Mitapivat improves markers of erythropoietic activity in long-term study of adults with alpha- or beta-non–transfusion-dependent thalassemia

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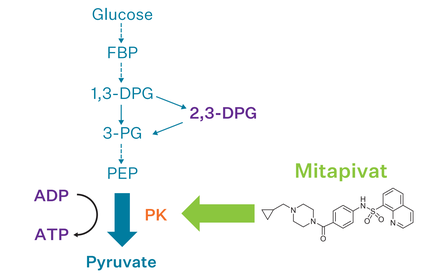
BACKGROUND

- Thalassemia is a group of genetic disorders impacting α- and/or β-globin genes, resulting in an imbalance of globin production[1,2]
  - Excess globin chains precipitate and are toxic to red blood cells (RBCs), directly leading to ineffective erythropoiesis and hemolysis[2]
- Thalassemic RBCs lack sufficient levels of ATP to meet the increased energy demands associated with degradation of globin chain precipitates and cellular oxidative stress responses[3,4]
- Although patients with non–transfusion-dependent thalassemia (NTDT) do not require regular blood transfusions for survival, it can result in chronic anemia and serious complications[1,2]
  - Treatment options for NTDT are supportive only, highlighting an unmet need for disease-modifying therapies[5]
- Mitapivat is an investigational, first-in-class, oral, small-molecule allosteric activator of pyruvate kinase (PK) in RBCs, a key enzyme that regulates ATP production[6]
- Mitapivat activates PK in RBCs, which catalyzes the final step of glycolysis (**Figure 1**)[7]

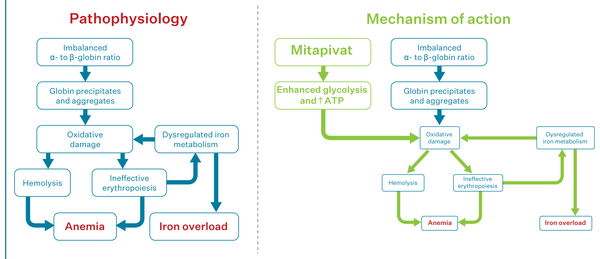
Figure 1. Mitapivat's mechanism of action



ADP, adenosine diphosphate; ATP, adenosine triphosphate; DPG, diphosphoglyceric acid; FBP, fructose 1,6-bisphosphate; PEP, phosphoenolpyruvic acid; PG, phosphoglyceric acid; PK, pyruvate kinase

- Activation of wild-type and mutant PK increases RBC ATP levels[6,7]
  – ATP generation is essential for RBC function and stability[6,8]
- Mitapivat increased PK activity and ATP levels *ex vivo* in RBCs from patients with β-thalassemia (**Figure 2**)[9]
- Mitapivat ameliorated ineffective erythropoiesis, iron overload, and anemia in the $Hbb^{th3/+}$ mouse model of β-thalassemia (**Figure 2**)[10]

Figure 2. Pathophysiology and proposed mitapivat mechanism of action in thalassemia



ATP, adenosine triphosphate

METHODS

- This is a phase 2, open-label study to determine the efficacy, safety, pharmacokinetics, and pharmacodynamics of mitapivat in adult subjects with α- or β-NTDT (**Figure 3**)

Figure 3. Design of open-label, phase 2 study of mitapivat in adults with α- or β-NTDT[a]

Core period[11]
Primary endpoint
- Hb response, defined as ≥1.0 g/dL increase in Hb concentration from baseline at 1 or more assessments between Weeks 4 and 12, inclusive

Key inclusion criteria
- β-thalassemia ± α-globin gene mutations, HbE β-thalassemia, or α-thalassemia (HbH disease)
- Hb ≤10.0 g/dL
- Non–transfusion-dependent

Long-term extension[12]
Key inclusion criteria
- Completed 24-week core period
- Achieved a primary Hb response, or achieved a delayed Hb response (Hb increase of ≥1.0 g/dL at ≥1 assessment after Week 12)
- No ongoing grade ≥3 TEAEs related to study drug

[a]EudraCT 2018-002217-35, ClinicalTrials.gov: NCT03692052; BID, twice daily; dL, deciliter; Hb, hemoglobin; HbE, hemoglobin E; HbH, hemoglobin H; NTDT, non-transfusion-dependent thalassemia; TEAE, treatment-emergent adverse event

Results from core period (previously presented)[11]
- The primary endpoint of hemoglobin (Hb) response was met in 80.0% (16/20) of patients
- Improvements in markers of hemolysis and erythropoietic activity were also observed
- Mitapivat was generally well tolerated at both the initial 50 mg twice-daily dose and the increased 100 mg twice-daily dose
  – The most common adverse events were initial insomnia (50%), dizziness (30%), and headache (25%)

Results from long-term extension (LTE) period (previously presented)[12]
- In the LTE period, the increase in Hb was sustained with a mean Hb (SD) increase of 1.7 g/dL (0.5) at Week 72
- Improvements in erythropoietin, total bilirubin, and lactate dehydrogenase were maintained up to data cutoff at Week 72
- Mitapivat was generally well tolerated, and the safety profile was consistent with that of previously published mitapivat studies

OBJECTIVE

- **To report erythropoietic activity, hemolysis, and iron homeostasis from the LTE period through Week 72 (data cutoff 27March2022)**

RESULTS

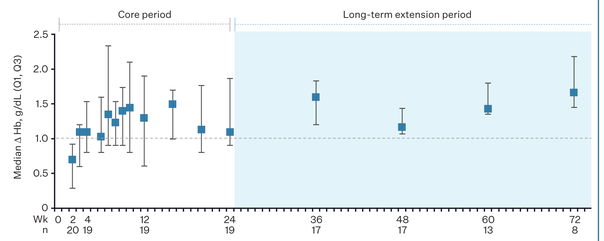
- The baseline characteristics of the subset of patients who entered the LTE (N=17) were similar to those of the core period full analysis set (N=20)
- At baseline, biomarkers were consistent with ineffective erythropoiesis and hemolysis (**Table 1**)
- Sustained improvements in Hb were observed throughout the extension period (**Figure 4**)
- Markers of erythropoietic activity remained stable or improved through Week 72 (**Figure 5**)
- Improvements in markers of hemolysis were observed through Week 72 (**Figure 6**)
- Markers of iron homeostasis remained stable or improved through Week 72 (**Figure 7**)

Table 1. Patient demographics and baseline[a] characteristics for patients in the core study period

Patient demographics and baseline characteristics from the core period[11]	All patients (N=20)
Sex, n (%)	
Male	5 (25)
Female	15 (75)
Age, median (Q1, Q3), years	44 (35, 56)
Race, n (%)	
Asian	10 (50)
White	4 (20)
Black or African	1 (5)
Native Hawaiian or other Pacific Islander	1 (5)
Other	3 (15)
Not reported	1 (5)
Thalassemia type, n (%)	
α-thalassemia	5 (25)
β-thalassemia	15 (75)
Baseline biomarkers from the core period[11]	**All patients (N=20)**
Hb baseline, median (Q1, Q3), g/dL	8.4 (6.78, 8.98)
Erythropoietin, median (Q1, Q3), IU/L	79.0 (29.0, 137.0)
Erythroferrone, median (Q1, Q3), ng/L	10,760.0 (3627.5, 17,712.5)
Indirect bilirubin, median (Q1, Q3), μmol/L	21.0 (15.5, 36.1)
Reticulocytes/erythrocytes, median (Q1, Q3), fraction of 1	0.04 (0.030, 0.044)
Hepcidin, median (Q1, Q3), ng/L	40,750.0 (27,250.0, 53,750.0)
Soluble transferrin receptor, median (Q1, Q3), nmol/L	174.1 (90.59, 268.24)

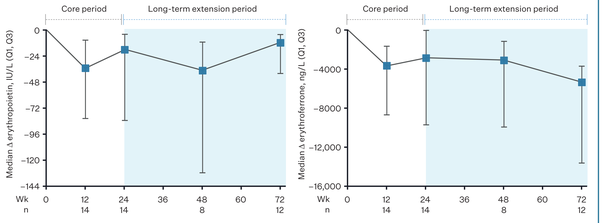
[a]Baseline is defined as the last assessment on or before the start of study treatment in the core period
Hb, hemoglobin; Q, quartile

Figure 4. Median Hb change from baseline over time



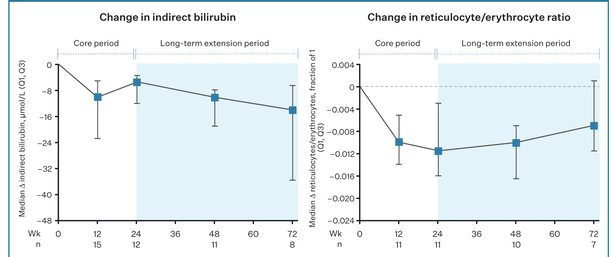
Hb, hemoglobin; Q, quartile; Wk, week

Figure 5. Markers of erythropoietic activity



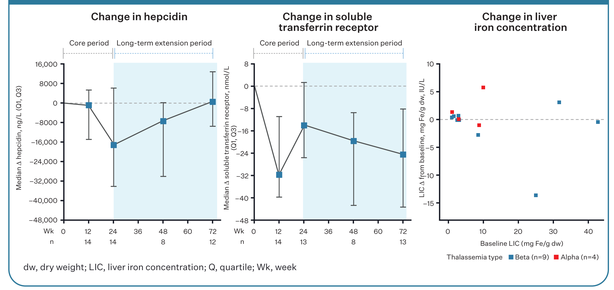
Q, quartile; Wk, week

Figure 6. Markers of hemolysis



Q, quartile; Wk, week

Figure 7. Markers of iron homeostasis



dw, dry weight; LIC, liver iron concentration; Q, quartile; Wk, week

CONCLUSIONS

- **Along with long-term improvements in Hb concentration, improvements in markers of erythropoietic activity and hemolysis were observed through Week 72 in patients with α- or β-NTDT treated with mitapivat**
- **Markers of iron homeostasis remained stable or improved through Week 72**
- **These new data suggest that mitapivat's mechanism of action may ameliorate multiple aspects of the complex pathophysiology underlying α- or β-NTDT**
- **Phase 3 studies[a,b] in patients with α- and β-NTDT and transfusion-dependent thalassemia are ongoing**

[a]EudraCT 2021-000211-23, ClinicalTrials.gov: NCT04770753; [b]EudraCT 2021-000212-34, ClinicalTrials.gov: NCT04770779

Mitapivat may offer a novel disease-modifying approach with potential long-term benefits in hemolysis, erythropoiesis, and iron homeostasis for patients with α- or β-NTDT

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