at inducing full biochemical control compared to the current standard medical therapy, Sandostatin® LAR® (octreotide/IM injection). These data were presented at the 2012 joint 15th International Congress of Endocrinology and 14th European Congress of Endocrinology meeting (ICE/ECE) in Florence, Italy(1).

Acromegaly is a rare endocrine disorder characterized by enlargement of the hands, feet and internal organs, as well as changes in facial structure(2),(3). The majority of acromegaly cases are caused by a non-cancerous tumor in the pituitary gland that secretes excess growth hormone (GH), leading to elevated levels of insulin like growth factor (IGF-1)(4).

The study met its primary endpoint, with significantly more patients treated with pasireotide LAR (31.3%) experiencing full control of their disease (defined as the combination of both GH <2.5µg/L and age- and sex-matched normalized IGF-1 levels) than those taking octreotide LAR (19.2%) (p=0.007). Patients treated with pasireotide LAR were 63% more likely to achieve control of their disease than those on octreotide LAR. The safety profile of pasireotide LAR was similar to that of octreotide LAR with the exception of a higher degree of hyperglycemia(1).

Growth hormone and IGF-1 levels are typically used to determine control of the disease with the most commonly used standard medical therapy, somatostatin analogs(4). Currently, only 20-25% of acromegaly patients naïve to previous somatostatin analog treatment achieve full control over their disease when treated with current somatostatin analogs, as measured by these two levels(1).

While Sandostatin LAR is an effective treatment, inadequate control of GH and IGF-1 remains an issue for many patients with acromegaly and new therapeutic approaches are needed for these patients to better control their disease, said Annamaria Colao, MD, lead study investigator and Professor of Endocrinology, Chief of the Neuroendocrine Unit at the Department of Molecular and Clinical Endocrinology and Oncology, Federico II University of Naples. We are very encouraged by the findings of this study, the largest ever in this population, which found that pasireotide LAR provided full control in nearly a third of study participants.

Investigators also presented data from a 6-month extension study, where patients who did not achieve full biochemical control after 12 months on therapy could switch to the other treatment. After an additional 6 months of treatment, 21% of the 81 patients who switched to pasireotide LAR achieved full control of their disease. By contrast, of the 38 patients who switched to octreotide LAR, 2.6% achieved full control(5).

The positive results seen in the Phase III trial point to the potential role of pasireotide LAR in treating patients with acromegaly, a condition for which there remains an unmet need, said Hervé Hoppenot, President, Novartis Oncology. These findings are welcome news as we continue our research efforts to discover treatments for patients with pituitary-related conditions.

In addition to acromegaly, Novartis is committed to studying other pituitary-related conditions including continued study in Cushing s disease. Data also presented at this meeting include long-term follow-up results from the Phase III registrational trial which led to the recent EU approval of Signifor® (pasireotide) for the treatment of Cushing s disease. Additionally, researchers presented data from a Phase I proof-of-concept trial for the investigational 11 -hydroxylase inhibitor, LCI699, in Cushing s disease(6),(7).

About the Study

This study, known as PASPORT-ACROMEGALY (PASireotide clinical trial PORTfolio - ACROMEGALY), is a randomized, double-blind, Phase III study evaluating the efficacy and safety of pasireotide LAR compared to the current standard medical therapy, octreotide LAR, in 358 patients with active acromegaly, who were *de novo* with a visible adenoma on MRI or medically-naïve (no previous medical therapy, but prior pituitary surgery). Patients were randomized to receive intramuscular injections of pasireotide LAR 40mg (n=176) or octreotide LAR 20mg (n=182) every 28 days for 12 months. At months three and seven, dose titration to pasireotide LAR 60mg or octreotide 30mg was permitted if patients had GH ≥2.5µg/L and/or IGF-1 > upper limit of normal (ULN). The primary endpoint was to compare the proportion of patients in the pasireotide LAR and octreotide LAR treatment arms with GH <2.5µg/L and normal IGF-1 at 12 months. Key secondary endpoints included comparison of the effect of pasireotide LAR and octreotide LAR on reduction of GH to <2.5µg/L alone and normalization of IGF-1 alone. Reductions of tumor volume, symptoms and prolactin levels were also assessed(1).

The 12-month study was completed by 80.1% (141/176) and 85.7% (156/182) of pasireotide LAR and octreotide LAR recipients, respectively, with dose up-titration performed in 50.6% and 67.6% of pasireotide LAR and octreotide LAR recipients(1).

At baseline, mean GH was 21.9 µg/L and 18.8µg/L in the pasireotide LAR and octreotide LAR arms, respectively; mean IGF-1 was 2.6xULN and 2.8xULN. The primary endpoint was achieved by 31.3% of pasireotide LAR recipients and 19.2% of octreotide LAR recipients (p=0.007). Mean GH and IGF-1 decreased by month three and remained suppressed. At month 12, 48.3% of patients receiving pasireotide LAR had mean GH<2.5µg/L compared to 51.6% of those on octreotide LAR (p=0.536), while normal IGF-1 was achieved by 38.6% of patients receiving pasireotide LAR and 23.6% of patients receiving octreotide LAR (p=0.002). Additionally, investigators reported that both pasireotide LAR and octreotide LAR were effective in reducing GH levels and tumor volume, and improving health-related quality of life and signs/symptoms of the disease(1).

Most adverse events (AEs) were mild or moderate. The most common AEs reported by investigators with pasireotide LAR versus octreotide LAR were diarrhea (39.3% vs. 45%), cholelithiasis (25.8% vs. 35.6%), headache (18.5% vs. 26.1%) and hyperglycemia (28.7% vs. 8.3%)(1).

Study Extension

At the end of the 12-month study, eligible patients could enroll in an optional, double-blind, 6-month extension phase. In this phase of the study, patients that did not achieve

full biochemical control could switch treatment at month 13 to either pasireotide LAR 40mg every 28 days (n=81) or octreotide LAR 20mg every 28 days (n=38), with dose titration allowed at 3-month intervals. Patients with GH <2.5µg/L and normal IGF-1 at month 12 could continue on their randomized therapy(5).

Most AEs observed through the end of the study extension were mild or moderate. The most common AEs during the 19 month treatment period with pasireotide LAR versus octreotide LAR were hyperglycemia (25.9% vs. 7.9%), diarrhea (21.0% vs. 15.8%), nasopharyngitis (16.0% vs. 18.4%) and headache (18.5% vs. 10.5%)(5).

About acromegaly

Acromegaly is a chronic hormonal disorder that occurs when excess growth hormone is produced. Commonly, acromegaly presents in middle-aged men and women and can result in changes in metabolism and an increased risk of mortality. People with acromegaly may also suffer from changes to facial structure, such as enlargement of forehead and jaw with pronounced under- or overbite, spreading teeth and enlarged tongue(3). More serious problems may include accelerated cardiovascular disease, hypertension, diabetes mellitus and possibly an increased risk of colon cancer(2). Worldwide, the estimated annual prevalence of acromegaly is 60 people per million and the estimated incidence is three to four people per million(3).

About pasireotide

Pasireotide (SOM230) is an investigational multireceptor targeting somatostatin analog (SSA) that binds with high affinity to four of the five somatostatin receptor subtypes (sst 1, 2, 3 and 5). Pasireotide is approved in the EU as Signifor® for the treatment of adult patients with Cushing s disease for whom surgery is not an option or for whom surgery has failed. Additional regulatory submissions for pasireotide for the treatment of Cushing s disease are under way worldwide.

Information about Novartis clinical trials for pasireotide can be obtained by healthcare professionals at www.pasporttrials.com.

Important Safety Information about Signifor (pasireotide)

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.

About Sandostatin LAR

Sandostatin® LAR® is a long-acting, injectable depot formulation of octreotide acetate that is indicated for the treatment of patients who are adequately controlled on s.c. treatment with Sandostatin; in patients in whom surgery or radiotherapy is inappropriate or ineffective; in the interim period until radiotherapy becomes fully effective. Treatment of patients with symptoms associated with functional gastro-entero-pancreatic endocrine tumors: carcinoid tumors with features of the carcinoid syndrome, VIPomas, glucagonomas, gastrinomas/Zollinger-Ellison syndrome, insulinomas, GRFomas. Treatment of patients with advanced neuroendocrine tumors of the midgut or unknown primary tumor location.

Sandostatin LAR was first approved in France in June 1995 and is currently approved in 95 countries. For more than a decade, Sandostatin LAR has achieved a long-standing track record of sustained efficacy with a well-established safety profile.

Not all indications are approved in every country.

Important Safety Information about Sandostatin LAR (octreotide/IM injection)

Patients who have a known hypersensitivity to octreotide or to any of the excipients should not take Sandostatin LAR. Dose adjustments of drugs, such as beta-blockers, calcium channel blockers or agents to control fluid and electrolyte balance may be necessary. Caution should be used in patients with insulinomas; patients with diabetes mellitus. Thyroid function should be monitored if receiving prolonged treatment with octreotide. Patients receiving Sandostatin LAR should receive periodic examination of the gallbladder; and patients who have a history of vitamin B12 deprivation should have their vitamin B12 levels monitored. Caution should be used in patients who are pregnant; patients should be advised to use adequate contraception, if necessary. Patients should not breast-feed during Sandostatin LAR treatment. The use of Sandostatin LAR may increase the bioavailability of bromocriptine, impair intestinal absorption of cyclosporin and delay that of cimetidine. Drugs mainly metabolized by CYP3A4 and which have a low therapeutic index should be used with caution.

Very common (≥1/10) adverse drug reactions in clinical studies with Sandostatin LAR were diarrhea, abdominal pain, nausea, constipation, flatulence, headache, cholelithiasis, hyperglycemia and injection-site localized pain. Common (≥1/100, <1/10) adverse drug

reactions were dyspepsia, vomiting, abdominal bloating, steatorrhea, loose stools, discoloration of feces, dizziness, hypothyroidism, thyroid dysfunction (e.g., decreased thyroid stimulating hormone, decreased Total T4 and decreased Free T4), cholecystitis, biliary sludge, hyperbilirubinemia, hypoglycemia, impairment of glucose tolerance, anorexia, elevated transaminase levels, pruritus, rash, alopecia, dyspnea and bradycardia.

The uncommon (≥1/1000, <1/100) adverse drug reactions were dehydration and tachycardia. The following adverse reactions have been reported postmarketing: anaphylaxis, allergy/hypersensitivity reactions, urticaria, acute pancreatitis, acute hepatitis without cholestasis, cholestatic hepatitis, cholestasis, jaundice, cholestatic jaundice, arrhythmia, increased alkaline phosphatase levels and increased gamma glutamyl transferase levels.

Disclaimer

The foregoing release contains forward-looking statements that can be identified by terminology such as encouraged, potential, committed, or similar expressions, or by express or implied discussions regarding potential new indications or labeling for pasireotide, potential future marketing approvals for LCI699, or regarding potential future revenues from these medicines. You should not place undue reliance on these statements. Such forward-looking statements reflect the current views of management regarding future events, and involve known and unknown risks, uncertainties and other factors that may cause actual results with pasireotide to be materially different from any future results, performance or achievements expressed or implied by such statements. There can be no guarantee that pasireotide will be approved for any additional indications or labeling in any market, or that LCI699 will be submitted or approved for sale in any market. Nor can there be any guarantee that either pasireotide or LCI699 will achieve any particular levels of revenue in the future. In particular, management s expectations could be affected by, among other things, unexpected clinical trial results, including unexpected new clinical data and unexpected additional analysis of existing clinical data; unexpected regulatory actions or delays or government regulation generally; competition in general; government, industry and general public pricing pressures; unexpected manufacturing issues; the company s ability to obtain or maintain patent or other proprietary intellectual property protection; the impact that the foregoing factors could have on the values attributed to the Novartis Group s assets and liabilities as recorded in the Group s consolidated balance sheet, and other risks and factors referred to in Novartis AG s current Form 20-F on file with the US Securities and Exchange Commission. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those anticipated, believed, estimated or expected. Novartis is providing the information in this press release as of this date and does not undertake any obligation to update any forward-looking statements contained in this press release as a result of new information, future events or otherwise.

About Novartis

Novartis 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 and diagnostic tools, over-the-counter and animal health products. Novartis is the only global company with leading positions in these areas. In 2011, the Group s continuing operations achieved net sales of USD 58.6 billion, while approximately USD 9.6 billion (USD 9.2 billion excluding impairment and amortization charges) was invested in R&D throughout the Group. Novartis Group companies employ approximately 124,000 full-time-equivalent associates and operate in more than 140 countries around the world. For more information, please visit http://www.novartis.com.

Novartis is on Twitter. Sign up to follow @Novartis at http://twitter.com/novartis.

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SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

Novartis AG

Date:	May 7, 2012	By:	/s/ MALCOLM B. CHEETHAM
		Name:	Malcolm B. Cheetham
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