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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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

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

• Caused by mutations in the PKLR gene coding for red cell PK (PK-R), resulting in defective glycolysis and decreased red cell lifespan
• Lifelong hemolytic anemia
• Iron overload and jaundice
• Infection risk post splenectomy

• PK-R enzyme activity and genetic testing
• Supportive treatment: transfusions, splenectomy, iron chelation

DRIVE PK study design

• Phase 2, open-label, dose-ranging study (NCT02476196).
• Main eligibility criteria: adult patients with PK deficiency who are not regularly transfused; Hb ≥12.5 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.

PK-deficient patients who are regularly transfused

• These patients represent a small subset of the overall population of patients with PK deficiency.
  - 23% (12%) adults in the PK deficiency natural history study
• Heterogeneous transfusion practices in PK deficiency:
  - Data are consistent with mild apheresis inhibition.
  - Most sex hormone values remained within normal limits in females; interpretation is confounded by variability in menopausal status and contraceptive use.

DRIVE PK cumulative safety summary

• 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, hemolytic crisis, pharyngitis and nausea, pleural effusion.

• There were 14 serious AEs in 11 patients.
  - Five treatment-related serious AEs in four patients: anemia, hemolysis, 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 (550 mg BID).
  - Data are consistent with mild aromatase inhibition.

• Two patients had a history of gynecomastia that resolved with treatment with AG-348.

PK deficiency: mutation type

AG-348 in PK deficiency

AG-348 is a novel, first-in-class, small-molecule allosteric activator of PK-R in clinical testing as an erythroid disease-targeting PK deficiency drug.

PKR-deficient patients who are regularly transfused

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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.

Study status

• ACTIVATE-T is currently open and enrolling patients at participating sites globally.

• The additional ACTIVATE-T 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

• Patients who are eligible for the ACTIVATE-T trial may be enrolled in the PK deficiency global registry.

• Collection of transfusion history:
  - Number of transfusions and transfusion triggers for all transfusions

• Pharmacokinetic and pharmacodynamic data:
  - AG-348 binding enhances the affinity of PK-R for its physiological substrate phosphoenolpyruvate (PEP).

• Population PK-R tetramer

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

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

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
• Median to the first observation of an Hb increase >1.0 g/dL, baseline Hb <10.0 g/dL

Key exclusion criteria

• Hematologically normal individuals with no history of PK deficiency
• History of transfusion reactions, severe adverse events, or non-compliance more than once every 6 weeks during the past 52 weeks
• Significant medical condition that complicates or confounds the interpretation of data

Figure 3. PKR-deficient patients who are regularly transfused

Types of PK-R mutations found in 163 patients with PK deficiency

AG-348: PKR-deficient patient

AG-348 binds to the PK-R dimer–transferrin interface, away from the active site and the most common mutations.

PK-R tetramer

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Patients who remain on the study until the end of Part 2 can be eligible for an extension study.

Screening

• Collection of transfusion history:
  - Dates of all transfusions
  - Packed RBC units transfused (100% of transfusions)
  - Number of blood units transfused for all transfusions

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