Results from the single and multiple ascending dose study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of AG-946 in healthy volunteers

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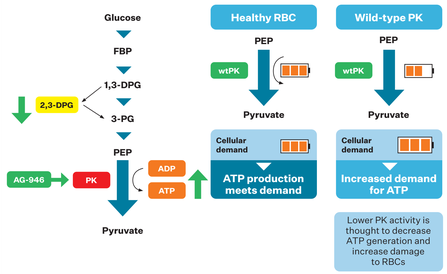
BACKGROUND

- Pyruvate kinase (PK) red cell isoform catalyzes the final step of adenosine triphosphate (ATP) production via glycolysis in red blood cells (RBCs), which is critical for maintaining RBC function and stability[1–4]
- PK activation leading to reduced levels of the glycolytic metabolite 2,3-diphosphoglycerate (2,3-DPG) and enhanced ATP production is under investigation as a potential therapeutic approach in various hemolytic anemias
- AG-946 is an investigational, potent, small-molecule, allosteric activator of PK that has the potential to enhance RBC functionality and survival by increasing glycolysis and ATP production (**Figure 1**)

Figure 1. AG-946, an investigational, oral activator of PK[5–11]



ADP, adenosine diphosphate; ATP, adenosine triphosphate; DPG, diphosphoglycerate; FBP, fructose-1,6-biphosphate; PEP, phosphoenolpyruvate; PG, phosphoglycerate; PK, pyruvate kinase; RBC, red blood cell; wt, wild-type

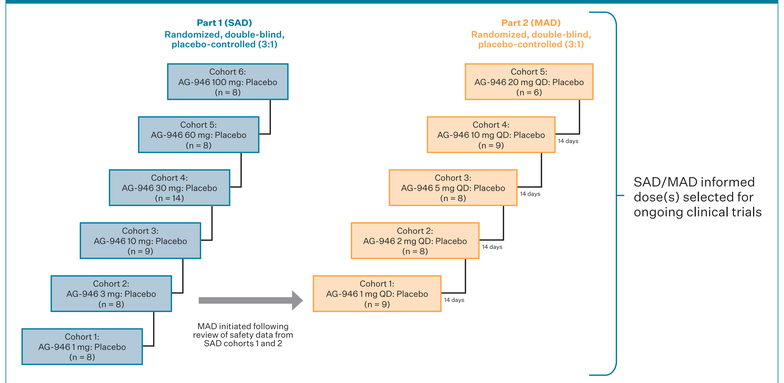
OBJECTIVE

- To assess safety, pharmacokinetic, and pharmacodynamic results from the Phase 1 study of AG-946 in healthy volunteers (NCT04536792)

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 were administered to healthy men and women (18–55 years of age) in sequential cohorts (**Figure 2**)
  - In SAD:
    - 6 cohorts of 8 subjects each were randomized to receive a single dose of AG-946 (n=6) or placebo (n=2) under fasted conditions, with 2 subjects initially randomized (1:1) and then 6 subjects randomized (5:1) to receive AG-946 or placebo
    - Dose levels studied in SAD were 1, 3, 10, 30, 60, and 100 mg
  - In MAD:
    - 5 cohorts of 8 subjects each were randomized (3:1) to receive AG-946 or placebo once daily (QD) under fasted conditions for 14 days
    - Dose levels studied in MAD were 1, 2, 5, 10, and 20 mg QD

Figure 2. Study design for SAD and MAD[a]



[a]Cohorts and subject numbers included in this presentation represent the study as conducted. MAD, multiple ascending doses; QD, once daily; SAD, single ascending doses

- Safety assessments included vital signs, physical exams, electrocardiograms, clinical laboratory parameters, and adverse events
- Serial blood samples were 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 h (Day 8) for SAD with follow-up visits occurring at 264 h (Day 10)
  - At least 504 h (Day 21) for MAD with follow-up visits occurring at 816 h (Day 35)

RESULTS

Demographic and baseline characteristics were balanced

Table 1. Demographic and baseline characteristics: SAD cohorts

Baseline characteristics	Placebo (n = 14)	AG-946 (n = 41)
Age, median (range), years	29.0 (21, 55)	35.0 (22, 54)
Male, n (%)	14 (100.0)	32 (78.0)
Race, n (%)		
Black/African American	5 (35.7)	13 (31.7)
White	9 (64.3)	28 (68.3)
BMI, median (range), kg/m^2	27.2 (21.7, 31.7)	27.8 (20.5, 31.9)

Table 2. Demographic and baseline characteristics: MAD cohorts

Baseline characteristics	Placebo (n = 9)	AG-946 (n = 31)
Age, median (range), years	39.0 (22, 51)	36.0 (21, 56)
Male, n (%)	9 (100.0)	31 (100)
Race, n (%)		
Asian	0	1 (3.2)
Black/African American	5 (55.6)	13 (41.9)
Native Hawaiian/ Other Pacific Islander	0	1 (3.2)
White	4 (44.4)	15 (48.4)
Multiple	0	1 (3.2)
BMI, median (range), kg/m^2	26.1 (19.6, 29.7)	28.1 (19.2, 31.7)

BMI, body mass index; MAD, multiple ascending doses; SAD, single ascending doses

SAD safety results: AG-946 was well tolerated in healthy adult subjects

- Overall, 6 (14.6%) of the 41 subjects treated with AG-946 in SAD experienced treatment-emergent adverse events (TEAEs)
  - No serious TEAEs, no grade ≥3 TEAEs, and no treatment-related TEAEs were reported
- The frequency of subjects with TEAEs was similar for the placebo (14.3%) and AG-946 (14.6%) treatment arms

MAD safety results

Table 3. MAD safety results

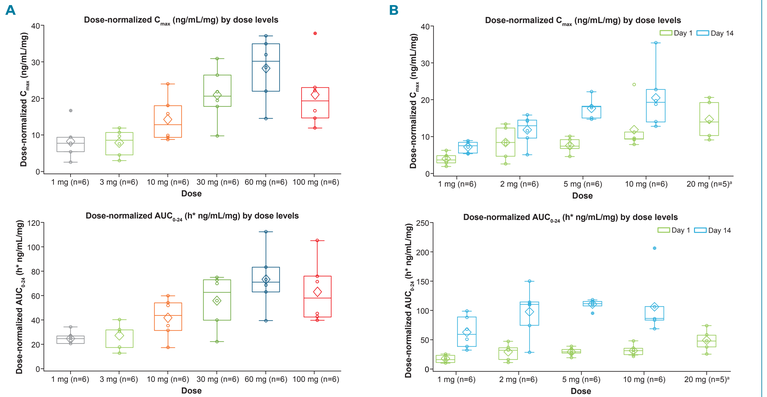
Frequency of subjects with events	Placebo (n = 9)	AG-946 1 mg QD (n = 7)	AG-946 2 mg QD (n = 6)	AG-946 5 mg QD (n = 6)	AG-946 10 mg QD (n = 7)	AG-946 20 mg QD (n = 5)	Pooled AG-946 (n = 31)
Any TEAE, n (%)	4 (44.4)	2 (28.6)	0	1 (16.7)	4 (57.1)	5 (100)	12 (38.7)
Any grade ≥3 TEAE, n (%)	0	0	0	0	0	1 (20.0)	1 (3.2)
Any treatment-related TEAE, n (%)	0	0	0	0	1 (14.3)	5 (100)	6 (19.4)
Any TEAE leading to treatment discontinuation, n (%)	0	0	0	0	1 (14.3)	5 (100)	6 (19.4)
Any serious TEAE, n (%)	1 (11.1)	0	0	0	0	0	0

QD, once daily; TEAE, treatment-emergent adverse event

- Overall, 12 (38.7%) of the 31 subjects treated with AG-946 in MAD experienced TEAEs
- The frequency of subjects with TEAEs was similar for the placebo (44.4%) and AG-946 (38.7%) treatment arms
- No serious TEAEs were reported in subjects receiving AG-946; 1 serious TEAE (Grade 2) of rhabdomyolysis was reported in 1 subject receiving placebo
- Treatment-related TEAEs of decreased platelets occurred in 6 subjects treated with AG-946
  - None at doses <10 mg QD, 1 at 10 mg QD (Grade 1), and 5 at 20 mg QD (4 Grade 1, 1 Grade 3)
  - Decreased platelet events were asymptomatic and reversible with treatment discontinuation
- All other TEAEs in subjects receiving AG-946 occurred in only 1 subject each, were Grade 1–2 in severity, and were not related to treatment

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

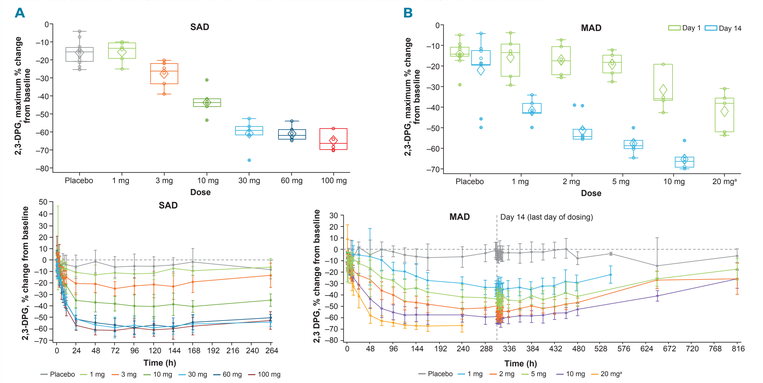
Overproportional increases in AG-946 exposure were observed in SAD, with ~3- to 4-fold accumulation observed following 14 days of dosing in MAD



[a]In the 20 mg QD cohort, subjects started discontinuing from the study on Day 9, with all subjects discontinued by Day 13. AUC_{0-24}, area under the plasma concentration versus time curve from 0 to 24 hours; C_{max}, maximum observed plasma concentration; MAD, multiple ascending doses; QD, once daily; SAD, single ascending doses

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

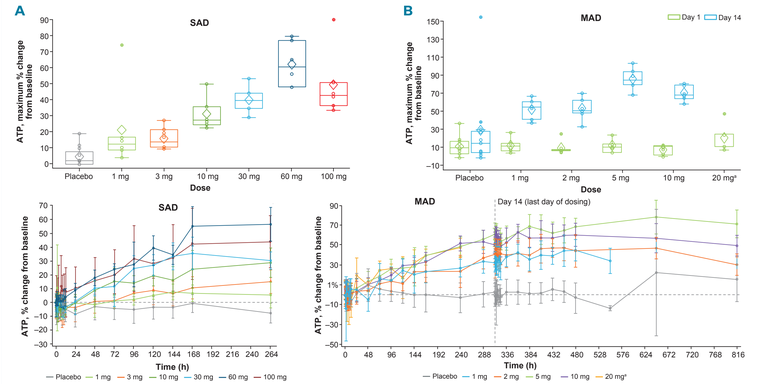
In both SAD and MAD cohorts, an increase in AG-946 dose was associated with a decrease in 2,3-DPG concentrations



Per protocol, the last planned pharmacodynamic sample was collected at the follow-up visit (Day 24, 25, or 26) for the 1 mg QD cohort and on Day 35 for the 2, 5, 10, and 20 mg QD cohorts. [a]In the 20 mg QD cohort, subjects started discontinuing from the study on Day 9, with all subjects discontinued by Day 13. DPG, diphosphoglycerate; MAD, multiple ascending doses; QD, once daily; 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

In both SAD and MAD cohorts, an increase in AG-946 dose was associated with an increase in ATP concentrations



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CONCLUSIONS

- AG-946, an oral, potent PK activator, showed a favorable safety profile at pharmacologically active doses
- The pharmacokinetic profile of AG-946 supports QD dosing, and is accompanied by sustained dose-dependent decreases in 2,3-DPG and increases in ATP consistent with activation of the glycolytic pathway
- Doses of AG-946 up to 5 mg QD are currently being evaluated in clinical trials

AG-946 supported a QD regimen and showed potent, sustained activation of the glycolytic pathway in RBCs with prolonged effects on pharmacodynamics (2,3-DPG, ATP), supporting further clinical advancement

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