ELSEVIER

Blood 142 (2023) 1085–1086

The 65th ASH Annual Meeting Abstracts

POSTER ABSTRACTS

101.RED CELLS AND ERYTHROPOIESIS, EXCLUDING IRON

Safety and Efficacy of Mitapivat in Adult Patients with Erythrocyte Membranopathies (SATISFY)

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Background:
Membranopathies encompass hemolytic disorders arising from genetic defects in erythrocyte membrane proteins and include hereditary spherocytosis and stomatocytosis. Congenital dyserythropoietic anemia type II (CDA II) is associated with *SEC23B* gene variants and its phenotype may be similar to hereditary spherocytosis. Anemia with or without the need for chronic transfusion, jaundice, splenomegaly, iron overload are complications common in both hereditary membranopathies and CDA II. Current treatment options for membranopathies and CDA II [1], apart from splenectomy, are primarily supportive. Mitapivat, an investigational pyruvate kinase-R (PKR) activator, has demonstrated efficacy in improving anemia and reducing hemolysis in adult patients with PK deficiency, thalassemia, sickle cell disease, and a mouse model of hereditary spherocytosis.

Study Design and Methods:
This study (NCT05935202) is an investigator initiated, prospective, multicenter, single-arm phase 2 trial. The study will be conducted in the European Union in Denmark and The Netherlands. It is the first clinical study in the context of the European Reference Network EuroBloodNet and will be sponsored by its closely associated non-for-profit EuroBloodNet *Association*. A sibling study in Toronto, Canada will be registered separately, and data will be pooled in a prespecified statistical analysis plan.
The study will include approximately twenty-five adult patients (aged 18 years and older) diagnosed with a membranopathy or CDA II. Diagnosis must be confirmed genetically. Average hemoglobin concentration (Hb) must be less than 13.0 g/dL for males and 11.0 g/dL for females. Patients with average Hb >10.0 g/dL for males and females at screening must meet at least one of the following additional criteria: Splenomegaly, fatigue attributed to hemolysis, or paraclinical hemolysis. Adequate organ function is required. Patients cannot be included if they have a diagnosis of PK deficiency or if they have received red blood cell (RBC) transfusions (≥5 units the last 12 months or any within the last 3 months).
During the 8-week Dose Escalation Period, subjects will receive an initial dose of 50 mg mitapivat twice daily (BID). Based on safety and changes in Hb levels, dosing may be increased to 100 mg BID at week 4. Patients who tolerate mitapivat may be eligible to continue in two consecutive 24-week Fixed Dose Periods, with an interim analysis in between the two fixed dose periods.
The primary objective of this study is to evaluate the safety of mitapivat, assessed through the occurrence of treatment-emergent adverse events. Secondary objectives include assessing the effects of mitapivat on Hb concentration (≥1.0 g/dL increase sustained at two scheduled visits), hemolysis, erythropoiesis, patient-reported outcome measures, and spleen size.

Exploratory endpoints include enzyme activity and stability of PK, Hb oxygen affinity, proteomics and metabolomics. To assess how activation of PK will impact RBC function we will measure RBC deformability (osmotic gradient ektacytometry and cell membrane stability) in whole blood and in different RBC subpopulations.

Acknowledgement:
This project is carried out within the framework of European Reference Network on Rare Haematological Diseases (ERN-EuroBloodNet)-Project ID No 101085717. ERN-EuroBloodNet is partly co-funded by the European Union within the framework of the Fourth EU Health Programme.
The study is funded by a grant from Agios Pharmaceuticals.

References:

1. Iolascon A, Delaunay J, Wickramasinghe SN, et al. Natural history of congenital dyserythropoietic anemia type II. *Blood*. 2001;98(4):1258-1260.

Disclosures Glenthoej: *Bristol Myers Squibb:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Agios:* Consultancy, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Pharmacosmos:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *bluebird bio:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Sanofi:* Research Funding; *Novartis:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Novo Nordisk:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Saniona:* Research Funding. **Van Beers:** *Agios:* Consultancy, Research Funding; *Novartis:* Research Funding; *Pfizer:* Research Funding; *RR Mechatronics:* Research Funding. **van Wijk:** *Agios:* Consultancy, Research Funding; *Pfizer/GBT:* Research Funding. **Rab:** *Axcella Health Inc.:* Research Funding; *Pfizer:* Research Funding; *Agios Pharmaceuticals Inc.:* Consultancy, Research Funding. **Fenaux:** *AbbVie:* Consultancy, Honoraria, Research Funding; *Bristol Myers Squibb:* Consultancy, Honoraria, Research Funding; *Janssen:* Consultancy, Honoraria, Research Funding; *Jazz:* Consultancy, Honoraria, Research Funding; *Novartis:* Consultancy, Honoraria, Research Funding; *French MDS Group:* Honoraria. **Kuo:** *Novo/Nordisk:* Consultancy, Honoraria; *Bioverativ/Sanofi/Sangamo:* Membership on an entity's Board of Directors or advisory committees; *Pfizer:* Consultancy; *Forma Therapeutics:* Consultancy; *Bristol Myers Squibb:* Consultancy, Honoraria; *Alexion Pharmaceuticals:* Consultancy; *Agios Pharmaceuticals:* Consultancy, Research Funding; *Vertex Pharmaceuticals:* Consultancy.

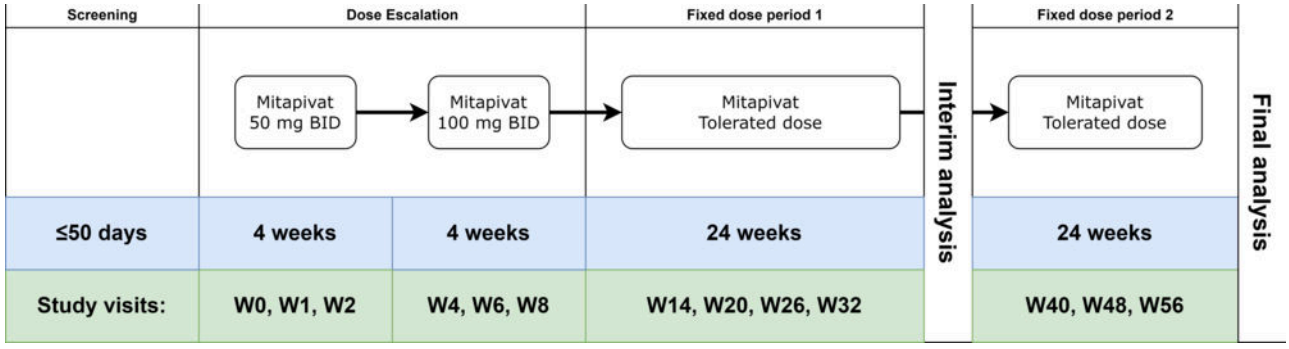

Figure 1

https://doi.org/10.1182/blood-2023-173147