

Population Pharmacokinetics and Pharmacodynamics of AG-348 in Healthy Human Volunteers Guide Dose Selection for the Treatment of Pyruvate Kinase Deficiency

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Abstract



INTRODUCTION: Pyruvate kinase (PK) deficiency is a glycolytic enzymopathy that results in non-spherocytic hemolytic anemia with a variable clinical presentation, ranging from mild or fully compensated forms to life-threatening neonatal anemia and life-long chronic hemolytic anemia associated with severe, debilitating co-morbidities. PK deficiency is caused by mutations in the *PKLR* gene, which in the red blood cell (RBC) results in defective pyruvate kinase isoform R (PK-R). PK-R catalyzes the final, irreversible step in glycolysis, the process on which mature RBCs rely almost exclusively to generate the energy carrier molecule adenosine triphosphate (ATP). PK-deficient RBCs and their progenitors are characterized by changes in metabolism associated with defective glycolysis, including a build-up of phosphoenolpyruvate (PEP) and 2,3-diphosphoglycerate (2,3-DPG), and lowered ATP levels. AG-348 is an orally available, allosteric activator of PK-R. It is hypothesized that intervention with AG-348 restores glycolytic pathway activity and normalizes RBC metabolism *in vivo* (Kung C et al. *Blood*, 2013). Biochemical experiments demonstrate that AG-348 is a potent pan-activator of many PK-R alleles associated with PK deficiency. Treatment of PK-deficient patient RBCs *ex vivo* with AG-348 results in

increased ATP levels, and reductions in PEP and 2,3-DPG, consistent with pharmacological activation of the PK-R enzyme. This analysis integrates the pharmacokinetic and pharmacodynamic (PK/PD) properties of AG-348 in healthy human volunteers using population PK/PD modeling and simulation.

METHODS: PK/PD modeling using a non-linear mixed effects approach was performed to understand the pharmacokinetics of AG-348 and PK/PD relationship of AG-348 to 2,3-DPG and ATP in humans. The PK/PD model integrated data from two phase 1, single-center, randomized, double-blind, placebo-controlled, dose escalation studies (one single and one 14-day multiple ascending dose) that enrolled a total of 96 healthy volunteers (Yang H et al. EHA Learning Center, 2015). AG-348 dose level ranged from 15-2500 mg given once (QD) or twice (BID) daily. Blood was collected from all patients to assess AG-348 pharmacokinetics, and for determination of levels of ATP and 2,3-DPG. Population simulations using the final model were performed to examine the dose-exposure-biomarkers relationship at various dose levels and duration of dosing.

RESULTS: AG-348 showed rapid absorption following oral administration. Plasma exposure of AG-348 increased in a dose-proportional manner following a single dose. A three-compartmental model with a non-linear absorption compartment and a saturable induced enzyme compartment best described the pharmacokinetics of AG-348. Time-varying clearance was added to describe the observed decrease in exposure over time with multiple dosing; this is consistent with pre-clinical data that AG-348 is a moderate inducer of CYP3A4, the major oxidation pathway of AG-348. The multiple-dose data were well described by a semi-mechanistic autoinduction model with an indirect model and a saturable induction compartment. The PK/PD relationship between plasma AG-348 to ATP and 2,3-DPG showed best fit with a turnover model where the drug effect was described by an $E_{\max}$ model. Model simulations predicted maximum enzyme induction and PD response 3 weeks after the first dose following BID dosing. Population PK/PD simulations further supported the choice of 50 mg and 300 mg BID doses for the phase 2 study (**Fig 1** and **2**). The proposed current model incorporating PK/PD data over a wide range of AG-348 exposures and time-varying changes in clearance provides a useful tool for prediction of AG-348 pharmacokinetics that can be used to optimize AG-348 dosing for PK deficiency treatment. Furthermore, the population PK/PD model of AG-348 to ATP and 2,3-DPG biomarkers in healthy volunteers provides a good foundation to facilitate the analysis and understanding of patient data in the ongoing phase 2 study.

CONCLUSION: This study represents the first comprehensive longitudinal analysis of AG-348 and its PD activity in humans. This integrated PK/PD model, incorporating time-varying PK/PD properties, forms the basis for understanding the exposure-response relationship in the ongoing phase 2 and future clinical studies of AG-348, as well as providing guidance on dosing selection to optimize the treatment of PK deficiency.

Figure 1.

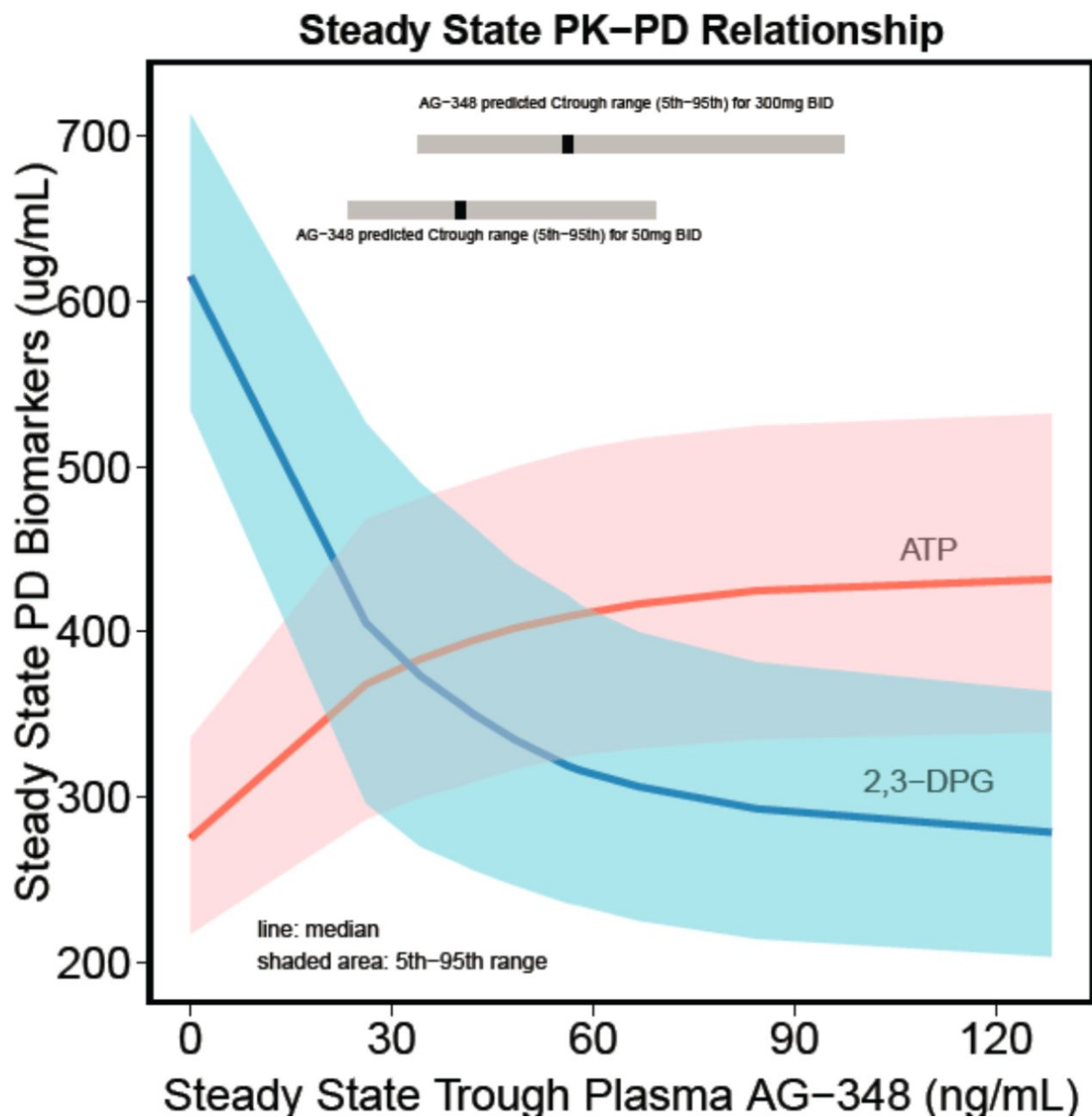
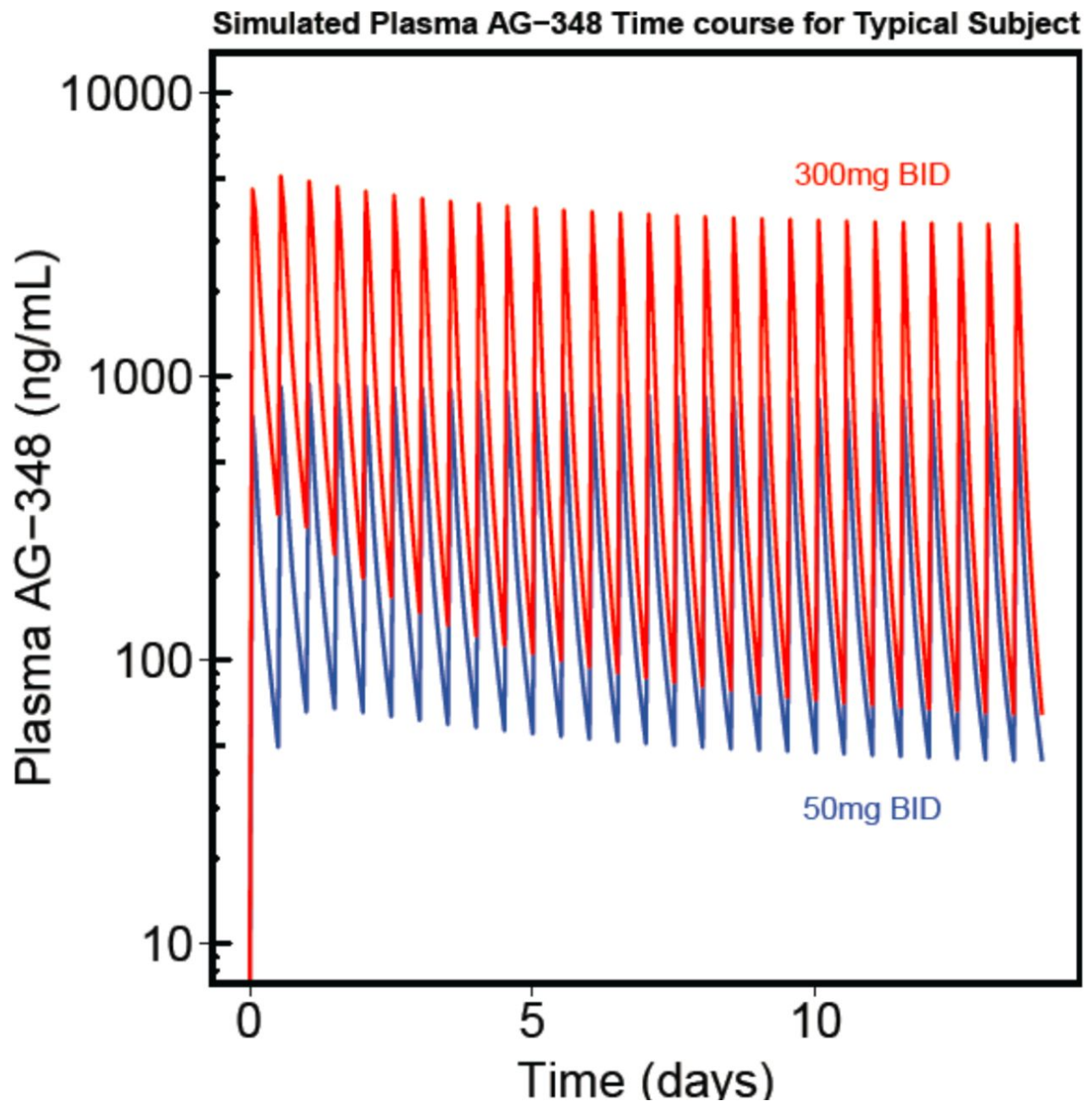


Figure 2.



Disclosures

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