Effects of AG-348, a pyruvate kinase activator, in patients with pyruvate kinase deficiency: Updated results from the DRIVE PK study

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BACKGROUND

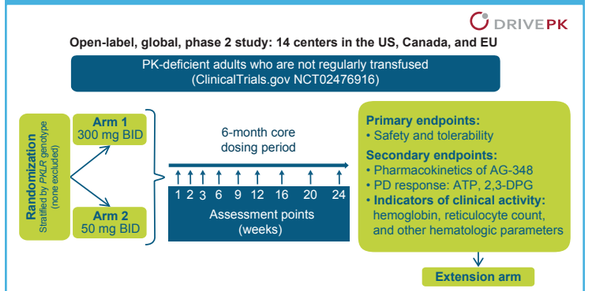
- Pyruvate kinase (PK) deficiency is an under-recognized hereditary disease caused by mutations in the *PKLR* gene, which results in lifelong hemolytic anemia.[1,2]
- Acute and chronic complications of supportive care (e.g. transfusions, splenectomy, or iron chelation) may additionally burden patients with PK deficiency.

OBJECTIVE

- To report updated data from the ongoing DRIVE PK study (ClinicalTrials.gov NCT02476916), an open-label dose-ranging trial of AG-348 in adults with PK deficiency who are not receiving regular blood transfusions.

METHODS

Figure 1. Study design

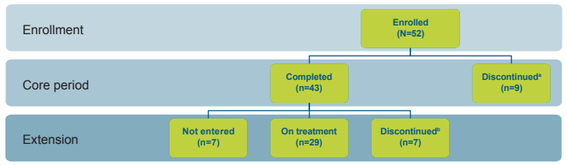


Not regularly transfused = no more than 3 units of red blood cells transfused in the 12 months prior to the first day of study dosing and no transfusions within 4 months of the first day of study dosing
All patients provided written informed consent
2,3-DPG = 2,3-diphosphoglycerate; BID = twice daily; PD = pharmacodynamic

- Enrollment is complete as of November 2016.
- Data cutoff: July 14, 2017.
- Cumulative safety results are summarized for the Core + Extension periods by randomized treatment group (50 mg BID, 300 mg BID, and overall).
- Clinical activity and sex hormone levels were analyzed by the dose received for the longest duration in the Core period.
- Dose changes were allowed per protocol for various reasons:
  - Dose decrease: adverse events (AEs) and/or hemoglobin (Hb) exceeding the midpoint of the normal range (male: >15.0 g/dL; female: >13.5 g/dL).
  - Dose increase: lack of Hb response.

RESULTS

Figure 2. Patient disposition



[a]AEs (n=4), investigator decision (n=2), patient withdrew consent (n=3)
[b]Investigator decision (n=4), patient withdrew consent (n=1), lack of response (n=2)

Table 1. Demographic characteristics

Characteristic	50 mg BID n=27	300 mg BID n=25	Total N=52
Male, n (%)	18 (66.7)	14 (56.0)	32 (61.5)
Age at randomization, median (range), years	28 (18–58)	40 (21–61)	34 (18–61)
White[a], n (%)	22 (81.5)	21 (84.0)	43 (82.7)
Hb baseline, median (range), g/dL	9.6 (6.9–12.3)	8.6 (6.5–12.0)	8.9 (6.5–12.3)
Splenectomy, n (%)	23 (85.2)	20 (80.0)	43 (82.7)
Cholecystectomy, n (%)	19 (70.4)	19 (76.0)	38 (73.1)
Mutation category, n (%)			
Missense/missense	15 (55.6)	17 (68.0)	32 (61.5)
Missense/non-missense	6 (22.2)	4 (16.0)	10 (19.2)
Non-missense/non-missense	6 (22.2)	4 (16.0)	10 (19.2)
Iron chelation prior to enrollment, n (%)	14 (51.9)	11 (44.0)	25 (48.1)
Duration of AG-348 treatment, median (range), weeks	34.6 (13.0–92.4)	38.7 (12.9–86.4)	37.5 (12.9–92.4)

[a]Other races: not reported (n=3), Asian (n=3), other (n=3)

Cumulative safety summary

- AG-348 was generally well tolerated.
- The majority of AEs were grade 1–2.
- Treatment-related AEs leading to discontinuation (n=4):
  - Hemolytic anemia, hypertriglyceridemia, pharyngitis/nausea, pleural effusion.
- There were 14 serious AEs in 11 patients.
  - Five treatment-related serious AEs in four patients: anemia, hypertriglyceridemia, osteoporosis, withdrawal hemolysis followed by anemia.

Table 2. Most common AEs regardless of causality or grade (occurring in >15% of patients)

AE	50 mg BID n=27		300 mg BID n=25		Total N=52	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Patients experiencing ≥1 AE, n (%)	26 (96.3)	8 (29.6)	25 (100.0)	7 (28.0)	51 (98.1)	15 (28.8)
Headache	10 (37.0)	0	14 (56.0)	0	24 (46.2)	0
Insomnia	6 (22.2)	1 (3.7)	16 (64.0)	1 (4.0)[a]	22 (42.3)	2 (3.8)
Nausea	10 (37.0)	0	10 (40.0)	0	20 (38.5)	0
Viral upper respiratory tract infection	8 (29.6)	0	4 (16.0)	1 (4.0)	12 (23.1)	1 (1.9)
Arthralgia	5 (18.5)	0	4 (16.0)	0	9 (17.3)	0
Hot flush	2 (7.4)	0	7 (28.0)	0	9 (17.3)	0
Cough	4 (14.8)	0	4 (16.0)	0	8 (15.4)	0
Diarrhea	4 (14.8)	1 (3.7)	4 (16.0)	0	8 (15.4)	1 (1.9)
Dizziness	5 (18.5)	0	3 (12.0)	1 (4.0)[a]	8 (15.4)	1 (1.9)
Fatigue	4 (14.8)	0	4 (16.0)	0	8 (15.4)	0
Influenza	7 (25.9)	1 (3.7)	1 (4.0)	0	8 (15.4)	1 (1.9)
Vomiting	3 (11.1)	0	5 (20.0)	0	8 (15.4)	0

AEs graded using National Cancer Institute Common Terminology Criteria, version 4.03
Other grade ≥3 AEs not included in the table: colitis (n=1), mesenteric vein thrombosis (n=1), pharyngitis (n=2), hypertriglyceridemia[a] (n=3), hemolytic anemia[a] (n=2), hemolysis[a] (n=1), postprocedural hemorrhage (n=1), hypertension (n=1)
[a]Related to study drug as assessed by the investigator

Effect of AG-348 on sex hormones

- Modest changes from baseline in sex hormone levels were observed in males at planned pivotal trial dose levels (≤50 mg BID).
  - Data are consistent with mild aromatase inhibition.
- Most sex hormone values remained within normal limits in females (data not shown).
  - Interpretation is confounded by variability in menopausal status and contraceptive use.

Figure 3. Sex hormone values over time in males

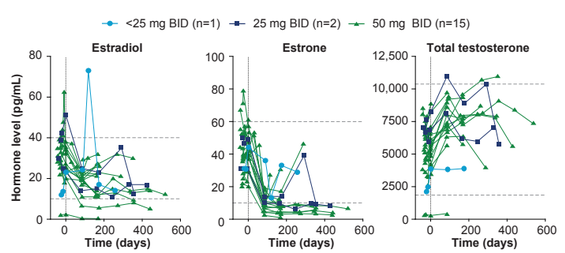
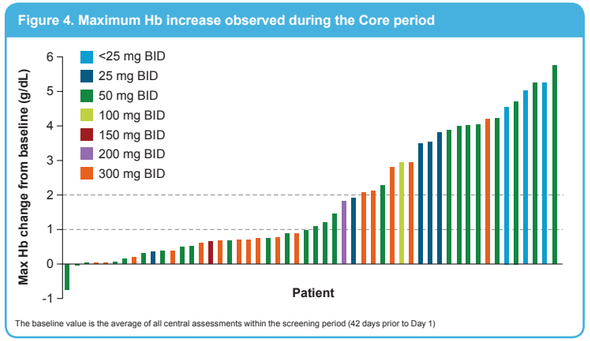


Figure shows data for the subset of males on actual doses ≤50 mg BID. Normal reference upper and lower limits shown as horizontal dashed lines

Clinical activity

- 26 of 52 (50.0%) patients had a maximum Hb increase of >1.0 g/dL.
  - The mean maximum increase was 3.4 g/dL (range 1.1–5.8 g/dL).

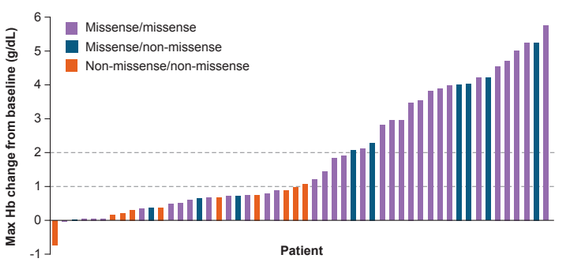
Figure 4. Maximum Hb increase observed during the Core period



The baseline value is the average of all central assessments within the screening period (42 days prior to Day 1)

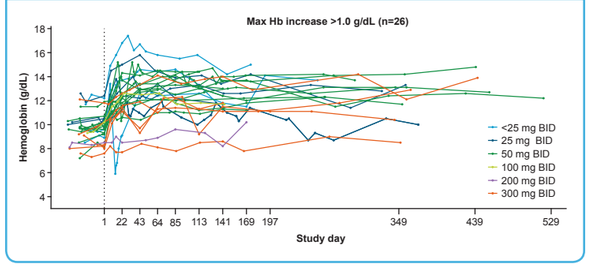
- 25 of 42 (59.5%) patients who had ≥1 missense mutation had an Hb increase >1.0 g/dL.

Figure 5. Maximum Hb increase observed by genotype



- Median time to the first observation of an Hb increase >1.0 g/dL above baseline was 10 days (range 7–187 days).
  - Median baseline Hb in patients who experienced a maximum Hb increase of >1.0 g/dL was 9.7 g/dL (range 7.3–12.3 g/dL) versus 8.0 g/dL (range 6.5–10.1 g/dL) in patients who did not.
- In nine patients, the dose had to be held or reduced due to a rapid rise in Hb.

Figure 6. Majority of Hb increases are rapid and sustained



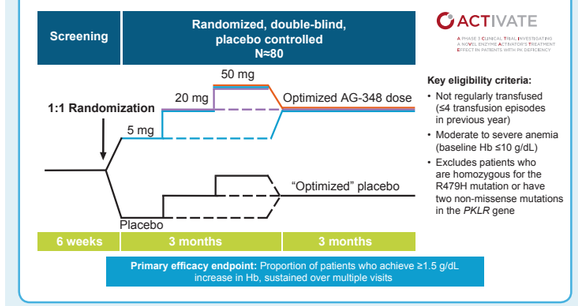
CONCLUSIONS

- AG-348 is a novel, first-in-class, PK-R activator in clinical testing as a potential disease-altering therapy for patients with PK deficiency.
- Chronic daily dosing with AG-348 is well tolerated.
  - Consistent safety profile over the duration of treatment (median 37.5 weeks).
  - Ongoing follow-up will continue to assess the clinical impact of mild aromatase inhibition.
- Patients who respond to AG-348 have rapid and durable responses.
  - 26 of 52 (50%) patients had a maximum Hb increase of >1.0 g/dL.
  - The mean maximum increase in Hb was 3.4 g/dL in patients with an Hb increase >1.0 g/dL.
  - Genotype–Hb response correlations informed eligibility criteria for pivotal trials.
- Pivotal trials in adults with PK deficiency are starting in the first half of 2018:

ACTIVATE N=80
A PHASE 3 CLINICAL TRIAL INVESTIGATING A NOVEL ENZYME ACTIVATOR'S TREATMENT EFFECT IN PATIENTS WITH PK DEFICIENCY

ACTIVATE-T N=20
A PHASE 3 CLINICAL TRIAL INVESTIGATING A NOVEL ENZYME ACTIVATOR'S TREATMENT EFFECT IN PK DEFICIENCY PATIENTS WITH HIGH TRANSFUSION BURDEN

Figure 7. Pivotal trial design for patients who are not regularly transfused



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Disclosures

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RFG: Agios – advisory committee, research funding. DML: Agios – consultancy, speaker bureau; Alexion – UK PNH Physician Network; UCB – consultancy. FG: Addmedica – advisory committee. WB: Agios – honoraria, research funding; Alexion – honoraria; Novartis – honoraria. EvB: Agios – consultancy. HY: Baxalta, Bayer, Octapharma, CSL Behring – consultancy, advisory committee; Baxalta – honoraria, advisory committee. YR: Agios – study investigator. KHMK: Abtero – scientific collaboration; Agios – consultancy, study investigator; Alexion – consultancy, honoraria, study investigator; Celgene – consultancy, study investigator; Novartis – consultancy, honoraria; Pfizer – study investigator; Phoenicia Biosciences – scientific collaboration. SS: ApoPharma, Bluebird Bio, Celgene, Novartis – consultancy. JLK: Agios – consultancy, honoraria; Appharma – research funding; Bluebird Bio – advisory committee, research funding; Ionis – consultancy, honoraria; Novartis – research funding. BS: Agios – consultancy. CK, HY, PAK, LH: Agios – employment, stockholder. VI: Agios – employment, stockholder; Novartis – stockholder. AB: Agios – employment, stockholder at time of study. BG: Agios – advisory committee. CR, DHM – no relevant financial relationships to disclose.

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