S830

Preclinical pharmacokinetics and pharmacodynamics of AG-519, an allosteric pyruvate kinase activator

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Disclosures

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- All authors are Agios employees and stockholders
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Background: Pyruvate kinase (PK) deficiency

Description

- A rare genetic disease causing chronic hemolytic anemia
- Symptoms vary in severity
- Current treatments are supportive only

Etiology

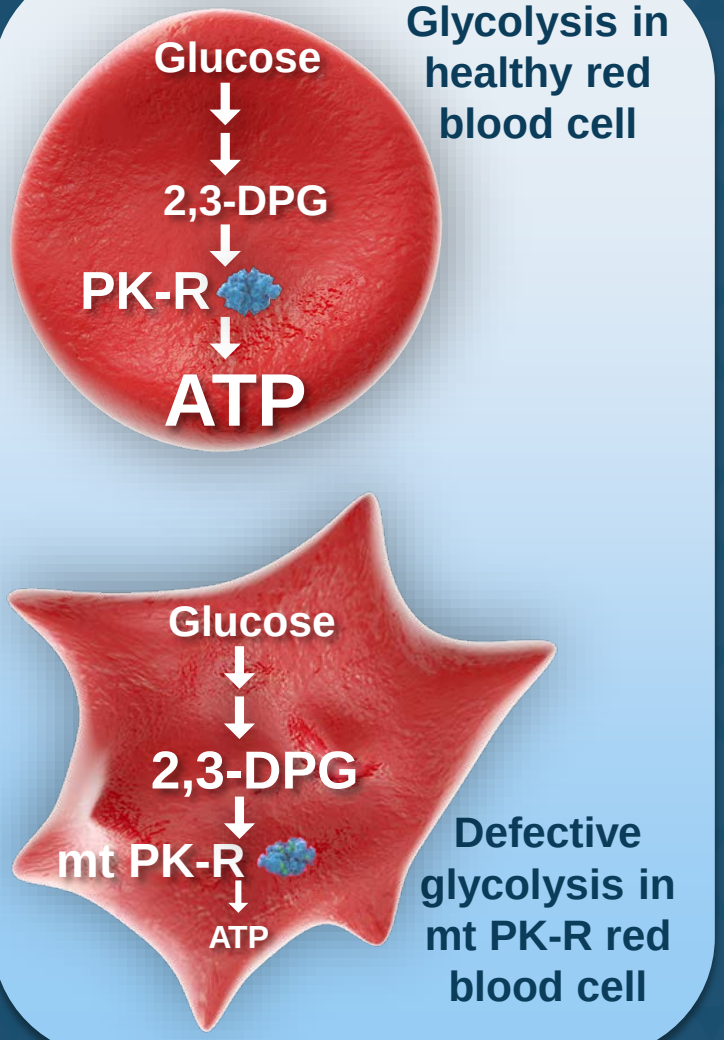
- Caused by mutations in the red blood cell isoform of PK (PK-R), a key enzyme in red blood cell glycolysis

Biology

- Leads to increases in the upstream metabolite 2,3-DPG and decreases in the product ATP in blood

Therapeutic concepts

- Activation of mt PK-R could repair the metabolic defect
- Increase hemoglobin levels and decrease hemolysis, leading to patient benefit



Yang et al. 20th EHA Congress, 2015, Abstract S138.

2,3-DPG = 2,3-diphosphoglycerate; ATP = adenosine triphosphate; mt PK-R = mutant PK-R

PK-R activators for the treatment of PK deficiency

- Activation of PK-R resulting in increases in ATP and decreases in 2,3-DPG in healthy volunteers has been observed with an earlier molecule (AG-348)

- Early AG-348 clinical data demonstrate proof-of-concept with rapid and sustained Hb increases in patients with PK deficiency[1]

- AG-519 is a potent, highly selective, orally bioavailable second PK-R activator developed with the aim of eliminating off-target aromatase inhibitory effects of AG-348

[1] Presentation S466. Hb = hemoglobin

Objectives

- To explore the pharmacokinetic/pharmacodynamic (PK/PD) relationships of AG-519 with PK-R activity, ATP and 2,3-DPG in wild type PK-R mice

- To use data from animal studies to project the pharmacokinetic profile and efficacious dose of AG-519 in humans

Human efficacious dose and dosing regimen projection

- Human pharmacokinetics projection
  - Pharmacokinetic studies in different species
  - *In vitro* metabolism
  - Plasma protein binding and *in vitro* CL_{int}
- Human efficacious exposure estimation
  - Cell biology and biochemistry studies
  - PK/PD studies

Modeling simulation for human projection

CL_{int} = intrinsic clearance

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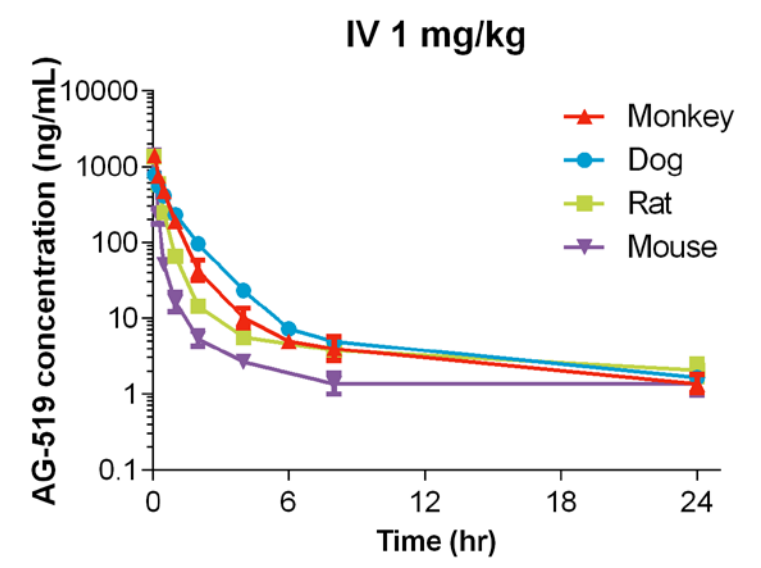
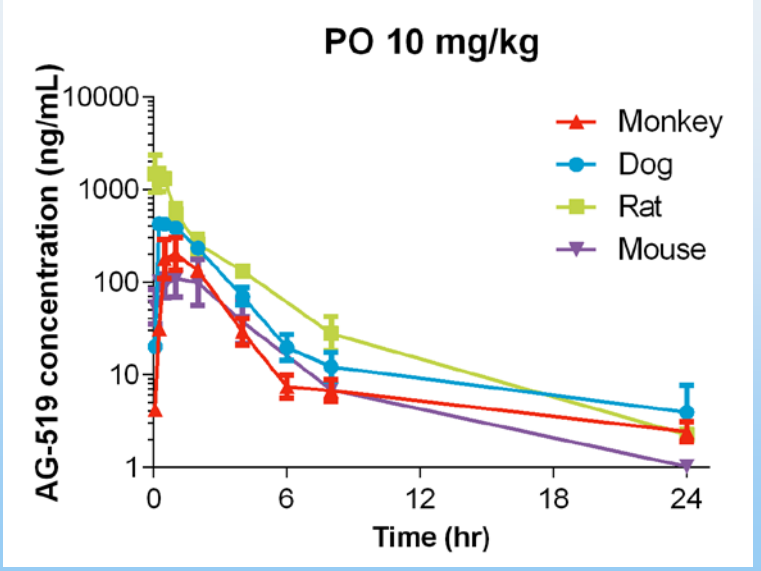
Comparable AG-519 pharmacokinetics across species





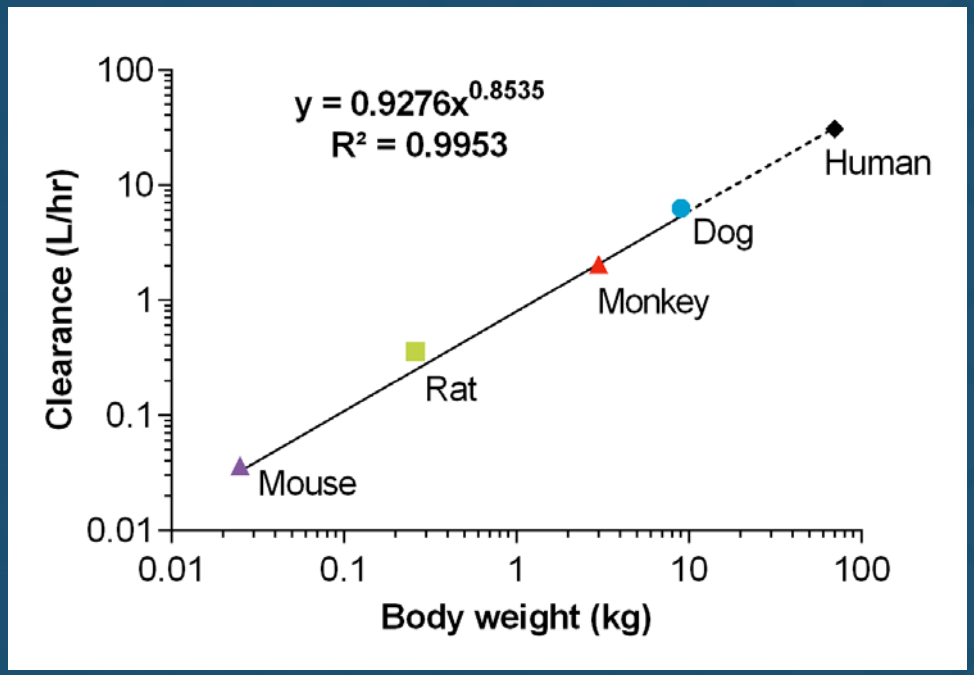
- Moderate clearance (1.13–2.51 L/hr/kg), moderate to high volume of distribution (2.08–6.44 L/kg) and similar plasma protein binding (79.3% - 87.3%) in mouse, rat, dog and monkey
- Rapid absorption (T_{max} ≤1.2 h) and moderate oral bioavailability (6.9–19.5%)
- Good *in vitro* to *in vivo* correlation in the CL estimates across species

CL = clearance; T_{max} = time to maximum plasma concentration

Human pharmacokinetic projections

- Pharmacokinetic parameters in mouse, rat, dog and monkey used for human pharmacokinetic projection
- *In vitro* metabolism data used as a correction factor
- Allometric scaling conducted for human pharmacokinetic projection

Corrected for Eh



Projected human pharmacokinetic parameters:

- CL: 0.4 L/hr/kg
- V_{SS}: 3.0 L/kg
- Effective $t_{½}$: 4 – 7 hr
- Bioavailability: 22%

Eh = hepatic extraction ratio; CL = clearance; V_{SS} = volume of distribution at steady state; $t_{½}$ = half-life

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Mouse PK/PD study design

Female C57/BL6 mice
PK-R WT

Oral AG-519

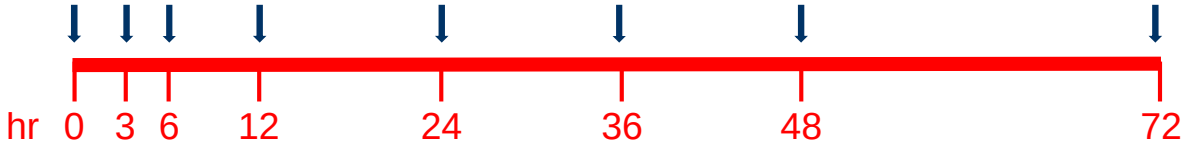
Dosing

Vehicle* | 1 mg/kg | 10 mg/kg | 50 mg/kg | 150 mg/kg

Single dose | 5 doses (BID) | 13 doses (BID)

Sampling

Serial sample collections for PK/PD evaluation up to 72 hr after last dose



n=4 mice per time point in each dose group

Read out

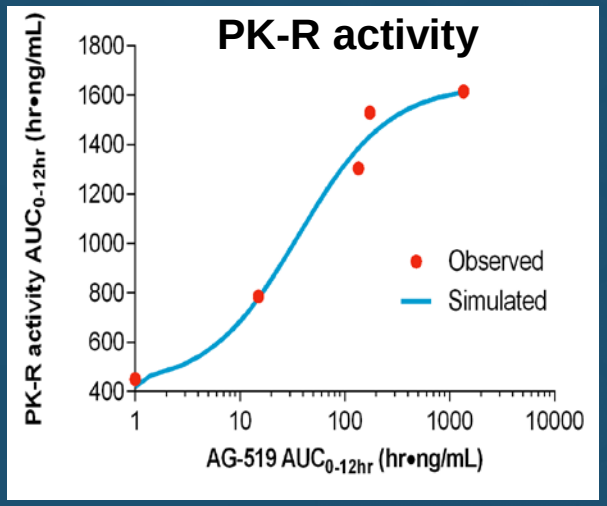
Plasma AG-519 | Whole blood ATP | Whole blood 2,3-DPG | Whole blood PK-R activity

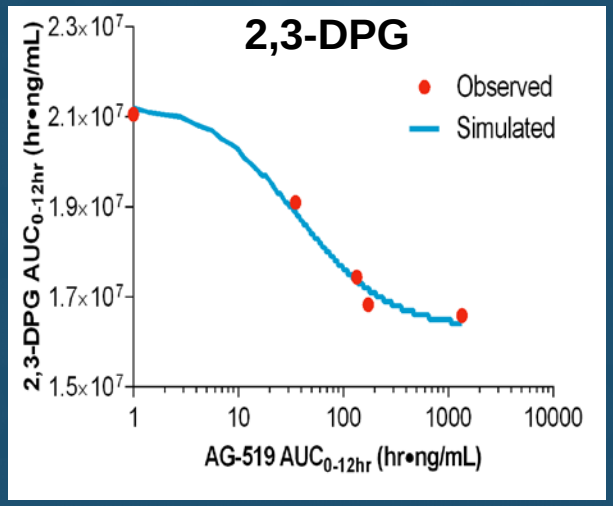
PK/PD steady state achieved after 5 BID doses

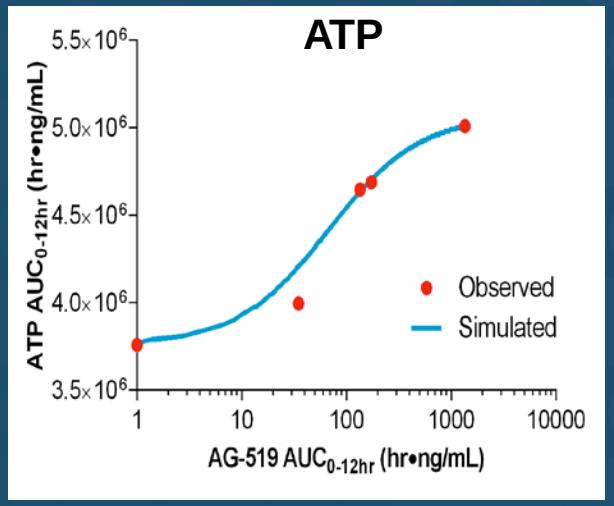
*0.5% methyl cellulose in water

Using mouse PK/PD to estimate human efficacious exposure

- Drug exposure-dependent response observed for all three markers
- The exposure-response relationship is described by an E_{max} model
- $EAUC_{90}$ (421 hr•ng/mL) for ATP increase used for human efficacious dose prediction







Parameter (13 BID doses)	PK-R activity	2,3-DPG	ATP
AG-519 free AC_{50} (nM)	0.55	0.32	0.72
AG-519 $EAUC_{90}$ (hr•ng/mL)	320	187	421

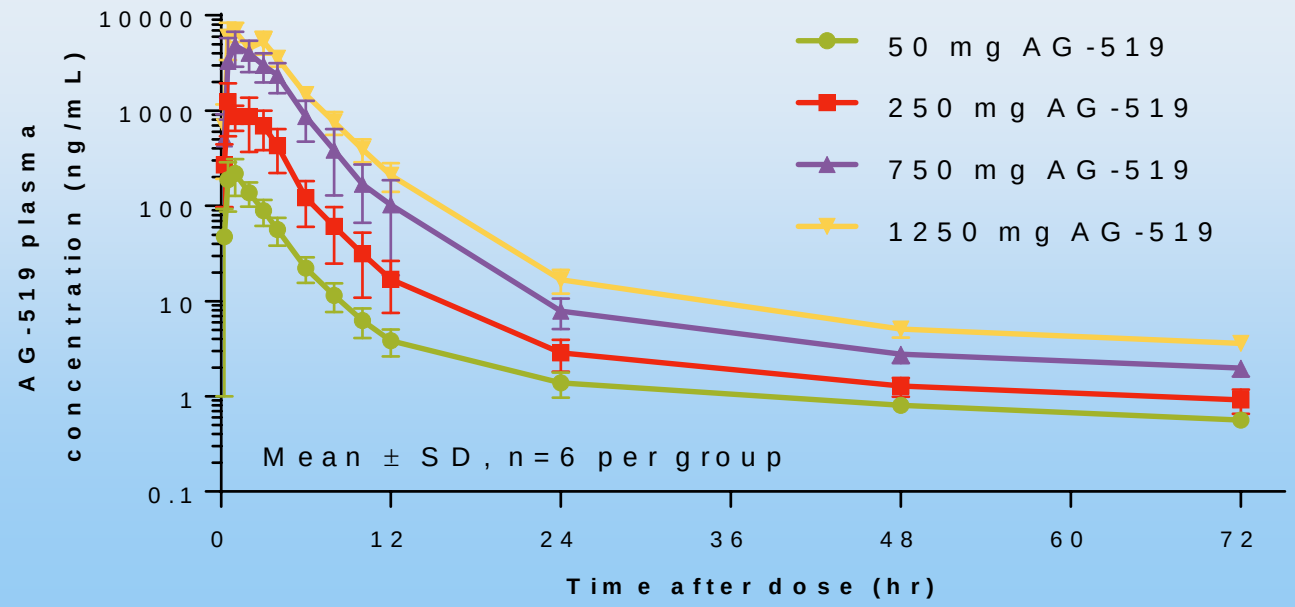
AC_{50} = half-maximal activity concentration; $EAUC_{90}$ = area under the curve at 90% maximum effect

AG-519 human dose projection

- Favorable pharmacokinetics in multiple species
- Clear PK/PD relationship established in the mouse model enabled the prediction of the AG-519 efficacious dose in humans
- Projected human efficacious dose and dosing schedule:
  - **62–134 mg, orally twice daily**
- These data supported the decision to bring AG-519 into a phase 1 healthy volunteer study

AG-519 has favorable clinical pharmacokinetics: Poster 752

Plasma concentration-time profiles of AG-519 following a single oral dose

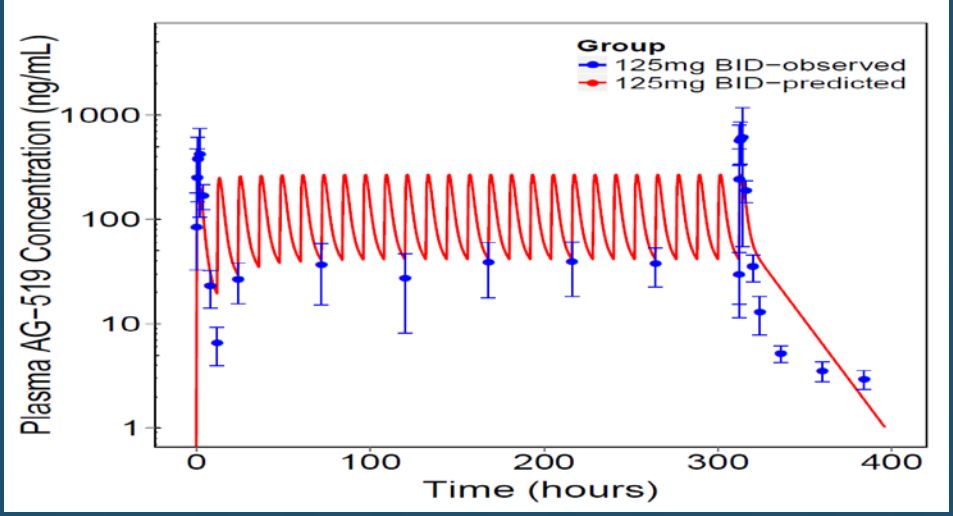


- Rapid absorption, moderate variability
- Exposure is dose-proportional or slightly greater than dose-proportional
- Effective $t_{1/2}$ of approximately 6 hr

Effective $t_{1/2}$: elimination $t_{1/2}$ in the therapeutic relevant concentration range, in this case $t_{1/2}a$

Comparison: projected vs actual human pharmacokinetics

- Human pharmacokinetic profile was simulated using animal data, the projected human pharmacokinetic parameters, and a 2-compartment model
- Animal AG-519 pharmacokinetic data translate well to healthy volunteers
- The actual human pharmacokinetic profile is similar to the simulated
  - Slightly higher than projected C_{max}; good C_{trough} projection
  - As projected, pharmacokinetic profile supported oral BID dosing regimen

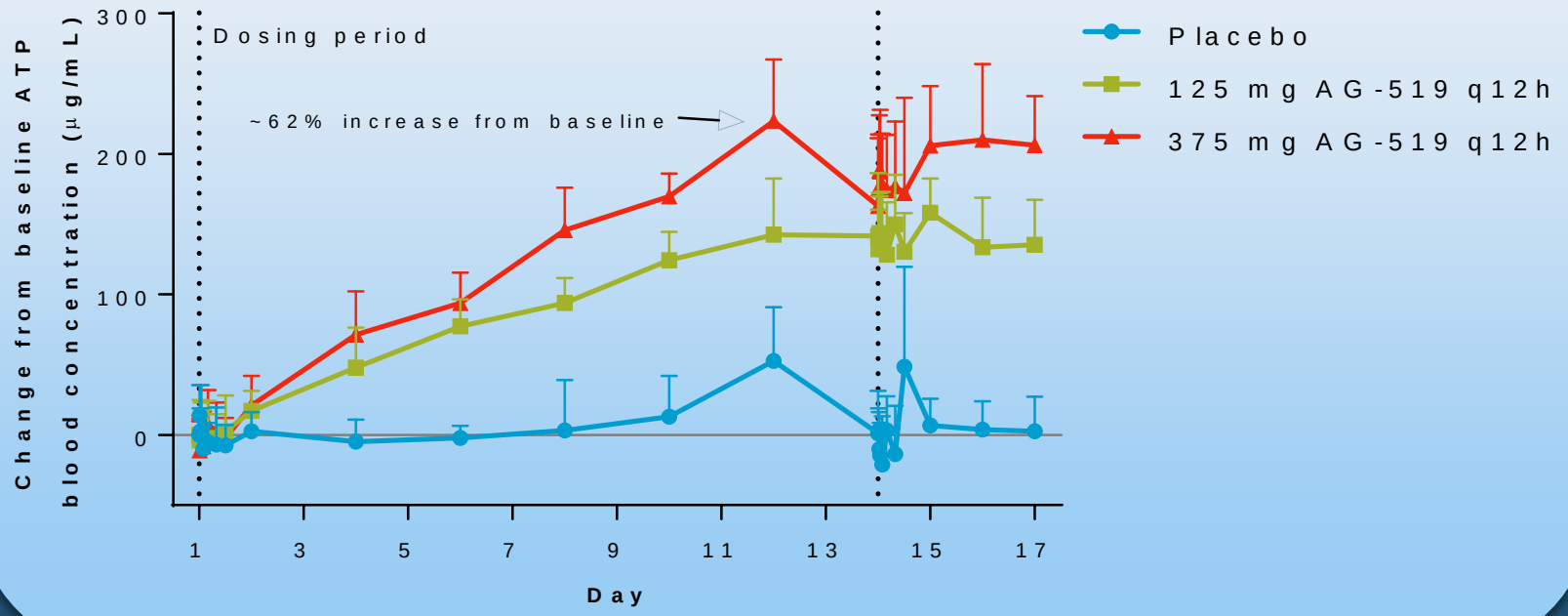


	Projected	Actual
CL/F, L/hr/kg	1.8	0.66–1.0
Effective $t_{1/2}$, hr	4–7	6

BID = twice-daily; CL/F = oral clearance; C_{max} = maximum plasma concentration; C_{trough} = lowest plasma concentration

Dose-dependent changes in ATP and 2,3-DPG blood levels are consistent with PK-R activation: Poster 752

Mean (+ SD) change in blood concentration-time profiles of ATP following multiple oral doses of AG-519 (cohorts 1 and 2 only)



Conclusions

- AG-519 shows favorable pharmacokinetic profiles in multiple species
- Preclinical PK/PD relationship and favorable pharmacokinetics enabled prediction of human efficacious dose and dosing regimen
  - AG-519 has favorable pharmacokinetic profile in humans
  - Dose-dependent PD response consistent with PK-R activation
  - AG-519 has a favorable safety profile to date, and it does not demonstrate the inhibition of aromatase previously observed with AG-348
- The PK/PD data from healthy subjects will inform dose selection for future studies of AG-519 in patients with PK deficiency

Please see Posters 752 and 742. PD = pharmacodynamic

Acknowledgements

- Agios PK-R discovery team
- Agios PK-R development team
- The volunteers taking part in the AG-519 phase 1 study