EUROPEAN HEMATOLOGY ASSOCIATION

EHA2021 VIRTUAL

S263

THE SAFETY, PHARMACOKINETICS & PHARMACODYNAMIC EFFECTS OF IMR-687, A HIGHLY-SELECTIVE PDE9 INHIBITOR, IN ADULTS WITH SICKLE CELL DISEASE: PHASE-2A PLACEBO-CONTROLLED & OPEN-LABEL EXTENSION STUDIES

Topic: 26. Sickle cell disease

Keywords: Clinical trial | Hemoglobinopathy | Phase II | Sickle cell disease

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Background: IMR-687 is a highly-selective phosphodiesterase 9 (PDE9) inhibitor being developed as an orally-administered therapy for patients with sickle cell disease (SCD) and beta-thalassemia. IMR-687 increases intracellular cGMP levels by activating the NO-cGMP pathway and has been shown in preclinical studies to increase fetal hemoglobin (HbF) expression and reduce hemolysis and sickling of RBCs, pivotal to the reduction of sickle cell crisis.

Aims: The objective of this Phase 2a study is to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of IMR-687 as a monotherapy and in combination with hydroxyurea (HU) when administered to subjects with SCD. An open label extension (OLE) of the Phase 2a study is ongoing to assess the long-term safety and benefit of IMR-687 administered for up to 4 years.

Methods: This Phase 2a, randomized, double-blind, placebo-controlled study (IMR-SCD-102) of IMR-687 was conducted in adult subjects with SCD as a monotherapy or in combination with HU. Subjects received placebo or IMR-687 (50 mg escalated to 100 mg or 100 mg escalated to 200 mg) once daily for 4-6 months. On the OLE, subjects received 200 mg IMR-687 once daily. PK, PD parameters [e.g., HbF, F-cells, hemoglobin (Hb) and markers of hemolysis] and vaso-occlusive crises (VOCs) were measured. In preliminary post-hoc analyses of Phase 2a results, longitudinal data of absolute change from baseline in PD parameters were analyzed using mixed model repeated measures (MMRM) with fixed effect of treatment, visit week, treatment-by-visit-week interaction and covariates of baseline value and baseline-by-visit-week interaction.

Results: A total of 93 subjects were randomized and treated in the 'parent' Phase 2a study. As of data cut-off (31-Dec-2021), 24 subjects from the parent study enrolled in the OLE, with ~12 subjects with evaluable PD data at 4 months. Results to date indicate that IMR-687 was generally safe and well-tolerated as a monotherapy and in combination with HU and had no substantial PK effect on HU. No treatment-related serious adverse events were reported, and the most frequent adverse events (≥10%) were sickle cell anemia with crisis, headache and nausea. In subjects treated with IMR-687 without HU (parent study), the LS mean (SEM) absolute change from baseline to Week 24 in F-cells (%) was +5.66 (2.87) in the 100/200 mg group (N=13), compared with -6.00 (3.77) in the placebo group (N=7), for an LS mean difference of 11.66 (SEM=4.72; p=0.0190). A trend for improvement in HbF (%) was

observed in active groups without HU (compared to placebo group). Absolute changes in F-cells (%) and HbF (%) were highly-correlated in the IMR-687 groups without HU after 24 weeks (N=19, r=0.75, p<0.0001). In subjects on the OLE, at month 4, HbF (%) and F-cells (%) showed a mean absolute change of +1.9 and +7.3, respectively, with minimal changes in Hb. Two patients with the longest time on study (18 and 8 months) showed a 64% and 69% reduction, respectively, in rate of VOCs (relative to same time prior to treatment) as well as sustained changes in HbF, F-cells and markers of hemolysis.

Summary/Conclusion: Results from the Phase 2a and OLE studies (as of data cut-off) demonstrate that daily dosing of up to 200 mg IMR-687 was safe and well-tolerated as a monotherapy or in combination with HU. Treatment with 200 mg IMR-687 was shown to increase F-cells (%) with trends for improved HbF, markers of hemolysis and rate of VOCs. Based on these encouraging data, a Phase 2b study testing IMR-687 at higher doses was initiated to further explore IMR-687 as a disease-modifying therapy for SCD.

Abstract Book Citations: Authors, Title, HemaSphere, 2021;5:(S2):pages. Abstract Book, DOI:
http://dx.doi.org/10.1097/HS9.0000000000000566