Phase 1 Single and Multiple Ascending Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of AG-946 in Healthy Volunteers

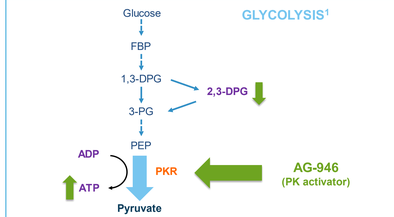
Poster #2043

Varsha Iyer, PhD[1], Elizabeth Merica[2], Sebastien Ronseaux, PhD[1], Tressa Gamache[1], Nancy J. Mulrow, MD[3], Anja Belcijan, MS[4], Michael U. Callaghan, MD[1]

[1]Agios Pharmaceuticals, Inc., Cambridge, MA, USA; [2]Merica Clinical Consulting, Boston, MA, USA; [3]Mulrow & Associates Consulting, LLC, Boston, MA, USA; [4]PPD Pharmaceuticals, Barcelona, Spain

BACKGROUND

Figure 1. AG-946 activates PKR, and may decrease 2,3-DPG levels and increase ATP levels in RBCs



ADP = adenosine diphosphate; ATP = adenosine triphosphate; DPG = diphosphoglycerate; FBP = fructose-1,6-biphosphate; PEP = phosphoenolpyruvate; PG = phosphoglycerate; PK = pyruvate kinase; PKR = RBC-specific form of PK; RBC = red blood cell.

- Activating the red blood cell (RBC) isoform of pyruvate kinase (PKR) has been shown to increase flux in the glycolytic pathway, thereby reducing levels of 2,3-diphosphoglycerate (2,3-DPG) and increasing levels of ATP in RBCs[1,2]
- ATP generation is critical for maintaining RBC function and stability[1,3,4]
- Increased levels of 2,3-DPG in sickle cell disease (SCD) lead to lower oxygen affinity, which promotes sickle hemoglobin (HbS) polymerization and RBC sickling[5]
- In previous clinical studies in pyruvate kinase deficiency (mutant PKR), thalassemia, and SCD (both wild-type), treatment with mitapivat, a pyruvate kinase (PK) activator, led to improvements in hemoglobin (Hb) and markers of hemolysis[6–10]
- AG-946 is an investigational, oral, potent PK activator (**Figure 1**)
- AG-946 is under investigation as a potential therapy for hemolytic anemias by:
  - Increasing ATP, leading to increased RBC viability by improving RBC hydration and health[1,3,4]
  - Decreasing 2,3-DPG, leading to decreased HbS polymerization and RBC sickling by increasing Hb oxygen affinity and intracellular pH[5,11,12]

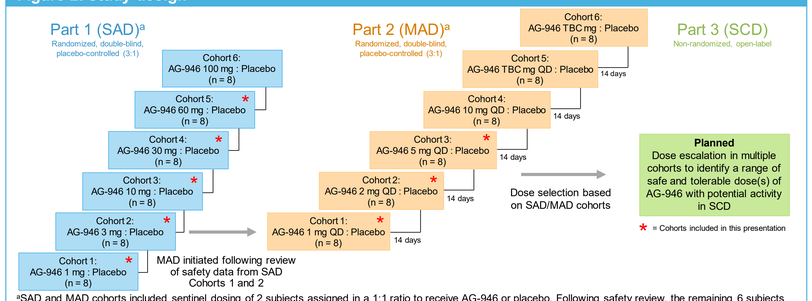
OBJECTIVE

- To report preliminary blinded results from an ongoing phase 1 study (NCT04536792) assessing the safety, tolerability, pharmacokinetic and pharmacodynamic profile of AG-946, an oral, potent PK activator, in healthy volunteers

METHODS

- In this phase 1, randomized, double-blind, placebo-controlled study, single ascending doses (SAD) or multiple ascending doses (MAD) of AG-946 or placebo are administered under fasting conditions to healthy men and women (18–55 years of age) in sequential cohorts (**Figure 2**)

Figure 2. Study design



[a]SAD and MAD cohorts included sentinel dosing of 2 subjects assigned in a 1:1 ratio to receive AG-946 or placebo. Following safety review, the remaining 6 subjects were randomized in a 5:1 ratio to receive AG-946 or placebo. Overall randomization was in a 3:1 ratio to receive AG-946 or placebo. MAD = multiple ascending doses; QD = once daily; SAD = single ascending doses; SCD = sickle cell disease; TBC = to be confirmed.

- Safety assessments include vital signs, physical exams, electrocardiograms, clinical laboratory parameters and adverse events
- Serial blood samples are drawn for pharmacokinetic and pharmacodynamic (2,3-DPG, ATP) assessments at regular intervals throughout the study period
- Safety, pharmacokinetic, and pharmacodynamic evaluations were performed through at least 168 hours post-dose (ie, Day 8 for SAD, Day 21 for MAD)

RESULTS

- As of 24Jun2021, 47 subjects (median age 33 years; 39 male) in SAD cohorts and 25 subjects (median age 36 years; 25 male) in MAD cohorts received AG-946 or placebo
- Demographic and baseline characteristics were balanced across the SAD and MAD cohorts (**Table 1** and **Table 2**)

Table 1. Demographic and baseline characteristics of SAD cohorts

Baseline characteristics	Total (N = 47)
Age, median (range), years	33.0 (21, 55)
Male, n (%)	39 (83.0)
Race, n (%)	
Black/African American	16 (34.0)
White	31 (66.0)
Ethnicity, n (%)	
Hispanic/Latino	21 (44.7)
Not Hispanic or Latino	26 (55.3)
BMI, median (range), kg/m^2	27.80 (20.5, 31.9)

BMI = body mass index; SAD = single ascending doses.

Table 2. Demographic and baseline characteristics of MAD cohorts

Baseline characteristics	Total (N = 25)
Age, median (range), years	36.0 (21, 56)
Male, n (%)	25 (100)
Race, n (%)	
Asian	1 (4.0)
Black/African American	12 (48.0)
White	11 (44.0)
Multiple	1 (4.0)
Ethnicity, n (%)	
Hispanic/Latino	9 (36.0)
Not Hispanic or Latino	16 (64.0)
BMI, median (range), kg/m^2	27.80 (19.2, 31.7)

BMI = body mass index; MAD = multiple ascending doses.

- There were 6 (SAD cohorts, n = 5; MAD cohorts, n = 1) early discontinuations; all were unrelated to study treatment (**Table 3** and **Table 4**)

Table 3. Study discontinuations in SAD cohorts

	Total (N = 47)
Discontinued from study, n (%)	5 (10.6)
COVID-19	1 (2.1)
Other: temporary site closure due to ice storm in Texas	4 (8.5)

SAD = single ascending doses.

Table 4. Study discontinuations in MAD cohorts

	Total (N = 25)
Discontinued from study, n (%)	1 (4.0)
Other: incarceration	1 (4.0)

MAD = multiple ascending doses.

Safety

- In SAD cohorts, 4/47 (8.5%) subjects experienced ≥ 1 treatment-emergent adverse event (TEAE; [**Table 5**]) all TEAEs were assessed to be mild (grade 1) and unrelated to study treatment
- In MAD cohorts, 5/25 (20%) subjects experienced ≥ 1 TEAE (**Table 6**); all TEAEs except for rhabdomyolysis were mild (grade 1), and all were considered unrelated to study treatment

Table 5. TEAEs in SAD cohorts

	Total (N = 47)
Any TEAE, n (%)	4 (8.5)[a]
Urethritis	1 (2.1)
Nasopharyngitis	1 (2.1)
Coronavirus infection	1 (2.1)
Headache	1 (2.1)
Medical device site dermatitis	1 (2.1)

[a]One subject experienced 2 TEAEs.
SAD = single ascending doses; TEAE = treatment-emergent adverse event.

Table 6. TEAEs in MAD cohorts

	Total (N = 25)
Any TEAE, n (%)	5 (20.0)[a]
Abdominal distension	1 (4.0)
Flatulence	1 (4.0)
Seasonal allergy	1 (4.0)
Skin abrasion	1 (4.0)
Decreased appetite	1 (4.0)
Rhabdomyolysis	1 (4.0)
Dry skin	1 (4.0)

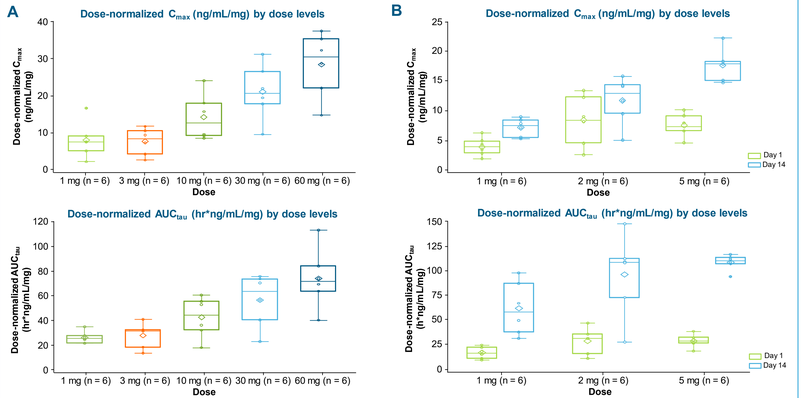
[a]Two subjects experienced 2 TEAEs.
MAD = multiple ascending doses; TEAE = treatment-emergent adverse event.

- One subject in the MAD cohort (AG-946 2 mg once daily [QD]) experienced a serious TEAE (grade 2) of exercise-induced rhabdomyolysis 14 days after the last dose; this was considered unrelated to study treatment
- All other TEAEs in SAD and MAD cohorts were also considered unrelated to study treatment

Pharmacokinetics

- In both SAD and MAD cohorts, AG-946 exhibited rapid absorption with median time to maximum concentration (T_{max}) ranging from 0.5 to 1 hour
- Following SAD, dose-normalized AG-946 exposures (AUC [area under the curve] and C_{max} [maximum concentration observed]) increased with increasing AG-946 doses, suggesting a greater than dose proportional increase in exposure over the tested dose range (**Figure 3A**)
- Following MAD, AG-946 exposures were higher on Day 14 compared with Day 1; mean accumulation ratios for AUC were 3.6 at 1 mg QD, 3.3 at 2 mg QD, and 3.8 at 5 mg QD (**Figure 3B**)

Figure 3. Dose-normalized AG-946 exposures versus dose for (A) SAD and (B) MAD cohorts

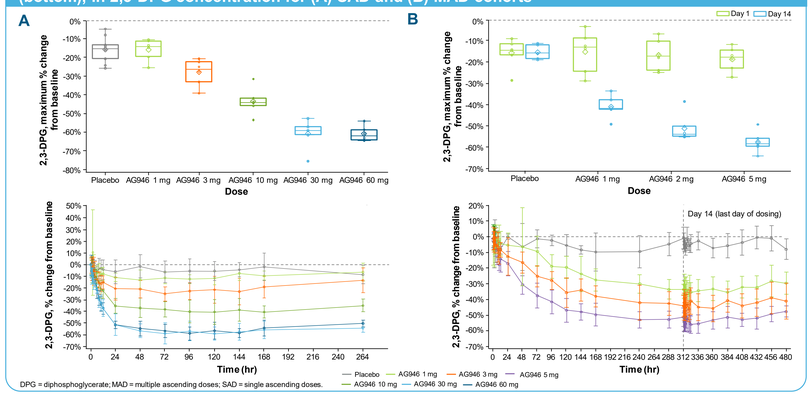


AUC_{tau} = area under the curve over the dosing interval; C_{max} = maximum concentration observed; MAD = multiple ascending doses; SAD = single ascending doses.

Pharmacodynamics

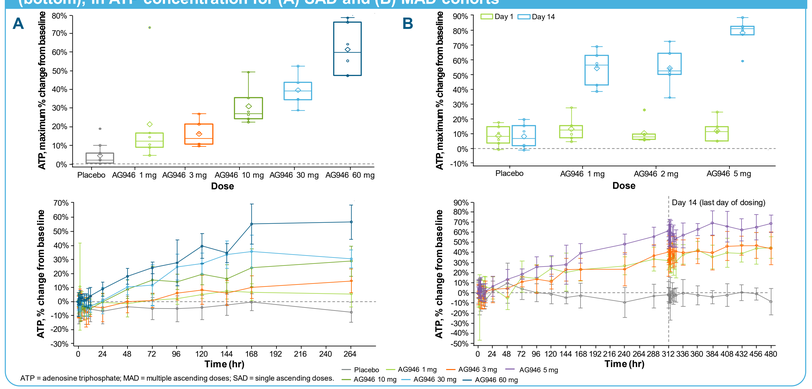
- In both SAD and MAD cohorts, an increase in AG-946 dose was associated with a decrease in 2,3-DPG concentrations (**Figure 4**), and an increase in ATP concentrations (**Figure 5**)
- These pharmacodynamic changes were sustained for at least 10 days after a single dose and for at least 7 days after the last day of multiple QD dosing
- As expected, no clinically significant changes in Hb have been observed in the SAD or MAD healthy volunteer cohorts, to date

Figure 4. Maximum percent change from baseline (top) and percent change from baseline over time (bottom), in 2,3-DPG concentration for (A) SAD and (B) MAD cohorts



DPG = diphosphoglycerate; MAD = multiple ascending doses; SAD = single ascending doses.

Figure 5. Maximum percent change from baseline (top) and percent change from baseline over time (bottom), in ATP concentration for (A) SAD and (B) MAD cohorts



ATP = adenosine triphosphate; MAD = multiple ascending doses; SAD = single ascending doses.

CONCLUSIONS

- AG-946, an oral, highly potent PK activator, was well tolerated in healthy volunteers following single dose administrations up to 60 mg and multiple 14-day dosing with 1 mg QD, 2 mg QD, and 5 mg QD
- The pharmacokinetic profile of AG-946 supports QD dosing, and is accompanied by sustained dose-dependent increases in ATP and decreases in 2,3-DPG, consistent with activation of the glycolytic pathway
- Enrollment into additional SAD (100 mg) and MAD (10 mg QD) cohorts is ongoing and will be followed by an open-label phase in subjects with SCD

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Disclosures

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[a]**S. Ronseaux** was an employee at Agios at the time of his contribution to this work and is now employed at Cedilla Therapeutics

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