FUNDACIÓN TEÓFILO HERNANDO
I+D del Medicamento / Drug Discovery

Multicenter, open-label, single arm, phase II exploratory study to evaluate the effect of a one-year consolidation treatment with Ponatinib 15 mg on treatment free-remission rate in patients with Philadelphia-Positive Chronic Myeloid Leukemia, who had previously achieved a deep molecular response with Imatinib

Clinical Study Report

Version 1.0

16/01/2025

1 TITLE PLAGE

STUDY TITLE: Multicenter, open-label, single arm, phase II exploratory study to evaluate the effect of a one-year consolidation treatment with ponatinib 15 mg on treatment free-remission rate in patients with Philadelphia-Positive Chronic Myeloid Leukemia, who had previously achieved a deep molecular response with imatinib.

INVESTIGATIONAL PRODUCT: Ponatinib (Iclusig®, Incyte)

INDICATION STUDIED: Chronic Myeloid Leukemia

STUDY DESIGN: Multicenter, open-label, single arm, phase II exploratory study

NAME OF THE SPONSOR: Fundación Teófilo Hernando

PROTOCOL IDENTIFICATION CODE: PonaZero_study

EUDRA-CT: 2017-004565-27

STUDY INITIATION Date (first subject enrolled): 25/06/2019

STUDY COMPLETION DATE (last subject completed): 29/04/2024

INVESTIGATORS:

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This clinical study and the archive of the essential documents have been conducted in accordance with the guide of good clinical practice.

DATE OF THE REPORT: 16/01/2025

2 SYNOPSIS

Name of the Sponsor: Fundación Teofilo Hernando **Name of the finished products: Iclusig®** **Name of Active Ingredients: Ponatinib**	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*

Title of Study: Multicenter, open-label, single arm, phase II exploratory study to evaluate the effect of a one-year consolidation treatment with ponatinib 15 mg on treatment free-remission rate in patients with Philadelphia-Positive Chronic Myeloid Leukemia, who had previously achieved a deep molecular response with imatinib.

Investigators:

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Study Centres:

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Publication (reference): Lucía Pérez-Lamas, Juan Carlos Hernandez Boluda, *et al.*; Efficacy of Consolidation Therapy with Ponatinib 15mg on Treatment-Free Remission Rate in Patients with Chronic Myeloid Leukemia. Results of the Ponazero Trial. *Blood* 2023; 142 (Supplement 1): 1795. doi: https://doi.org/10.1182/blood-2023-184989

Study Period:

Start (first patient enrolled): 25/06/2019
End (last patient last visit): 29/04/2024

Objectives:

Primary objective:

To evaluate the proportion of patients without confirmed loss of MR4 or loss of MMR within 48 weeks following ponatinib therapy cessation.

Secondary objectives:

1) To evaluate the proportion of patients without confirmed loss of MR4 or loss of MMR within 72, and 96-weeks following cessation of ponatinib therapy.
2) To estimate progression-free survival (PFS) from the date of ponatinib cessation to the date of the earliest of this event.
3) Treatment-free survival (TFS), defined as lack of any of the following: loss of MMR, confirmed loss of MR4, restart of imatinib treatment, progression of AP/BC, or death from any cause.

4) To estimate overall survival (OS), defined as the time from the date of cessation of ponatinib therapy to the date of death from any cause.
5) Proportion of patients who regain MR4 within 48 weeks of imatinib treatment re-initiation following confirmed loss of MR4 or loss of MMR in the first 48 weeks subsequent to ponatinib cessation.
6) Kinetics of BCR-ABL transcript levels (IS) after restart of imatinib therapy.

Safety objectives:

- Adverse events
- Laboratory abnormalities
- Other (vital signs and ECG)

Exploratory objectives:

- Pharmacokinetics of ponatinib
- Immunological and virological analyses

Methodology: This was a single-arm, open label multicentre study designed to determine the rate of successful TFR in patients who achieved and maintained MR4 on ponatinib.

Number of Subjects (planned and analysed):

- **Planned**: 40 patients
- **Analysed**: 23 patients

Diagnosis and main criteria for inclusion:

1. Male or female patients ≥ 18 years of age.
2. ECOG performance status of 0, 1, or 2.
3. Patient with diagnosis of BCR-ABL positive CML-CP.
4. Patient has received a minimum of 4 years of imatinib treatment, as unique TKI therapy.
5. Patient has achieved MR4 during at least 12 months with imatinib treatment and determined by PCR lab assessment at screening.
6. Adequate end organ function as defined by:
   a. Direct bilirubin ≤ 1.5 x ULN.
   b. SGOT(AST) and SGPT(ALT) ≤ 2.5 x ULN (upper limit of normal),
   c. Serum lipase and amylase ≤ 1.5 x ULN,
   d. Alkaline phosphatase ≤ 2.5 x ULN,
   e. Serum creatinine ≤ 1.5 x ULN.
7. Patients must have the following electrolyte values ≥ LLN limits or corrected to within normal limits with supplements prior to the first dose of study medication:
   a. Potassium
   b. Magnesium
   c. Total calcium (corrected for serum albumin)
8. Patients must have normal marrow function as defined below:
   a. Absolute neutrophil count (ANC) ≥ 1.5 x 109/L,
   b. Platelets ≥ 100 x 109/L,
   c. Hemoglobin > 9.0 g/dL
9. Patients with preexisting, well-controlled, diabetes are not excluded.

10. Have normal QTcF interval on screening ECG evaluation, defined as QTcF of ≤ 450 ms in males or ≤ 470 ms in females.
11. Have a negative pregnancy test documented prior to enrollment (for females of childbearing potential). Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, must have a negative serum pregnancy test before initiation of study treatment and must also use highly effective methods of contraception while enrolled in the study. The use of highly effective contraception should continue for at least 14 days after the last dose of study treatment or until the last day of TFR or for the duration of a monthly cycle of oral contraception, whichever is longer.
12. Be willing and able to comply with scheduled visits and study procedures.
13. Written informed consent obtained prior to any screening procedures.

Test product, dose and mode of administration, batch number: Ponatinib (15 mg/day orally).

Duration of Treatment: 48 weeks with ponatinib

Reference therapy, dose and mode of administration, batch number: Not applicable

Criteria for Evaluation:

Primary efficacy:

- Proportion of patients without confirmed loss of MR4 or loss of MMR within 48 weeks of ponatinib TFR.

Secondary efficacy variables:

1) Proportion of patients without documented loss of MR4 or loss of MMR at 72 and 96 weeks after discontinuation of ponatinib treatment.
2) Estimation of Progression Free Survival (PFS) after discontinuation of ponatinib.
3) Estimation of Treatment-Free Survival (TFS) after discontinuation of ponatinib.
4) Estimation of Overall Survival (OV) after discontinuation of ponatinib.
5) Proportion of patients who regained MR4 within 48 weeks of imatinib treatment re- initiation.
6) Kinetics of BCR-ABL transcript levels (IS) after restart of imatinib therapy.

Statistical Methods:

For the primary efficacy variable, the rate of successful TFR is presented together with an exact 95% Clopper-Pearson confidence interval. The null hypothesis is rejected and successful TFR demonstrated if the lower limit of the 95% confidence interval is greater than 0.10. Primary efficacy analysis was performed on the FAS. For the primary efficacy variable, the analysis time point is when all patients who enter the TFR phase and completed 48 weeks of TFR phase or terminated the study earlier.

For the primary analysis of the rate of successful TFR, patients dropping out early from the study during the TFR phase will be considered to be unsuccessful TFR and will be included in the FAS.

Analyses Methods for Secondary Objectives

The rate of molecular responses at the time points defined in the protocol after starting the TFR phase as well as the rate of patients who failed to achieve MR4 and MMR with imatinib retreatment are presented together with an exact 95% Clopper-Pearson confidence interval. Kinetics of BCR-ABL transcript levels after restart of imatinib therapy are presented by a box-plot of BCR-ABL ratio over time.

All time to event endpoints including duration of retreatment required to regain MMR and MR4, TFS, PFS and OS were analyzed using the KM method and are presented by KM plots.

PFS on study (including the survival follow-up period) and OS on study is determined separately in patients who never enter the TFR phase.

Safety analysis

The incidence of treatment-emergent adverse events (new or worsening from baseline) are summarized by system organ class and/or preferred term, severity (based on CTCAE grades), type of adverse event, relation to study treatment by the phases or subsets previously described.

Other safety data collected (e.g., ECG, vital signs) is listed and summarized using descriptive statistics as appropriate.

Summary – Efficacy and safety data:

Efficacy data:

23 CML patients that were included in this study. Of these, 22 were included in the efficacy analysis. 19 completed the 1-year consolidation phase maintaining their molecular response and discontinued the treatment. 6 of the patients who entered the TFR phase lost molecular response (confirmed loss of MR4 or loss of MMR) and resumed TKI treatment. Therefore, the proportion of patients without confirmed loss of MR4 or loss of MMR within 48 weeks following ponatinib TFR was (19-6)/19 = 13/19 = 0.684 or 68.4%.

This rate was maintained up until the end of the follow-up period at 96 weeks as all patients who lost MR after entering the TFR phase lost it relatively early, in the first few months after treatment discontinuation, between visits 14 and 17 (cycles 4 and 7 of the TFR phase).

At 175 days (25 weeks) of follow-up the percentage of treatment-free survival patients was 68.4% (50.4% - 92.9%).

Ponatinib favours the proliferation of the cytotoxic NK cells and Tγδ CD8- lymphocytes which could play a major role in the elimination of the HIV-1 infected cells and the viral reservoir of the virus.

Short-term treatment with ponatinib could induce a potent anticancer response in those CML patients in whom elevated levels of NK cells are observed at baseline. The monitoring of biomarkers such as the degranulation capacity of T-CD8+, as well as the increased TNF production from NKTlike cells, or the elevated levels of NKs in blood could act as prognostic markers of disease progression in people discontinuing CML treatment.

Safety data:

95.7% of the patients included in the safety analysis reported at least one AE, with a total of 161 AEs. 109 were reported during the ponatinib consolidation phase. Most of the events were mild. The most common AEs in the consolidation phase were musculoskeletal and connective tissue disorders (20.28%), followed by gastrointestinal disorders (15.6%) and general disorders (14.7%).

17 patients (73.9% of the recruited subjects) reported 36 putative AR to ponatinib. Most reactions (n=24) were considered mild, n=4 were moderate and n=8 severe. The most common putative adverse reactions were general disorders and administration site conditions (n=10), skin and subcutaneous tissue disorders (n=6) and gastrointestinal disorders (n=5) (Table 12). The most prevalents reactions were rash (n=6), asthenia (n=4) and constipation (n=3).

There were no SAEs reported during the study. There were 3 AESIs, 2 of them considered severe and probably related with the study medication intermittent claudication and superficial thrombophlebitis, which lead to the discontinuation of the patient. All AESIs were resolved.

3 patients withdrawn due to adverse events, two of them due to the onset of a series of different events and one due to the abovementioned AESIs.

There were no deaths and no disease progression during the study.

Overall, all safety data is in concordance with the actual understanding of the IMP's safety and tolerability and no relevant new safety hazards or changes in the severity, seriousness or frequency of the adverse reactions were detected in the study. The number of patients that have lost their molecular response after treatment discontinuation are within expected ranges, and all have recovered the molecular response.

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Conclusions:

- 1-year treatment with ponatinib can lead to a successful treatment discontinuation for CML patients for at least 2 years.
- The successful discontinuation rate achieved after one-year consolidation treatment with ponatinib appears to be higher than those previously observed with other TKIs, like imatinib and nilotinib.
- The safety data obtained is in alignment with current knowledge of ponatinib. No new safety data or concerns have arisen during the study.
- There is no apparent correlation between blood concentration of ponatinib and the probability of successful discontinuation of the treatment in CML patients.
- Immunological biomarkers like the degranulation capacity of lymphocytes T-CD8+, TNFα production from NKT-like cells or NK cells levels could act as prognostic biomarkers of relapse for treatment discontinuation strategies in LCM patients.
- Further studies shall be done to confirm discontinuation rates and establish the usefulness of the biomarkers analysed in this study to predict the individual likelihood of successful treatment discontinuation.

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