EP-808

Trial Design of Phase IIIb, Open-Label, Single Arm Study to Evaluate Efficacy and Safety of Pasireotide Long-Acting Release (LAR) in Patients with Inadequately-Controlled Acromegaly Despite Treatment with First-Generation Somatostatin Analogues

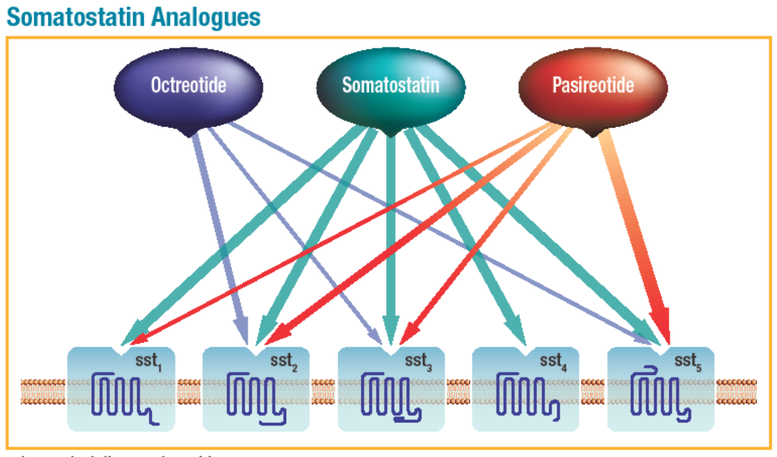
Monica R Gadelha,[1] Alberto M Pedroncelli,[2] Albert Kandra,[2] Karina Hermosillo Reséndiz,[3] AnnaMaria Colao[4]

[1]Division of Endocrinology, Medical School and Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil;
[2]Novartis Pharma AG, Basel, Switzerland; [3]Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA;
[4]Dipartimento di Medicina Clinica e Chirurgia, Università Federico II di Napoli, Naples, Italy

INTRODUCTION

- Acromegaly is a rare endocrine disorder, which is usually the result of a growth hormone (GH)-secreting pituitary adenoma. Management options for patients with acromegaly due to pituitary adenomas include transsphenoidal surgery, medical therapy, and radiotherapy.[1]
- One of the key treatment goals of acromegaly therapy is to achieve and maintain control of GH and insulin-like growth factor 1 (IGF-1), as inadequately controlled acromegaly is associated with significant morbidity and mortality.[1,2]
- Many patients remain uncontrolled despite medical treatment with first-generation somatostatin analogues (SSA) – octreotide long-acting repeatable and lanreotide Autogel (ATG).[3]
- Pasireotide, a next-generation SSA, has proven to be an effective treatment for patients with acromegaly.[4,5] Pasireotide has been recently approved for the treatment of acromegaly in US and Europe.[6,7]
- Pasireotide exerts its action by targeting the 2 most prevalent somatostatin subtype receptors (sst) 2 and 5 on GH-secreting pituitary adenomas; the binding affinity of pasireotide when compared with octreotide and lanreotide, is greater for sst_5 (39- and 85-fold, respectively), and similar for sst_2 (**Figure 1**).[8]

Figure 1. Preferential Binding Affinities of Somatostatin and Different Somatostatin Analogues



sst, somatostatin receptor subtype.

STUDY RATIONALE

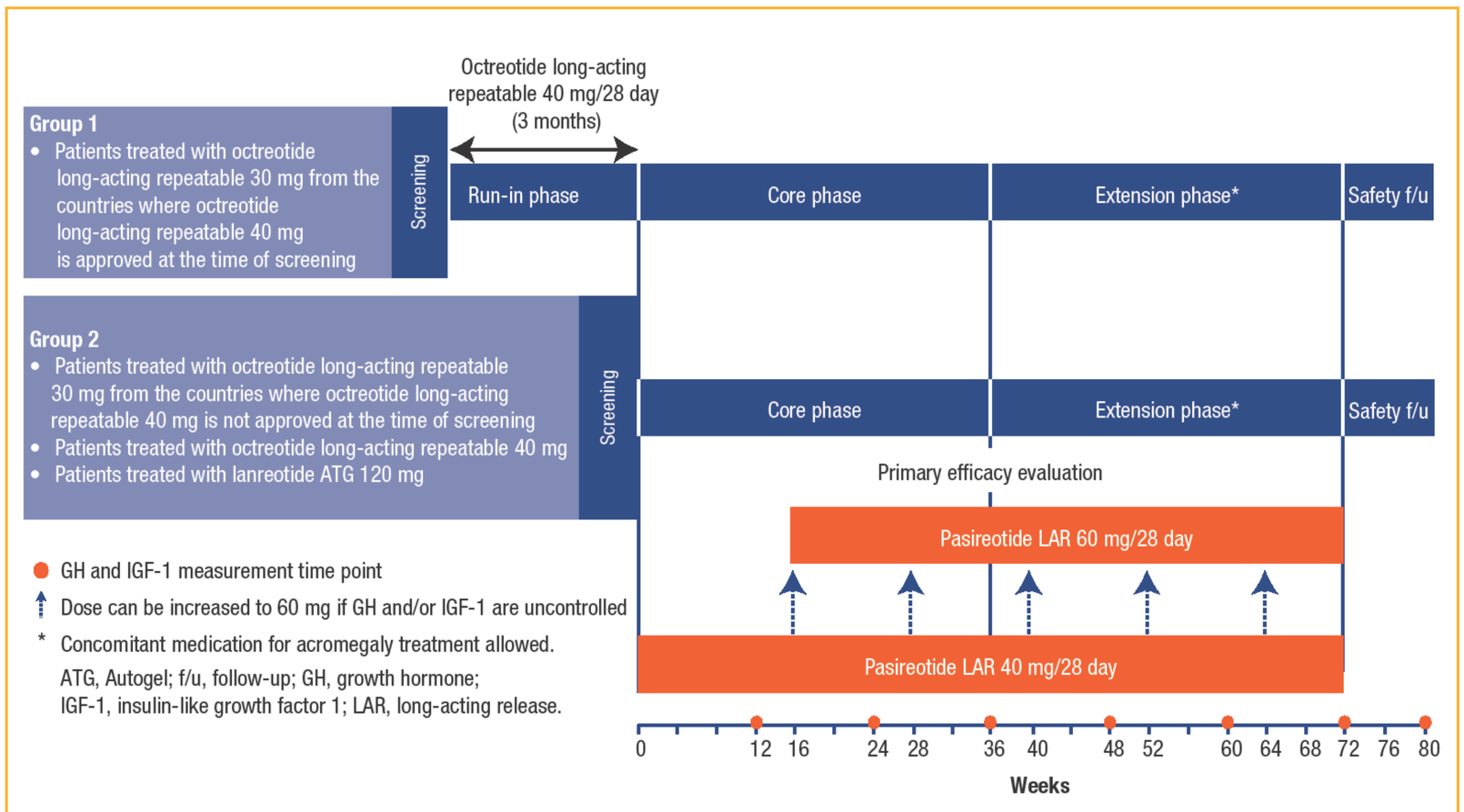
- Superior efficacy of pasireotide LAR (40 mg and 60 mg) vs continued treatment with octreotide long-acting repeatable or lanreotide ATG (active control) in providing biochemical control (mean GH levels < 2.5 µg/L and normalised IGF-1 for sex and age) has been demonstrated in patients with inadequately controlled acromegaly (PAOLA study).[5]
- The present phase IIIb, single-arm, open-label study (CSOM230C2413) is designed to evaluate the efficacy and safety of pasireotide LAR in patients with acromegaly inadequately controlled after receiving at least 3 months of treatment with the maximal approved doses of first-generation SSAs (**Table 1**).
- As per the current guidelines for medical treatment of acromegaly, the proposed GH cut-off is < 1 µg/L for biochemical control (in terms of normalising mortality rates);[2] this cut-off will be used in the current study to define response.
- In this study, supportive analyses will be carried out in 2 patient subgroups to evaluate pasireotide LAR by mean GH level at screening (**Table 1**).
  - In particular, a new patient population with mean GH between 1.0 µg/L and 2.5 µg/L at screening that was not studied in the PAOLA trial will be evaluated, in addition to patients with a mean GH > 2.5 µg/L.

Table 1. Study Endpoints

Primary
Proportion of patients with GH < 1 µg/L and IGF-1 < ULN at week 36
Supporting analyses for primary
Proportion of patients with GH < 1 µg/L and IGF-1 < ULN at week 36 in patients having mean GH level at screening between 1 µg/L and 2.5 µg/L
Proportion of patients with GH < 1 µg/L and IGF-1 < ULN at week 36 in patients having mean GH level at screening > 2.5 µg/L
Secondary (core phase)
Change in mean GH (5-point profile over a 2-hour period) from study baseline to week 36
Change in IGF-1 x ULN from study baseline to week 36
Proportion of patients (overall and by subgroups of mean GH level at screening) who achieved the following: • GH < 1 µg/L and IGF-1 < ULN at week 12 and 24 • GH < 1 µg/L at week 12, 24, and 36 • IGF-1 < ULN at week 12, 24, and 36
Adverse events that started or worsened after treatment. Laboratory incidences by Common Toxicity Criteria
Change in scores as measured by AcroQOL, EQ-5D-5L and signs and symptoms of acromegaly from baseline to weeks 12, 24, and 36

AcroQOL, Acromegaly Quality of Life Questionnaire; EQ-5D-5L, EuroQol - 5 Dimensions - 5 Levels; GH, growth hormone; HRQOL, health-related quality of life; IGF-1, insulin-like growth factor 1.

Figure 2. Study Design



METHODS

Patients

- Adults (≥ 18 years of age) with inadequately controlled acromegaly (mean GH ≥ 1.0 µg/L and sex- and age-adjusted IGF-1 > 1.3 × ULN) after at least 3 months of maximal approved doses of octreotide long-acting repeatable (30 mg or 40 mg) or lanreotide ATG (120 mg).

Study Design

- Phase IIIb, international, multicentre, open-label, single-arm study (**Figure 2**).

Run-in Phase (3 Months)

- Patients currently being treated with octreotide long-acting repeatable 30 mg, despite the availability of octreotide long-acting repeatable 40 mg at the time of screening, will enter run-in phase and will receive 3 injections (3 months) of octreotide long-acting repeatable 40 mg/28 days before being evaluated for eligibility to enter the core phase.

Core Phase (36 Weeks; Week 0-36)

- Patients will start on pasireotide LAR 40 mg/28 days.
- GH and IGF-1 will be evaluated every 12 weeks until the end-of-core phase.
- Dose adjustments will be carried out on week 16 and week 28 after biochemical control evaluations at week 12 and week 24, respectively (**Figure 2**).
  - Dose will be **increased** (to 60 mg/28 days) if patients remain uncontrolled and had no tolerability issues with pasireotide LAR 40 mg/28 days
  - Dose can be **decreased** (until 20 mg) in case of tolerability issues. Once the issue resolves, patients should resume to the previous dose
  - Same dose will be **maintained** if patients achieve biochemical control.
- During this phase, any concomitant medication for the treatment of acromegaly is prohibited.

Extension Phase (36 Weeks; Week 36-72)

- Patients will continue to receive the same dose as in core phase (40 mg/28 days or 60 mg/28 days).
- Doses of pasireotide LAR may be adjusted up to 60 mg at weeks 52 and 64 based on whether the patients achieve biochemical control at weeks 48 and 60, respectively (**Figure 2**).
- Patients remaining uncontrolled during extension phase will be allowed to receive concomitant treatment starting from week 40 with medications used to manage acromegaly as per investigator's judgment for exploratory purposes.

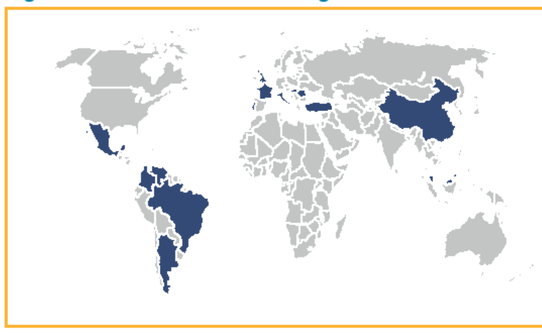
Safety Follow-up

- Safety and tolerability will be assessed throughout the study in patients who received at least one dose of study medication.
- Safety follow-up will be carried out for 8 weeks from the last study drug administration, after discontinuation from the study or completion of study treatment either at the core phase or extension phase of the study.

CURRENT TRIAL STATUS

- This study is currently enrolling patients.
- Target enrolment is a total of 112 patients (**Figure 3**).
- Clinical trial.gov identifier: NCT02354508.

Figure 3. Location of Recruiting Countries



CONCLUSIONS

- **This study will evaluate the efficacy and safety of pasireotide LAR in patients with inadequately controlled acromegaly after at least 3 months of treatment with maximal approved doses of first-generation SSAs.**
- **The definition used in this study for biochemical control is aligned with the current guidelines for medical treatment of acromegaly. Allowing the inclusion of patients with a baseline value of mean GH between 1 µg/L and 2.5 µg/L, in addition to patients with a mean GH > 2.5 µg/L, will provide data in a population not studied in the PAOLA trial.**

REFERENCES

1. Katznelson L, et al. *J Clin Endocrinol Metab*. 2014;99(11):3933-3951.
2. Giustina A, et al *Nat Rev Endocrinol.* 2014;10:243-248.
3. Carmichael JD, et al. *J Clin Endocrinol Metab.* 2014;99:1825-1833.
4. Colao A, et al. *J Clin Endocrinol Metab.* 2014;99(3):791-799.
5. Gadelha MR, et al. *Lancet Diabetes Endocrinol.* 2014;2(11):875-884.
6. Signifor LAR [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2014. Available at http://www.pharma.us.novartis.com/product/pi/pdf/signifor_lar.pdf (last accessed April 2015).
7. Novartis Pharma AG. Novartis drug Signifor approved in EU, marking an advance for patients with inadequately controlled acromegaly. 2014. Available at: http:// www.novartis.com/newsroom/media-releases/en/2014/1873488.shtml (last accessed April 2015).
8. Schmid HA. *Mol Cell Endocrinol.* 2008;286:69-74.

ACKNOWLEDGEMENT

We thank Swetha Sirimalla, Novartis Healthcare Pvt. Ltd. for providing medical editorial assistance with this poster.

Poster Presented at the European Congress of Endocrinology, Dublin, Ireland, May 16 to 20, 2015.

This study was sponsored by Novartis.

17 ECE 808--EP

Pituitary clinical

Monica Gadelha

DOI: 10.3252/pso.eu.17ece.2015

Poster presented at: ECE2015 16-20 May 2015 DUBLIN, IRELAND 17th EUROPEAN CONGRESS OF ENDOCRINOLOGY