

# Overview:

## *Signifor LAR C2305 & C2402 Clinical Trials*

Signifor® long-acting release (LAR)\* (pasireotide) for injectable suspension, for intramuscular use, a next-generation somatostatin analog (SSA), is approved in the US for the treatment of patients with acromegaly who have had an inadequate response to surgery and/or for whom surgery is not an option. The approval was based on two Phase III studies, C2305 and C2402, which both found higher rates of full biochemical control were achieved with Signifor LAR compared to a first generation SSA. Full biochemical control was defined as mean growth hormone (GH) level <2.5mcg/L and normal insulin-like growth factor-1 (IGF-1) levels.

### C2305

Multicenter, randomized, double-blind study evaluating the safety and efficacy of **Signifor LAR** vs. **the active comparator** in patients with active acromegaly who were not previously treated with medication (medically naïve), and had persistent disease despite prior surgery or who were ineligible for surgery

### C2402

Multicenter, randomized, study evaluating the safety and efficacy of double-blind **Signifor LAR** (40 mg and 60 mg) vs. continued open-label pre-trial SSA therapies at maximal or near maximal doses

### Trial Design



Enrolled  
**358**

medically naïve patients and patients with persistent disease despite prior surgery, or were ineligible for surgery

Enrolled  
**198**

patients with inadequately controlled acromegaly

#### Patients randomized 1:1 to receive:

- **Signifor LAR** (starting dose of 40 mg with possibility to up-titrate to 60 mg) or,
- **Active comparator**

#### Patients randomized 1:1 to receive:

- **Double-blind Signifor LAR** (40 mg and 60 mg) or,
- Pre-trial SSA therapies at maximal or near maximal doses

Defined biochemical control as mean GH level <2.5mcg/L and normal IGF-1 levels (age and sex-adjusted)

Defined inadequate control as mean GH level >2.5 mcg/L and IGF-1 >1.3 times the sex- and age-adjusted upper normal limit

# C2305

## Efficacy Endpoint



To determine the proportion of acromegaly patients achieving GH and IGF-1 biochemical control at month 12

# C2402



To compare the proportion of acromegaly patients achieving GH and IGF-1 biochemical control at 6 months



## Trial Results

### The efficacy endpoint was met:

The percentage of patients achieving biochemical control was 31.3% (55/176; 95% CI 24.5, 38.7) and 19.2% (35/182; 95% CI 13.8, 25.7) for **Signifor LAR** and **the active comparator**, respectively ( $P < .01$  for treatment difference).

Biochemical control was achieved early in the study (i.e., month 3) by 30.1% of patients in the **Signifor LAR** arm.

98% of patients treated with **Signifor LAR** had either a reduction or no change in tumor volume from baseline as assessed by MRI at month 12.

Ring size and acromegaly symptoms score (i.e., headache, fatigue, perspiration, paresthesia or tingling sensation in limbs, and osteoarthralgia or joint pain) were followed. At month 12, reductions in ring size and in symptom severity scores in both treatment groups compared to baseline were noted.

### The efficacy endpoint was met for both Signifor LAR doses at 6 months:

In the trial, 15.4% (10/65; 95% CI, 7.63, 26.48) and 20.0% (13/65; 95% CI, 11.10, 31.77) of patients treated with **Signifor LAR** 40 mg and 60 mg, respectively achieved full biochemical control compared with 0% in pre-trial SSA therapy control arm.

Biochemical control was achieved by month 3 in 15.4% and 18.5% of patients in the **Signifor LAR** 40 mg and 60 mg arms, respectively.

81% and 70% of patients treated with **Signifor LAR** 40 mg and 60 mg, respectively, had either a reduction or no change in tumor volume from baseline as assessed by MRI at month 6.

## Safety Findings

The most common adverse events (AEs) with **Signifor LAR** versus the active comparator were diarrhea (39% vs. 45%), cholelithiasis (26% vs. 36%), hyperglycemia (29% vs. 8%) and diabetes mellitus (26% vs. 4%).

The most common AEs associated with **Signifor LAR** 40 mg, 60 mg and pre-trial SSA therapies were hyperglycemia (33%, 30%, 14%) and diabetes mellitus (21%, 31%, 9%).

## For more information

For more information on the C2305 trial, please refer to the data publication in the January 2014 edition of *The Journal of Clinical Endocrinology*.

For more information on the C2402 trial, please refer to the data publication in the September 2014 edition of *The Lancet Diabetes & Endocrinology*.

## About Signifor LAR

Signifor long-acting release (LAR) (pasireotide) for injectable suspension, for intramuscular use, is now approved by the US Food and Drug Administration (FDA) for the treatment of patients with acromegaly who have had an inadequate response to surgery and/or for whom surgery is not an option.

The safety and efficacy profile of Signifor LAR has not yet been established in countries outside the US or the EU in patients with acromegaly. For various reasons, including the uncertainty of clinical trials, there is no guarantee that Signifor LAR will become commercially available for acromegaly anywhere else 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 LAR

Signifor LAR can cause serious side effects such as high blood sugar levels. Patients should tell their doctor right away if they experience signs and symptoms such as excessive thirst, high urine output, increased appetite with weight loss, and tiredness. Patients will be asked to monitor their blood glucose levels and may be given medicine to lower their blood sugar.

Signifor LAR can cause a patient's heart to beat slower or cause problems with the heart's electrical system. Patients should tell their doctor right away if they experience weakness, dizziness, and/or fainting since these can be signs of a slow heart beat or electrical problem with the heart. Patients should have their heart monitored by ECG testing before and during Signifor LAR treatment.

Signifor LAR can cause elevations in liver function tests. Patients liver function may be monitored during treatment.

Signifor LAR may affect patient's gallbladder. Patients should be monitored periodically to check for gallstones.

Signifor LAR may affect a patient's pituitary hormones. Patients may have their pituitary hormones monitored (such as thyroid, adrenal, gonadal) during treatment with Signifor LAR. Signifor LAR may cause symptoms associated with adrenal insufficiency.

Signifor LAR side effects include diarrhea, gallstones, high blood sugar, and diabetes mellitus.

Signifor LAR may interact with certain drugs and patients should tell their doctor about all of their medications. Potential drug interactions with Signifor LAR may include drugs to control heart beat (anti-arrhythmics), medicines that affect the electrical system in the heart, medicines to control blood pressure (beta-blockers or calcium channel blockers), medicines to control the electrolyte levels in the blood, cyclosporine (Gengraf<sup>®</sup>, Neoral<sup>®</sup>, Restasis<sup>®</sup>, Sandimmune<sup>®</sup>), and bromocriptine (Cycloset<sup>®</sup>, Parlodel<sup>®</sup>).

Please see full Prescribing Information for Signifor LAR.

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\*In the European Union, the long-acting release formulation of pasireotide for the treatment of acromegaly has been approved under the trade name Signifor<sup>®</sup>.

