Population pharmacokinetics and pharmacodynamics of AG-519, a pyruvate kinase activator for the treatment of pyruvate kinase deficiency, in human healthy volunteers

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BACKGROUND

- Pyruvate kinase (PK) deficiency is a nonspherocytic hemolytic anemia caused by a functional deficiency of the red blood cell glycolytic enzyme PK isoform R (PK-R) due to mutations in the *PKLR* gene.
- PK-R catalyzes the final irreversible step in glycolysis, which is the main source of the energy carrier molecule adenosine triphosphate (ATP) in red blood cells.
- PK deficiency is characterized by changes in metabolism associated with defective glycolysis, including a buildup of 2,3-diphosphoglycerate (2,3-DPG) and lowered ATP levels in whole blood.
- AG-348 and AG-519 are, respectively, the first and second small-molecule activators of PK-R (wild type and a range of mutants) to enter clinical trials.
- Increases in ATP and decreases in 2,3-DPG induced by small-molecule allosteric activation of PK-R by AG-348[1] and AG-519[2] have been observed in healthy volunteers.
- This analysis integrates the pharmacokinetic and pharmacodynamic (PK/PD) properties of AG-519 in healthy volunteers using population PK/PD modeling and simulation.

OBJECTIVES

- To characterize the population pharmacokinetics of AG-519 in healthy volunteers using data from a phase 1 single ascending dose (SAD) and multiple ascending dose (MAD) study.
- To characterize the dose and exposure response of three biomarkers (PK-R activity, 2,3-DPG, and ATP) in healthy volunteers.
- To compare the PK/PD relationships of AG-519 and AG-348.
- To use the population PK/PD analysis parameter values for simulated steady-state exposures and biomarker response to provide guidance on dose selection to inform future studies of AG-519.

METHODS

- PK/PD data from a phase 1, single-center, randomized, double-blind, placebo-controlled dose-escalation study (ClinicalTrials.gov NCT02630927) were included in this analysis.
- A total of 72 healthy volunteers received placebo or AG-519, either as a single dose or as multiple doses over 14 days.
- The AG-519 dose level ranged from 50 to 1250 mg once daily and from 10 to 375 mg twice daily (BID).
- Rich sampling was performed on Day 1 (SAD and MAD studies), and on Day 14 with sparse sampling in between (MAD study).
- Blood was collected from all subjects to assess AG-519 pharmacokinetics and concentrations of ATP and 2,3-DPG in blood, and from subjects receiving BID doses in the MAD study for determination of PK-R activity.
- PK/PD modeling using a nonlinear mixed effects approach was performed to understand the pharmacokinetics of AG-519 and the PK/PD relationship of AG-519 to 2,3-DPG, ATP, and PK-R activity in healthy volunteers.
- Population simulations using the final model were performed to examine the steady-state dose–exposure–biomarkers relationship at various dose levels.
- Modeling analysis and simulations were performed using NONMEM 7.3.

RESULTS

Pharmacokinetics

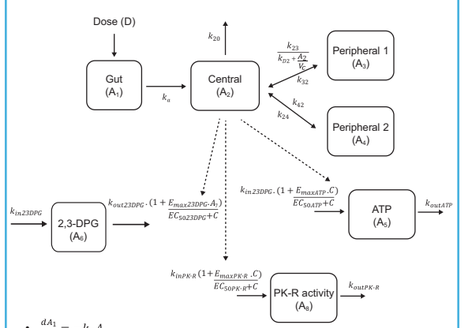
- The pharmacokinetics of AG-519 were described by a three-compartmental model with first-order absorption (**Figures 1** and **2A**).
- The model was able to describe the pharmacokinetic data, with the model prediction adequately reflecting individual pharmacokinetic profiles from the SAD and MAD cohorts when overlapped (MAD data shown in **Figure 2A**).
- First-order and time-independent clearance best describe the pharmacokinetics following multiple dosing, suggesting no auto-induction of metabolism is involved, evidenced by dose-proportional increase in exposure.[2]
- Intersubject variability of k_a, CL/F, and V_c/F modeled as exponential error (range 20–34%; **Table 1**).

Table 1. Model parameters

Parameter	Unit	Value	RSE, %	Intersubject variability, %
Pharmacokinetic parameters				
k_a	1/hr	0.8	18.3	20.2
CL/F	L/hr	58.2	7.2	33.7
V_c/F	L	80.5	21.2	27.8
Q1	L/hr	1098	11.7	
V_{p1}	L	34,305	14.8	
Q2	L/hr	17.5	11.3	
V_{p2}	L	43	10.1	
k_{b2}	µg/L	34.8	24.6	
Pharmacodynamic parameters				
BL_{ATP}	µg/mL	325		17.1
EC_{50ATP}	ng/mL	3.7		199.32
E_{maxATP}	Dimensionless	0.7		
k_{outATP}	1/hr	0.0052		
BL_{23DPG}	µg/mL	592		14.07
$EC_{5023DPG}$	ng/mL	54.6		56.27
$E_{max23DPG}$	Dimensionless	1.4		15.25
$k_{out23DPG}$	1/hr	0.052		35.01
k_{in}	1/hr	0.08		
BL_{PK-R}	nmol/sec/g	32.7	2.3	12.12
EC_{50PK-R}	ng/mL	17.1	7.3	
$E_{maxPK-R}$	Dimensionless	0.8	16.7	51.41
$EC_{50PK-R2}$	ng/mL	0.8	114.4	
$E_{maxPK-R2}$	Dimensionless	0.2	16.7	50.07
$k_{outPK-R}$	1/hr	0.02	60.7	

$BL_{ATP,0}$, $BL_{23DPG,0}$, $BL_{PK-R,0}$ = baseline 2,3-DPG and ATP concentrations, and PK-R activity, in the blood; CL/F = apparent total clearance of the drug from plasma after oral administration; EC_{50ATP} = half-maximal 2,3-DPG response concentration; EC_{50ATP} = half-maximal ATP response concentration; EC_{50PK-R} = half-maximal PK-R activity response concentration (direct, fast response); $EC_{50PK-R2}$ = half-maximal PK-R activity response concentration (delayed response); $E_{max23DPG}$ = maximal 2,3-DPG response; E_{maxATP} = maximal ATP response; $E_{maxPK-R}$ = maximal PK-R activity response; $E_{maxPK-R2}$ = maximal PK-R activity (delayed response); k_a = absorption rate constant; k_{12} = distribution rate constant; k_{23} = effect-compartment equilibrium rate constant; $k_{out23DPG}$ = 2,3-DPG degradation rate constant; k_{outATP} = ATP degradation rate constant; $k_{outPK-R}$ = PK-R activity degradation rate constant; Q1, Q2 = intercompartmental clearance; RSE = relative standard error; V_c/F = apparent central volume of distribution; V_{p1},V_{p2} = peripheral volume of distribution

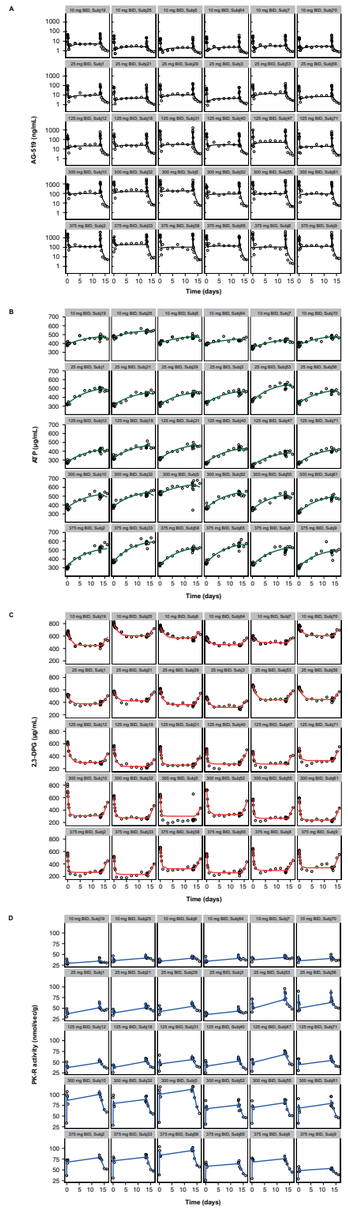
Figure 1. AG-519 PK/PD model schematic and model structure



- $\frac{dA_1}{dt} = -k_a A_1$
- $\frac{dA_2}{dt} = k_a A_1 - k_{23} \frac{A_2}{k_{b2}+\frac{A_2}{V_c}} + k_{32} A_3 - k_{24} A_2 + k_{42} A_4 - k_{20} A_2$
- $\frac{dA_3}{dt} = k_{23} \frac{A_2}{k_{b2}+\frac{A_2}{V_c}} - k_{32} A_3$
- $\frac{dA_4}{dt} = k_{24} A_2 - k_{42} A_4$
- $\frac{dA_5}{dt} = BL_{ATP} \cdot k_{outATP} \cdot (1 + E_{maxATP} \cdot \frac{\frac{A_2}{V_c}}{EC_{50ATP}+\frac{A_2}{V_c}}) - A_5 \cdot k_{outATP}$
- $\frac{dA_6}{dt} = BL_{23DPG} \cdot k_{out23DPG} - A_6 \cdot k_{out23DPG} \cdot (1 + E_{max23DPG} \cdot \frac{A_7}{EC_{5023DPG}+A_7})$
- $\frac{dA_7}{dt} = k_{eo} \cdot (\frac{A_2}{V_c} - A_7)$
- $\frac{dA_8}{dt} = BL_{PK-R} \cdot k_{outPK-R} \cdot \left(1 + E_{maxPK-R2} \cdot \frac{\frac{A_2}{V_c}}{EC_{50PK-R2}+\frac{A_2}{V_c}}\right) - A_8 \cdot k_{outPK-R}$
- $A_9 = A_8 \cdot \left(1 + E_{max\,PK-R} \cdot \frac{\frac{A_2}{V_c}}{EC_{50PK-R}+\frac{A_2}{V_c}}\right)$

A_1 = amount of AG-519 in gut; A_2 = amount of AG-519 in blood; A_2 = concentration of AG-519 in peripheral compartment 1; A_3 = amount of AG-519 in peripheral compartment 2; A_5 = ATP concentration in blood; A_6 = 2,3-DPG concentration in blood; A_7 = effect compartment; A_8 = PK-R activity elicited by long-term effect; A_9 = PK-R activity in blood; $k_{20} = CL/V_c$; $k_{23} = Q1/V_c$; $k_{32} = Q1/V_p$; $k_{42} = Q2/V_p$; $k_{24} = Q2/V_{p2}$

Figure 2. Model goodness of fit with profiles MAD cohorts: (A) plasma AG-519 concentration; (B) plasma ATP concentration; (C) plasma 2,3-DPG concentration; (D) PK-R activity in plasma



Pharmacodynamics

- The longitudinal time course of ATP and 2,3-DPG can be described by an indirect response model (**Figures 1** and **2B–C**).
  - Plasma AG-519 stimulates rate of production (k_{in}) of ATP and degradation (k_{out}) of 2,3-DPG, in accordance with the hypothesized mechanism of action of AG-519.
- The pharmacological effect on PK-R activity appears to be best described by two components: an immediate effect described by a direct E_{max} model, and a long-term delayed effect described by an indirect effect model, where AG-519 stimulates the rate of increase of PK-R enzyme activity (**Figure 2D**).
- 2,3-DPG and PK-R activity reached steady state at ~5 days, and ATP at ~30 days, following BID dosing (**Figure 3A–D**).
- Dose levels ranging from 10 to 70 mg BID would be predicted to result in a similar response to that seen with doses of AG-348 being evaluated in the ongoing phase 2 study of AG-348 in patients with PK deficiency (DRIVE-PK, ClinicalTrials.gov NCT02476916) (**Figure 3**, **Figure 4**).
- AG-519 is a potent PK-R activator, resulting in a similar pharmacological effect at slightly lower plasma exposures when compared with AG-348 (**Figure 4**).

Figure 3. Simulated time courses of plasma exposure and biomarker response (A–D), and steady-state plasma exposure–biomarker response and dose–exposure relationships (E–H), following AG-519 dosing

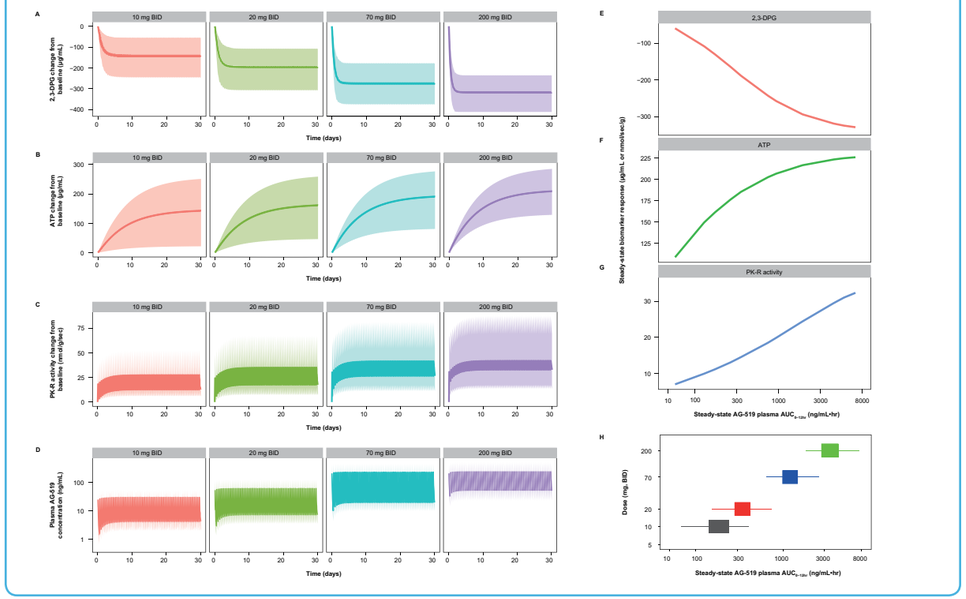
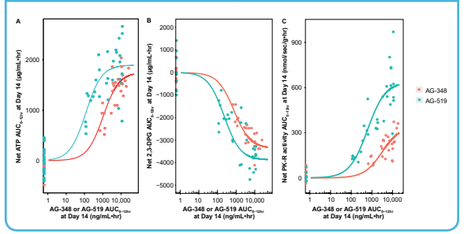


Figure 4. PK/PD comparison between AG-519 and AG-348: (A) ATP; (B) 2,3-DPG; (C) PK-R activity



CONCLUSIONS

- This study represents a comprehensive longitudinal PK/PD analysis of AG-519 and its pharmacodynamic activity in human healthy volunteers.
- AG-519 is a potent PK-R activator with favorable pharmacokinetic parameters.
- This integrated PK/PD model, incorporating time-varying PK/PD properties:
  - Forms the basis for understanding the exposure–biomarker response relationship in the phase 1 and future clinical studies of AG-519.
  - Provides guidance for dose selection to optimize the potential treatment of PK deficiency.
- The predicted steady-state exposure–biomarker response relationship can be combined with the biomarker response–clinical efficacy relationship, learned from the ongoing phase 2 DRIVE PK study of AG-348 in patients with PK deficiency, to provide cross-compound translation and guidance for dose selection in potential future studies of AG-519 in patients with PK deficiency.

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Disclosures

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