Abstract Submission

28. Enzymopathies, membranopathies and other anemias

EHA-1726

PHARMACOKINETIC MODELING AND SIMULATION TO SUPPORT MITAPIVAT DOSE SELECTION USED IN PEDIATRIC PHASE III STUDIES

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Background: Mitapivat (AG-348) is a first-in-class, oral, small molecule, allosteric activator of the red blood cell pyruvate kinase (PK) enzyme (PKR). The positive benefit-risk profile of mitapivat has been demonstrated in two recently completed phase 3 studies in adults with PK deficiency who are not regularly transfused (ACTIVATE, NCT03548220) or regularly transfused (ACTIVATE-T, NCT03559699). Currently, two phase 3 studies are being initiated to evaluate the efficacy and safety of mitapivat in pediatric subjects aged 1 to <18 years (yrs) with PK deficiency who are not regularly transfused (ACTIVATE-Kids, NCT05144256) or regularly transfused (ACTIVATE-KidsT, NCT05175105).
Aims: Conduct a pharmacometrics analysis to support the mitapivat dose selection in the phase 3 studies in pediatric subjects.
Methods: A three compartment population pharmacokinetic model with allometrically scaled parameters (clearances and volume of distribution) was applied. Dose simulations were conducted for various age subsets and body weight ranges using data from the National Health and Nutrition Examination Survey (NHANES) database. For subjects aged 1 to <2 yrs, in addition to allometric scaling, maturation factors (Salem F et al. *Clin Pharmacokinet*. 2014;53:625–36. Salem F et al. *Clin Pharmacokinet*. 2015;54:671) accounting for changes in cytochrome P450 (CYP) 3A activity were implemented. This approach was employed because mitapivat is metabolized primarily by CYP3A, and maturational changes in CYP3A ontogeny are known to occur during the first few yrs of life. The selected pediatric dose for each age subset and weight range was based on a dose that was predicted to achieve mitapivat exposure (ie, the area under the plasma concentration-time curve [AUC] during a dosing interval at steady state) similar to that achieved in adults receiving the recommended clinical dose for PK deficiency (dose titrations occurring every 4 weeks, from 5 mg twice daily [BID] to 20 mg BID, and then to the maximum recommended dose of 50 mg BID).
Results: The proposed dosing scheme is shown in the Table. For subjects aged 12 to <18 yrs who weigh ≥40 kg, the recommended dose used in adults would provide a similar mitapivat AUC to that achieved in adults; the predicted difference is <20%, and therefore is not considered to be clinically meaningful. For subjects aged 12 to <18 yrs who weigh <40 kg, or subjects aged 2 to <12 yrs, dosing according to body weight (≥40 kg, ≥20 to <40 kg, and <20 kg) would yield similar mitapivat AUC ranges between pediatric and adult subjects. For subjects aged 1 to <2 yrs, the proposed doses shown in the Table are predicted to provide <5% difference in mitapivat AUC as compared with adults.
Image:

Table. Proposed mitapivat dose scheme in phase 3 pediatric study

Age	Dose level 1: Starting dose (mg, BID dosing)	Dose level 2 (mg, BID dosing)	Dose level 3 (mg, BID dosing)
1 to <2 yrs	1	4	10
2 to <12 yrs			
Weight <20 kg	1	5	15
Weight ≥20 to <40 kg	2	10	20
Weight ≥40 kg	5	20	50
12 to <18 yrs[a]	5	20	50

[a]Dose to be administered only if patients 12 to <18 years of age weigh ≥40 kg. If patients 12 to <18 years of age weigh <40 kg, dosing by weight as described for the 2 to <12 years of age category should be followed. BID=twice daily; Yrs=years.

Summary/Conclusion: Population pharmacokinetic modeling and simulation was utilized to identify candidate doses for evaluation in mitapivat pediatric phase 3 studies. The selected doses for each pediatric age subset and body weight range are projected to provide mitapivat AUC similar to that achieved in adults receiving the recommended clinical dose.

Keywords: AG-348, Pediatric, Pharmacokinetic, Pyruvate kinase deficiency