An ongoing, global, longitudinal, observational study of patients with pyruvate kinase deficiency: The Peak Registry

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BACKGROUND AND OBJECTIVES

Pyruvate kinase (PK) deficiency: disease overview

Description	• Under-recognized hereditary disease[1] • Heterogeneous disease with variable severity among all ages[1,2] • Often presents in childhood[1,2]
Etiology	• Caused by mutations in the *PKLR* gene, which result in reduced red cell PK (PK-R) enzyme activity • Reduced PK-R enzyme activity leads to defective glycolysis and decreased red blood cell lifespan[3]
Disease burden	• Lifelong hemolytic anemia[1,2] • Iron overload and jaundice[1,2] • Infection risk post splenectomy[1,2] • Signs and symptoms negatively affect health-related quality of life[4]
Diagnosis/ treatment	• PK-R enzyme activity and genetic testing[1,2] • Supportive treatment: transfusions, splenectomy, iron chelation[1,2]

Rationale for development of a global registry

- The PK Deficiency Natural History Study (ClinicalTrials.gov NCT02053480) is an observational patient registry assessing the range and incidence of symptoms, treatments, and complications related to PK deficiency in 254 patients enrolled at 30 sites in six countries.[2]
- The Peak Registry (ClinicalTrials.gov NCT03481738) is a global, longitudinal, noninterventional study of PK deficiency that aims to integrate and extend the Natural History Study with additional patients and longer follow-up from an expanded geographical distribution.

Objectives

- To report the design elements of the Peak Registry and progress to date, and to provide information on the integration of data from the Natural History Study into the Peak Registry.

REGISTRY DESIGN

- The Peak Registry is a global, longitudinal, observational study for adult and pediatric patients with PK deficiency.
- The registry design is summarized in **Figure 1**.
  - The design is adaptable, allowing for substudies and inclusion of patient/caregiver-reported quality-of-life outcomes.
- The registry is governed by a steering committee, which comprises a diverse set of health care professionals, including representatives from different geographic areas, and clinicians and diagnosticians treating adult or pediatric patients.

Figure 1. Peak Registry design

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

Objectives

Primary

To develop an understanding of the longitudinal clinical implications of PK deficiency, including:
- Natural history
- Treatment and outcomes
- Variability in clinical care
- Disease burden

Secondary

Medical/clinical
- To understand the prevalence, incidence, and severity of complications associated with PK deficiency
- To evaluate pregnancy outcomes
- To provide longitudinal data to assist physicians with the clinical management of individual patients
- To act as a global repository for potential data from other PK deficiency–related studies to support aggregate and comparative analyses

Genetic
- To examine a possible phenotype-genotype correlation

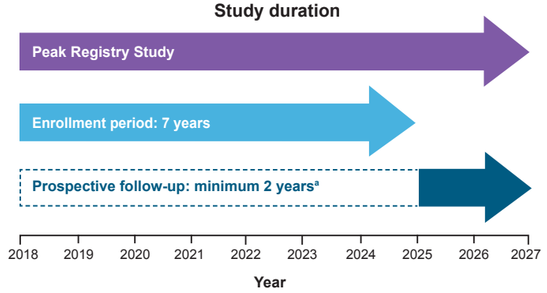
Participants

Inclusion criteria
- Patients of any age with a confirmed diagnosis of PK deficiency obtained by genetic testing
- Each participant or their parent/guardian must be willing and able to give written informed consent and/or assent

Exclusion criterion
- Patients who are actively enrolled in any Agios-sponsored clinical trial involving treatment with a PK activator are not eligible to enroll

Enroll approximately 500 eligible patients

Study duration



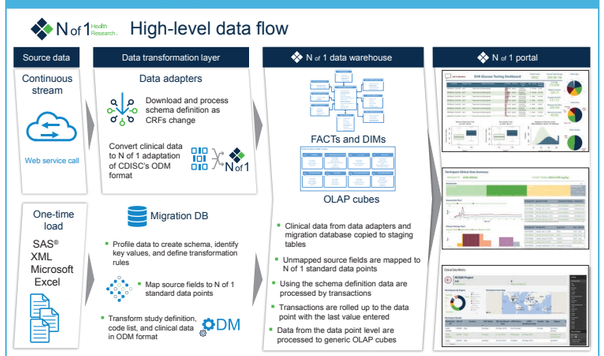
Data to be collected
- Diagnosis
- Demography
- Physical examination
- Key laboratory tests
- Complications related to PK deficiency and its management
- Reasons for treatment decisions
- Pregnancy outcomes
- Medical history and physical findings, with particular interest in:
  - Transfusion history
  - Splenectomy/cholecystectomy
  - Hepatic and cardiac iron load
  - Thrombosis
  - Bone imaging
  - Stem cell transplant
  - Prior and current medications, including iron chelation therapy

[a]Participants in the Peak Registry who were originally included in the Natural History Study conducted by Boston Children's Hospital, and for whom data are integrated within the Peak Registry, may have a cumulative follow-up exceeding 11 years

HARMONIZING PK DEFICIENCY NATURAL HISTORY STUDY AND PEAK REGISTRY DATA

- Digital harmonization of the data collected during the Natural History Study and the Peak Registry aims to maximize the amount of longitudinal data available (**Figure 2**).
- A digital platform (N of 1) is being developed to allow participating physicians to view their patients' aggregated clinical data.
- The portal will also allow migration of Natural History Study data to enable combined views of both Peak Registry and Natural History Study datasets.

Figure 2. Data harmonization between the Natural History Study and the Peak Registry



High-level data flow in the Peak Registry. Participating physicians can view their patients' aggregated Peak Registry data through the N of 1 portal. When patients have participated in the Natural History Study, datasets will be aggregated in a data warehouse so that a single patient's historical clinical data from both the Natural History Study and Peak Registry can be used to provide a complete clinical picture of the consented patient. All data access to the N of 1 portal is controlled by a data access policy developed in concert with the Peak Registry Steering Committee.

ENROLLMENT PROGRESS: DATA CUTOFF AS OF NOVEMBER 18, 2019

- 46 sites in 11 countries are active (**Figure 4**). Site startup has begun in Ireland, Japan, South Korea, Switzerland, Thailand, and Turkey.

Figure 3. Enrollment status by month

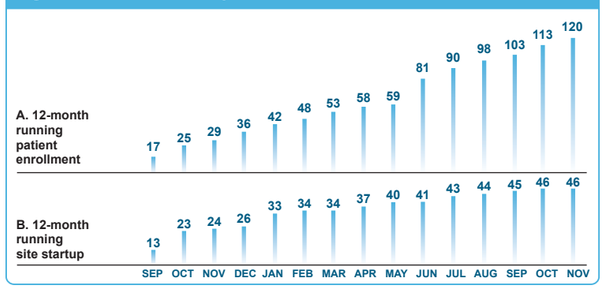
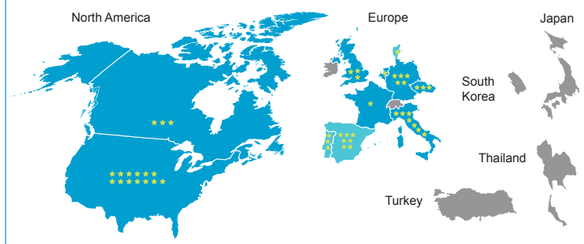


Figure 4. Peak Registry activity as of November 2019



- Natural History Study + Peak countries
- Peak-only countries (did not participate in Natural History Study)
- Peak active sites
- Startup activities for Peak ongoing (Ireland, Japan, South Korea, Switzerland, Thailand, and Turkey)

Central America/South America and Africa: no sites have been identified to date

Map not to scale; locations are approximate. Cities with multiple sites are indicated with a single star. Sites in Germany are pending activation.

SUMMARY

- The Peak Registry is a global noninterventional registry for adult and pediatric patients with PK deficiency that aims to extend the scope of the Natural History Study with additional patients from an expanded geographic distribution and longer follow-up.
- Site and patient recruitment are ongoing, with startup of registry sites in Thailand and feasibility assessment of sites in Japan and South Korea ongoing, and plans to activate sites in Ireland, Switzerland, and Turkey by year end.
- A portal has been developed to allow combined analyses of Peak Registry and Natural History Study datasets, and will be available to Peak Registry physician participants in 2020.
- Further information is available at https://peakregistry.com and www.clinicaltrials.gov, and from medinfo@agios.com.

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