ACTIVATE: a phase 3, randomized, multicenter, double-blind, placebo-controlled study of AG-348 in adults with pyruvate kinase deficiency who are not regularly transfused

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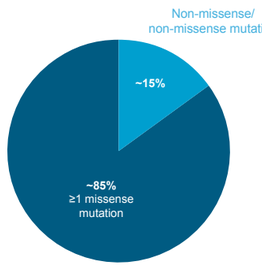
BACKGROUND

- Pyruvate kinase (PK) deficiency is a rare, hereditary, hemolytic anemia.
- AG-348 is being developed as a treatment for PK deficiency and has been tested in phase 1 and 2 (DRIVE PK) studies.
- A phase 3 study (ACTIVATE) is anticipated to open in June 2018.

PK deficiency: disease overview[1-3]

Description	• Under-recognized hereditary hemolytic anemia • Heterogeneous disease with variable severity among all ages • The most common form of nonspherocytic hemolytic anemia
Etiology	• Caused by mutations in the *PKLR* gene coding for red-cell PK (PK-R), resulting in defective glycolysis and decreased red blood cell lifespan
Disease burden	• Lifelong hemolytic anemia • Iron overload and jaundice • Infection risk post splenectomy
Diagnosis and treatment	• PK-R enzyme activity and genetic testing • Supportive treatment: transfusions, splenectomy, iron chelation

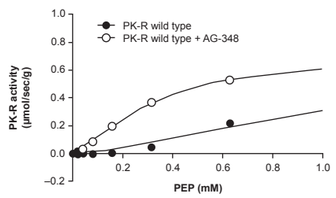
PK deficiency: mutation type[3]



Types of *PKLR* mutations found in 193 unrelated cases in the PK deficiency natural history study

AG-348[4]

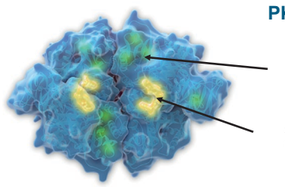
AG-348 is a novel, first-in-class, small-molecule allosteric activator of PK-R in clinical testing as a potential disease-altering therapy for PK deficiency



AG-348 binding enhances the affinity of PK-R for its substrate phosphoenolpyruvate (PEP)

(recombinant enzyme data shown)

PK-R tetramer[4]



Active PK-R is a tetramer; mutations (green) decrease the enzyme activity

AG-348 (yellow) binds at the PK-R dimer-dimer interface, away from the active site and the most common mutations

AG-348 in PK deficiency

***DRIVE PK study design*[5]**

- Phase 2, open-label, dose-ranging study (NCT02476916).
- Main eligibility criteria: adult patients with PK deficiency who are not regularly transfused; hemoglobin (Hb) ≤12.0 g/dL (if male) or ≤11.0 g/dL (if female).
- Main endpoints:
  - Primary: safety – adverse events (AEs), serum sex hormones, laboratory parameters, bone mineral density
  - Secondary: efficacy – Hb, markers of hemolysis, erythropoietin, markers of iron metabolism, pharmacokinetics, pharmacodynamics.
- Patients randomized to initial AG-348 dose of 50 mg twice daily (BID) or 300 mg BID.
- Core period (first 6 months) completed; extension period (4 years) ongoing.

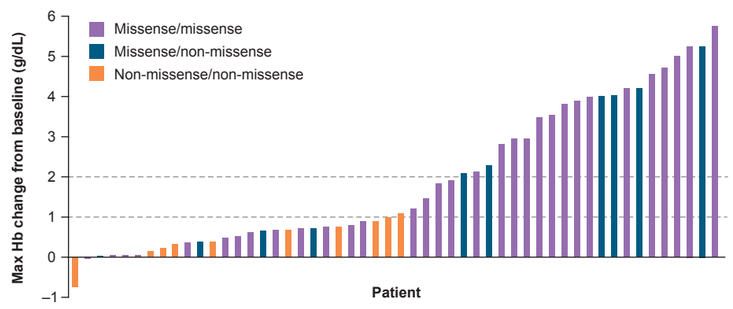
***DRIVE PK cumulative safety summary*[5]**

- AG-348 was generally well tolerated.
- The majority of AEs were grade 1–2.
- The safety profile was consistent over the duration of treatment (median 37.5 weeks).
- Treatment-related AEs leading to discontinuation (n=4):
  - Hemolytic anemia, hypertriglyceridemia, pharyngitis and 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.
- 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; interpretation is confounded by variability in menopausal status and contraceptive use.

***DRIVE PK efficacy (core period)*[5]**

- 25 of 42 (59.5%) patients who had ≥1 missense mutation had an Hb increase >1.0 g/dL (**Figure 1**).
- The mean maximum increase in Hb was 3.4 g/dL in patients with an Hb increase >1.0 g/dL.
- Median time to the first observation of an Hb increase >1.0 g/dL above baseline was 10 days (range, 7–187 days).
- The dose had to be held or reduced owing to a rapid rise in Hb in nine patients.

Figure 1. Maximum Hb increases observed by genotype in the DRIVE PK study



ACTIVATE STUDY

Summary

- The safety and efficacy data from the DRIVE PK study support the development of AG-348 in patients with PK deficiency.
- ACTIVATE is a phase 3, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of AG-348 in adult patients with PK deficiency who are not regularly transfused (NCT03548220; **Figure 2**).
- An independent data monitoring committee will review the study data periodically and provide safety oversight.

Study status

- ACTIVATE is expected to open in June 2018.

PK deficiency global registry

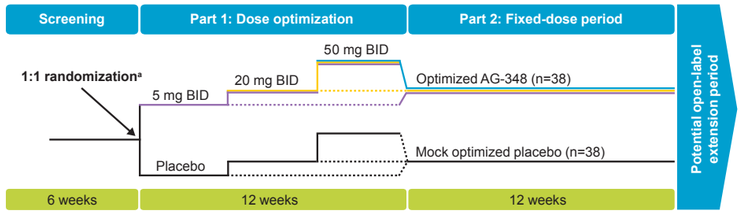
The Peak Registry
A Global Longitudinal Study of PK Deficiency
SPONSORED BY AGIOS PHARMACEUTICALS

- Patients who are not eligible for the ACTIVATE trial may be enrolled in the Peak Registry (NCT03481738).
- Goals of the Peak Registry:
  - Collect and aggregate longitudinal data (minimum 2 years, up to 9 years) from patients with PK deficiency who have been diagnosed via genetic analysis (all ages) worldwide (up to 20 countries)
  - Promote further understanding of PK deficiency disease parameters, e.g. transfusion dependency, treatment practices, Hb correlation with disease burden (refine/redefine and substantiate understanding based on data).

Figure 2. ACTIVATE study design

Key inclusion criteria
- ≥18 years of age
- Documented presence of at least two mutant alleles in *PKLR*, of which at least one is a missense mutation (based on genotype–Hb response correlations in DRIVE PK, see **Figure 1**)
- Hb concentration ≤10.0 g/dL, regardless of sex
- ≤4 transfusion episodes in the 12-month period up to the first day of study treatment, and no transfusions in the 3 months prior to the first dose
- Adequate organ function

Key exclusion criteria
- Homozygous for the R479H mutation or two non-missense mutations in *PKLR*
- Significant medical condition that confers an unacceptable risk to participating in the study, and/or that could confound the interpretation of data



[a]Stratified by average of screening Hb values (<8.5 g/dL vs ≥8.5 g/dL) and mutation category (missense/missense vs missense/non-missense)

Screening
- Eligible patients randomized to AG-348 or placebo

Part 1: Individualized dose optimization period
- All patients start on 5 mg BID AG-348 or matched placebo
- Dose can be increased from 5 to 20 mg BID and, subsequently, from 20 to 50 mg BID
- Dose should be increased if patient does not experience an increase in Hb of ≥1.5 g/dL, or could benefit from a greater increase in Hb

Part 2: Fixed-dose period
- Patient receives AG-348 or matched placebo at their optimized dose, with no planned adjustment for 12 weeks
- Dose can be reduced for safety reasons on a case-by-case basis throughout the study

Planned extension study
- For patients randomized to AG-348 who have experienced significant benefit from AG-348
- For all patients randomized to placebo

Main endpoints

Primary
- Hb response, defined as a ≥1.5 g/dL increase in Hb concentration from baseline that is sustained at two or more scheduled assessments at Weeks 16, 20, and 24 during the fixed-dose period

Secondary
- Average change from baseline at Weeks 16, 20, and 24 in Hb concentration
- Average change from baseline at Weeks 16, 20, and 24 in markers of hemolysis
- Average change from baseline at Weeks 16, 20, and 24 in markers of hematopoietic activity
- Change from baseline in HRQoL PRO scores: PK Deficiency Diary and PK Deficiency Impact Assessment
- Change from baseline at Week 24 in iron markers
- Safety: AEs, laboratory parameters, bone mineral density
- AG-348 pharmacokinetics
- Relationship between AG-348 pharmacokinetics and safety parameters

Exploratory
- Relationship between AG-348 pharmacokinetics and indicators of clinical activity
- Effects of AG-348 on pharmacodynamic markers of PK deficiency
- Transfusions
- Liver iron content, as quantified by magnetic resonance imaging

Statistics

Sample size
- Assuming a response rate of 35% in the active arm and 5% in the placebo arm, 76 patients (38 per arm) are needed to have 90% power to detect a treatment effect in Hb response rate, based on a two-sided Fisher's exact test at the 0.05 significance level

Primary efficacy analysis
- Patients' Hb response status will be analyzed using a logistic regression model that will include Hb response (yes vs no) as a dependent variable and treatment as an independent variable, adjusting for stratification factors, including screening Hb concentrations (<8.5 vs ≥8.5 g/dL) and *PKLR* mutation category (missense/missense vs missense/non-missense)

HRQoL PRO = health-related quality of life patient-reported outcome

Disclosures
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1. Grace RF et al. *Am J Hematol* 2015;90:825-30. **2.** Percy MJ et al. *Blood Cells Mol Dis* 2007;39:189-94. **3.** Grace RF et al. *Blood* 2018;131:2183-92. **4.** Kung C et al. *Blood* 2017;130:1347-56. **5.** Grace RF et al. *59th ASH Annual Meeting* 2017: Poster 2194.

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