**BACKGROUND**

**PK deficiency: disease overview**
- Under-recognized hereditary hemolytic anemia
- Heterogeneous disease with variable severity among all ages
- The most common form of non-spherocytic hemolytic anemia
- Caused by mutations in the PKLR gene, resulting in defective glycolysis and decreased red blood cell lifespan
- 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

**AG-348**
AG-348 is a novel, first-in-class, small-molecule allosteric activator of PK-R with potential for disease-modifying therapy for PK deficiency

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

**Figure 2. ACTIVATE study design**

**PK deficiency: mutation type**
- Approximately 70% of PK deficiency cases are due to missense mutations
- Approximately 30% of PK deficiency cases are due to non-missense mutations

**AG-348**
AG-348 binds PK-R with higher affinity than PK-R wild type, enhancing its activity

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

**AG-348 in PK deficiency**
**DRIVE PK study design**
- Phase 2, open-label, dose-ranging study (NCT02476916)
- Main eligibility criteria: patients with PK deficiency who are not regularly transfused; hemoglobin (Hb) ≥10.0 g/dL (females) or ≥11.0 g/dL (males)
- Main endpoints:
  - Primary: safety
  - Secondary: efficacy

**Figure 2. ACTIVATE study design**

**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**
- Patients who are not eligible for the ACTIVATE trial may be enrolled in the PK Registry (NCT03481173)
- Goals of the PK 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)