Abstract: LB2710

Title: TARGETED THERAPY OF UNCONTROLLED ERYTHROCYTOSIS IN POLYCYTHEMIA VERA WITH THE HEPCIDIN MIMETIC, RUSFERTIDE: - BLINDED RANDOMIZED WITHDRAWAL RESULTS OF THE REVIVE STUDY

Abstract Type: Oral Presentation

Session Title: Late-Breaking Oral Session

Background:

Polycythemia vera (PV) is a clonal myeloproliferative neoplasm characterized by uncontrolled erythrocytosis, systemic symptoms and an increased risk of thromboembolic (TE) and cardiovascular (CV) complications. Therapeutic phlebotomy (TP), with or without cytoreductive agents (CYTO) is used to control hematocrit (HCT) levels <45% to improve symptoms and decrease the risk of TE and CV complications. We previously reported results demonstrating that adding rusfertide to prior PV treatments more optimally controls HCT levels and decreases the need for TP (EHA 2022). Herein, we report results from the randomized withdrawal phase (Part 2) which was unblinded on March 2, 2023 and represents the primary objective of the REVIVE study.

Aims:

To investigate the effect of rusfertide, a first-in-class hepcidin mimetic, on the control of erythrocytosis in patients with PV.

Methods:

The REVIVE (PTG-300-04) trial (NCT04057040) consists of three stages (Fig 1). Eligibility criteria: diagnosis of PV (WHO 2016 criteria); ≥3 TPs in the 28 wk prior to enrollment with or without concurrent CYTO. Subcutaneous rusfertide was added to prior PV therapy. During Part 1 (28 wk), rusfertide dose was adjusted individually to control HCT <45%. During Part 2 (wk 29-41), the blinded randomized withdrawal phase, patients were randomized to either continue rusfertide or to matching placebo. A patient was defined as a responder if 3 criteria were met 1) HCT control without phlebotomy eligibility, 2) no TP, and 3) completed 12 wk of treatment. Need for TP was triggered by a) HCT ≥45% and ≥3% higher than wk 29 pre-randomization HCT or b) HCT>48% or c) ≥5% increase in HCT compared to wk 29 HCT. Responders and non-responders were allowed to participate in Part 3, a 3- yr open-label extension.

Results:

53 subjects were randomized (27 placebo, 26 rusfertide) and completed part 2. Demographics: Median age 58 yr (range, 27-77); 37 men (71.7%) 15 women (28.3%); concurrent therapy: PHL alone 29 (54.7%) PHL + CYTO 24 (45.3%). Response rate was 69.2% for rusfertide compared to 18.5% for placebo (p=0.0003; Fig 2A). Subgroup analysis showed superior efficacy for rusfertide relative to placebo in both concurrent therapy groups: TP alone (p=0.02, Fig 2B) and TP+CYTO (p=0.02, Fig 2C). Rusfertide significantly improved maintenance of response, absence of the need for TP and persistent HCT control compared to placebo (p<0.0001, Fig 3). In Part 1 the phlebotomy-free rate was 76.9% (wk 1-17) and 87.3% (wk 17-29). In Part 2, the rate was 92.3% for rusfertide cohort. Rusfertide was generally well tolerated; 83% of treatment-emergent adverse events (TEAEs) were grade 1-2, 17% were grade 3 with none grade 4 or 5. Most common TEAEs were injection site reactions (ISRs), which were localized, and grade 1-2 in severity. ISRs decreased in incidence with continued treatment. Only 2 TEAEs led to treatment discontinuation. Of the 70 patients enrolled, 52 (74.3%) have been treated for ≥1 year, 32 (45.7%) for ≥1.5 years, and 10 (14.3%) for ≥2 years, indicating long-term tolerability of rusfertide.

Summary/Conclusion:

The randomized withdrawal phase of the REVIVE study met its primary endpoint and demonstrated that rusfertide is a highly effective agent in patients with PV receiving TP with or without CYTO. Rusfertide is a novel hepcidin

mimetic that selectively targets uncontrolled erythrocytosis in PV. Rusfertide is well tolerated and produces sustained and durable HCT control, obviating the need for TP in PV patients.

Fig 1 - Trial Design PTG-300-04

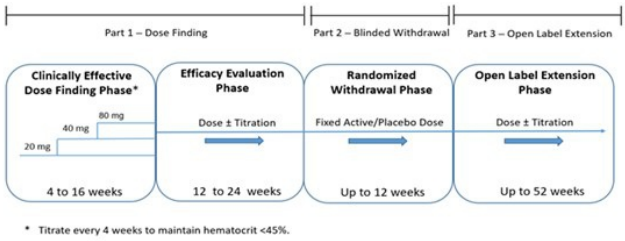

Fig 2 – Efficacy of Rusfertide and Placebo Treatment in Part 2. (A) Percent of Responders; (B) Efficacy in Phlebotomy Alone cohort; (C) Efficacy in Phlebotomy + Cytoreductive Therapy cohort

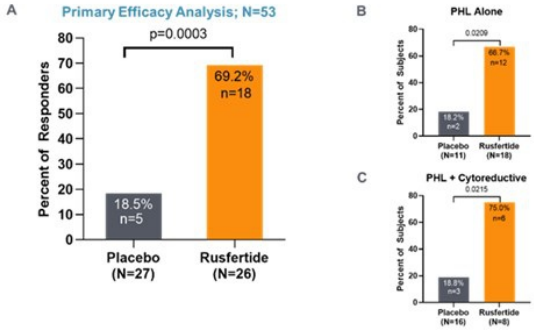

Fig 3 – Rusfertide Treatment Delays Time to Event on Multiple Outcomes Compared to Placebo