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

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Background:

- Membranopathies encompass hemolytic disorders arising from pathogenic genetic variants in erythrocyte membrane proteins, including hereditary spherocytosis and stomatocytosis.
- Congenital dyserythropoietic anemia type II (CDA II) is associated with the *SEC23B* gene and can exhibit phenotypic similarities to membranopathies.
- Current treatment options, apart from splenectomy, are primarily supportive.
- Mitapivat, an investigational pyruvate kinase (PK) activator, has demonstrated efficacy in increasing hemoglobin (Hb) levels in adult patients with PK deficiency, thalassemia, sickle cell disease, and a mouse model of hereditary spherocytosis.

Hypothesis:

We hypothesize that mitapivat will be safe, increase Hb and ameliorate hemolysis in patients with RBC membranopathies or CDAII.

Trial in progress:

- NCT05935202 / CTIS: 2023-503271-24-01
- Investigator initiated, prospective, multicenter, single-arm phase 2 trial.
- Approximately 25 adult patients:
  - Denmark and Netherlands: ~16 patients
  - Canada: ~9 patients (sibling study)
- First study to evaluate disease modifying therapy for membranopathies or CDAII.
- Enrollment: From early 2024.
- Sponsor: Non-profit EuroBloodNet *Association*.

Key Inclusion Criteria

- Membranopathy or CDAII
- Genetically confirmed *ACMG class 3, 4, or 5*
- Age ≥18 years
- Hb concentration:
  <13.0 g/dL for males
  <11.0 g/dL for females
- Adequate organ function

Key Exclusion Criteria

- PKLR — Pyruvate kinase deficiency diagnosed with decreased PK activity or two pathogenic PKLR alleles
- Blood transfusion within last 3 months or >5 units the last year
- Significant medical comorbidity
- Receiving hematopoietic stimulating agents

Figure 1: Key inclusion and exclusion critaria. CDAII: Congenital dyserythropoietic anemia type II.
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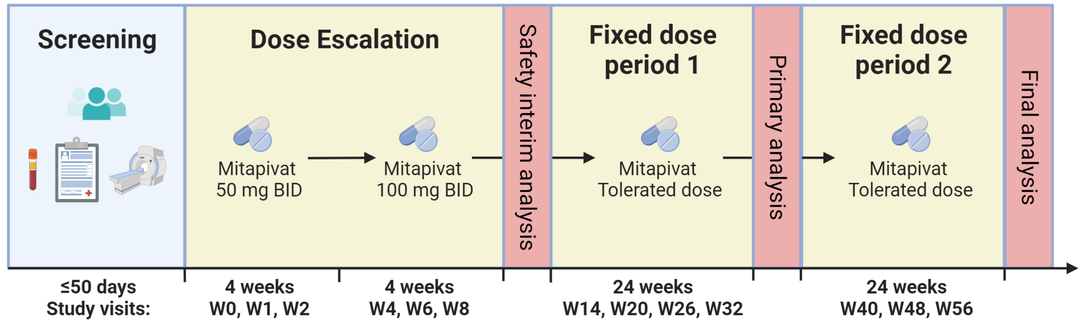

Figure 2: Study flowchart
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Primary objective

Safety
Type, incidence, severity and relationship of mitapivat to AE and SAE

Secondary objectives

Hemoglobin
≥1 g/dL increase
Average increase

Hemolysis
LDH, bilirubin, haptoglobin

Erythropoiesis
EPO, erythroferrone, sTfR

Health related quality of life
SF-36 v1
PKDIA

Spleen
Change in size in non-splenectomized

Exploratory objectives

Red blood cell
Lifespan
Metabolism
Membrane flexibility and stability

Iron metabolism
Hepcidin, ferritin, transferrin saturation
MRI: Hepatic and cardiac iron

Figure 3: Study objectives.
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