RESULTS FROM A PHASE 2 STUDY OF MITAPIVAT IN ADULTS WITH NON –TRANSFUSION-DEPENDENT ALPHA- OR BETA-THALASSEMIA

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Objectives: Thalassemias are characterized by ineffective erythropoiesis and hemolysis due to imbalanced production and precipitation of globin chains. Adenosine triphosphate (ATP) levels are reduced in thalassemic red blood cells (RBCs), despite increased energy demands to maintain RBC cell integrity. Mitapivat (AG-348) is an oral activator of RBC pyruvate kinase (PKR), an enzyme regulating ATP production via glycolysis. In mice, mitapivat increased ATP synthesis and survival of thalassemic RBCs. Mitapivat has been shown to increase hemoglobin (Hb) in patients (pts) with PK deficiency and sickle cell disease. Results of the 24-week (wk) core period of a phase 2 open-label trial of mitapivat in adults with α- or β-non–transfusion-dependent thalassemia (NTDT; NCT03692052) are reported here. **Material and methods:** Key inclusion criteria: β-thalassemia $\pm\alpha$-globin gene mutations, Hb E β-thalassemia, or α-thalassemia (Hb H disease); Hb $\leq$10.0 g/dL; $\leq$5 RBC units transfused in prior 24 wks and none in prior 8 wks. Pts received mitapivat 50 mg orally twice daily (BID), then increased to 100 mg BID at Wk 6 visit, if tolerated. Primary endpoint was % pts who achieved a Hb response (increase $\geq$1.0 g/dL from baseline [BL] at any time between Wks 4–12, inclusive). Secondary endpoints included sustained Hb response ($\geq$2 Hb increases of $\geq$1.0 g/dL vs BL during Wks 12–24 after achieving a primary Hb response), time to first $\geq$1.0 g/dL Hb increase, markers of hemolysis and erythropoiesis, and safety. **Results:** Of 20 pts (15 female) who received mitapivat, the mean age (SD) was 45.3 (11.8) yrs (range 29–67); mean (SD) BL Hb was 7.9 (1.4) g/dL (range 5.1–9.8). At Wk 6, all pts were escalated to 100 mg BID. Nineteen pts (95.0%) completed the core period, one discontinued due to adverse event (AE);17 pts continued to the extension period. Sixteen pts (80.0%, 90% CI 59.9, 92.9; $p < 0.0001$) achieved a Hb response, including 5/5 pts with α-thalassemia and 11/15 pts with β-thalassemia. Mean (SD) time to first Hb increase >1.0 g/dL was 4.5 (3.2) wks, and mean Hb (SD) increase from BL during Wks 12–24 was 1.3 (0.6) g/dL. A sustained response was achieved in 65% of pts, including 5/5 pts with α-thalassemia and 8/15 pts with β-thalassemia. Hb increases occurred across the spectrum of BL levels. Directional improvements in markers of erythropoiesis and hemolysis were also observed. The safety profile was consistent with previously published mitapivat studies. There was one serious grade 3 unrelated AE of renal impairment, leading to treatment discontinuation. There were three non-serious grade 3 AEs leading to dose reduction: 1 resulted in a permanent dose reduction to 50 mg BID, and 2 were successfully rechallenged at 100 mg BID. The most common non-serious AEs occurring in $\geq$25% of pts were initial insomnia (10/20), dizziness (6/20), and headache (5/20). Dose escalation to 100 mg BID was well tolerated and not associated with any increase in AEs. Twelve pts had DXA scans at BL and 6 months; no notable changes in bone mineral density were observed. **Discussion:** These results demonstrate that PKR activation with mitapivat was well tolerated and improved anemia, hemolysis, and ineffective erythropoiesis, and may represent a novel therapeutic approach for pts with α- or β-thalassemia. **Conclusion:** The study met its primary endpoint with 80% of pts achieving a Hb response.

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SEQUESTRO HEPÁTICO SECUNDÁRIO A INFECÇÃO POR EPSTEIN-BARR EM CRIANÇA COM DOENÇA FALCIFORME

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Relato de caso: Paciente masculino, 4 anos e 10 meses, portador de Doença Falciforme (padrão SS), esplenectomizado devido a história prévia de sequestro esplênico, em uso regular de hidroxiureia e penicilina benzatina. Foi admitido com quadro de dor abdominal e crise álgica em ombro, sem outros sintomas associados, em bom estado geral, anictérico e corado, sem visceromegalias. Exames laboratoriais na admissão: Hb 10,3 g/dL, Ht 30,4%, leucócitos 32300/μL (segmentados 23% - 7429/μL, bastonetes 2% - 646/μL, linfócitos 66% - 21318/μL, linfócitos atípicos 5% - 1615/μL), plaquetas 332.000/μL, reticulócitos 7,1%, bilirrubina total (BT) 1,7 mg/dL, bilirrubina direta (BD) 0,2 mg/dL, bilirrubina indireta (BI) 1,5 mg/dL, desidrogenase lática (DHL) 972 U/L e proteína C reativa (PCR) 4,4. Optado por internação hospitalar para controle álgico e antibioticoterapia endovenosa (ceftriaxone). Após 72 horas, paciente evoluiu com febre, obstrução nasal, linfonodomegalia cervical, exsudato em orofaringe, palidez e icterícia progressivas, associado à colúria e a hepatomegalia palpável a 8 cm do rebordo costal direito (RCD). Solicitados novos exames laboratoriais: Hb 7,7 g/dL, Ht 22,3%, leucócitos 64590/μL (segmentados 13% - 8397/μL, linfócitos 40% - 25836/μL, linfócitos atípicos 44% - 28420/μL), plaquetas 169000/μL, reticulócitos 4%, BT 9,2 mg/dL, BD 7,7 mg/dL, BI 1,5 mg/dL, DHL 1770, PCR 6,5, fosfatase alcalina 514 U/L, gama-glutamil transferase (gama-GT) 327 U/L, proteínas totais 6,1, albumina 3,1, globulina 3, aspartato aminotransferase (AST) 467 U/L, alanina aminotransferase (ALT) 372 U/L. Aventadas hipóteses diagnósticas de sequestro hepático (queda de Hb e de plaquetas e aumento abrupto de fígado) e hepatite transinfecciosa (aumento de transaminases e BD, em vigência de quadro