Activator Treatment for Pyruvate Kinase Deficiency – Results from Phase 1 and Overview of Phase 2 trial

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Pyruvate kinase (PK) deficiency is a rare genetic disorder of metabolism resulting in chronic hemolytic anemia, with comorbidities including iron overload and multi-organ dysfunction. Defective glycolysis in red blood cells leads to increases in the metabolic precursor, 2,3-diphosphoglycerate (2,3-DPG), and deficiency of the product, adenosine triphosphate (ATP). AG-348 is an oral allosteric activator of both wild type and multiple mutant PK-Rs.

Aims: To assess safety, tolerability, and pharmacokinetics/pharmacodynamics (PK/PD) of AG-348 in healthy volunteers and identify a dosing schedule for future trials in patients with PK deficiency.

Methods: A phase 1, single-center, randomized, double-blind, placebo-controlled MAD study (NCT02149966) was conducted in healthy men and women (18–60 years) in 6 sequential cohorts (each cohort: n=6 AG-348, n=2 placebo [P]). Subjects gave informed consent and received oral AG-348 at 15–700 mg twice daily (q12h) or 120 mg once daily (q24h) for 14 days with follow-up to Day 29. Adverse events (AEs), laboratory parameters, ECGs, and vital signs were monitored. Plasma AG-348 concentrations and whole blood 2,3-DPG and ATP levels were measured in serial blood samples for PK/PD assessment. Hormone levels were monitored due to pre-clinical data suggesting potential modulation.

Results: 48 subjects (42M/6F), mean age 41.5 (range, 25–60) years, enrolled. Final, un-blinded safety data showed ≥1 AE in 16/36 (44%) AG-348-treated and 4/12 (33%) Placebo subjects. Treatment-related AEs (≥1) were noted in 11/36 (31%) AG-348-treated and 3/12 (25%) Placebo subjects. All treatment-related AEs were mild or moderate in severity (only one grade 3 event) and often reversible despite continued dosing. The most frequent AG-348-related AEs were nausea and headache, 5/36 (14%) for each. Gastrointestinal AEs occurred in AG-348-treated subjects only at the highest dose, 700 mg q12h. One grade 3 AE occurred (AG-348 700 mg q12h, elevated liver function tests [LFTs], which resolved after treatment discontinuation). There were 4 AG-348 discontinuations: due to AEs in 2 subjects (grade 2 drug eruption, 60 mg q12h; grade 3 elevated LFTs, 700 mg q12h), and 2 subjects withdrew consent (both had grade 1/2 nausea and grade 1/1 vomiting; both at 700 mg q12h). The highest well-tolerated dose was 360 mg q12h (doses between 360 and 700 mg were not explored). Plasma AG-348 exposure was dose-dependent, with low to moderate variability in the PK parameters of AG-348 and its metabolite AGI-8702. There was a dose-dependent decrease in 2,3-DPG and increase in ATP with the effects plateauing at 360 mg q12h. Decrease in 2,3-DPG was robust after Dose 1, while the increase in ATP occurred gradually and was strongly evident at Day 8. Change from baseline in 2,3-DPG and ATP plateaued at ~300 µg/mL (~50% decrease) and ~175 µg/mL (~50% increase), respectively.

Summary/Conclusion: AG-348 showed a robust 2,3-DPG/ATP PD glycolytic profile at well-tolerated doses in healthy volunteers. The results support proceeding with a planned phase 2 trial in patients with PK deficiency.