PF385

ACTIVATE-T: a phase 3, open-label study to evaluate the efficacy and safety of AG-348 in regularly transfused adults with pyruvate kinase deficiency

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ACTIVATE-T

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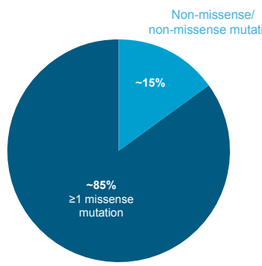
BACKGROUND

- 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-T) is currently open and enrolling patients.

PK deficiency: disease overview[1-3]

Description	• Under-recognized hereditary disease • Heterogeneous disease with variable severity among all ages • Often presents in childhood
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

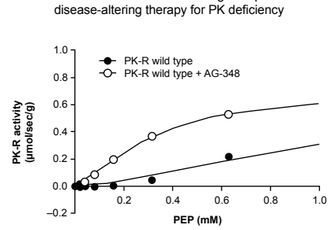
PK deficiency: mutation type[3]



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

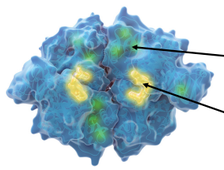
AG-348[4]

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 catalytic activity

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

PK-deficient patients who are regularly transfused

- These patients represent a small subset of the overall population of patients with PK deficiency.
  - 23/198 (12%) adults in the PK deficiency natural history study are regularly transfused.[3]
- Heterogeneous transfusion practices in PK deficiency:
  - No universally accepted transfusion guidelines
  - Transfusion frequency can vary from once per week to a few times per year
  - Transfusions administered at regularly scheduled intervals vs when hemoglobin (Hb) nadir reached, in addition to ad hoc/on demand (e.g. infection, patient feeling tired)
  - Patients requiring ≥6 transfusions/year are likely to require transfusions to maintain an acceptable Hb level.

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; 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.

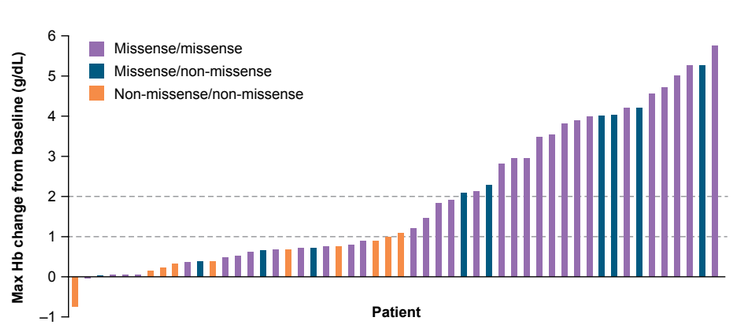
***DRIVE PK cumulative safety summary*[5]**

- 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-T STUDY

Summary

- The safety and efficacy data from the DRIVE PK study support the development of AG-348 in patients with PK deficiency.
- ACTIVATE-T is an open-label trial to evaluate the efficacy (reduction in transfusion burden) and safety of AG-348 in the ultra-rare population of adult patients with PK deficiency who are regularly transfused (**Figure 2**).
- An independent data monitoring committee will review the study data periodically and provide safety oversight.

Study status

- ACTIVATE-T is currently open and enrolling patients at participating sites globally.
- The additional ACTIVATE study is expected to open in June 2018, and 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.

PK deficiency global registry

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

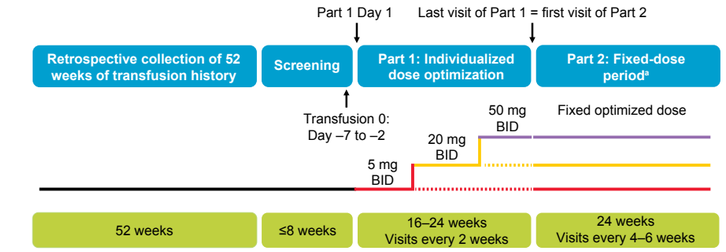
- Patients who are not eligible for the ACTIVATE-T trial may be enrolled in the Peak Registry (NCT03481738).
- Goals of the Peak Registry:
  - Collect and aggregate longitudinal data (minimum 2 years, up to 9 years) from patients with PK deficiency who have been diagnosed via genetic analysis (all ages) 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-T 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**)
- ≥6 transfusion episodes in the past 52 weeks
- Adequate organ function

Key exclusion criteria
- Homozygous for the R479H mutation or two non-missense mutations in *PKLR*
- History of transfusions occurring, on average, more frequently than once every 3 weeks during the past 52 weeks
- Significant medical condition that confers an unacceptable risk to participating in the study, and/or that could confound the interpretation of data

- Approximately 15–20 regularly transfused patients will be enrolled



[a]Patients who remain on the study until the end of Part 2 may be eligible for an extension study

Screening
- Collection of transfusion history:
  - Dates of all transfusions
  - Pretransfusion Hb for ≥80% of transfusions
  - Number of blood units transfused for all transfusions
- Transfusion history information used to:
  - Determine eligibility
  - Calculate mean transfusion frequency, which will be used to guide the timing of AG-348 dose-level increases
  - Calculate individual transfusion trigger (TT), mean of pretransfusion Hb
  - Calculate mean number of blood units (MNU) transfused per transfusion
  - Function as historical control data for the analysis

Part 1: Individualized dose optimization period
- All patients start on 5 mg BID
- 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 a reduction in transfusion frequency after 1–2 transfusions

Part 2: Fixed-dose period
- Patient receives AG-348 at their optimized dose, with no planned adjustment for 24 weeks
- Dose can be reduced for safety reasons on a case-by-case basis throughout the study

Transfusions throughout Part 1 and Part 2
- Patient transfused when their Hb reaches individual TT (±0.5 g/dL or ±0.31 mmol/L)
- Patient transfused with their MNU

Planned extension study
- For patients who have experienced significant benefit from AG-348

Main endpoints

Primary
- Reduction in transfusion burden (defined as a reduction of ≥33% in the number of red blood cell units transfused during the 24 weeks of the fixed-dose period compared with the historical transfusion burden standardized to 24 weeks)

Secondary
- Safety

Exploratory
- Liver iron status
- Health-related quality of life
- Pharmacokinetics
- Pharmacodynamics (levels of PK-R)

Statistics
- Sample size driven by feasibility (15–20 patients)
- With a sample size of 20, the power of the study will be 58% to detect a response rate of 30% compared with a null rate of 10%, based on a two-sided Fisher's exact test at the 0.05 significance level

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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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