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The Pyruvate Kinase Deficiency Global Longitudinal (Peak) Registry: rationale and study design

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ABSTRACT

Introduction Pyruvate kinase (PK) deficiency is a rare, under-recognised, hereditary condition that leads to chronic haemolytic anaemia and potentially serious secondary complications, such as iron overload, cholecystitis, pulmonary hypertension and extramedullary haematopoiesis. It is an autosomal recessive disease caused by homozygous or compound heterozygous mutations in the *PKLR* gene. Due to its rarity and clinical heterogeneity, information on the natural history and long-term clinical course of PK deficiency is limited, presenting major challenges to patient management, the development of new therapies and establishing disease-specific treatment recommendations. The Pyruvate Kinase Deficiency Global Longitudinal (Peak) Registry is an initiative to address the gaps in the knowledge of PK deficiency. This manuscript describes the objectives, study design and methodology for the Peak Registry.

Methods and analysis The Peak Registry is an observational, longitudinal, global registry of adult and paediatric patients with a genetically confirmed diagnosis of PK deficiency. The Peak Steering Committee is composed of 11 clinicians and researchers with experience in the diagnosis and management of PK deficiency from 10 countries, a patient representative and representatives from the sponsor (Agios Pharmaceuticals). The registry objective is to foster an understanding of the longitudinal clinical implications of PK deficiency, including its natural history, treatments and outcomes, and variability in clinical care. The aim is to enrol up to 500 participants from approximately 60 study centres across 20 countries over 7 years, with between 2 and 9 years of follow-up. Data will include demographics, diagnosis history, genotyping, transfusion history, relevant clinical events, medications, emergency room visits and hospitalisations.

Ethics and dissemination Registry protocol and informed consent forms are approved by institutional review boards/independent ethics committees at each study site. The study is being conducted in accordance with the Declaration of Helsinki. Registry data will be published in peer-reviewed journal articles and conference publications.

Trial registration number NCT03481738.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The patients with pyruvate kinase (PK) deficiency participating in the Peak Registry span a broad age range across a variety of geographical regions, which allows for the capture of disease management practices across a diverse patient population.
⇒ The longitudinal design of the Peak Registry and integration of PK Deficiency Natural History Study data allows for extended monitoring and follow-up (up to 9 years) of a large number of patients with PK deficiency, which will provide unique insight into this very rare disease and its related long-term complications.
⇒ The Peak Registry will encourage communication and collaboration among healthcare professionals and patients with PK deficiency around a common registry.
⇒ A limitation of the study is that Peak Registry centres may have variations in treatment patterns and routine care for patients, and consequently may not be representative of the entire PK deficiency healthcare treatment community.
⇒ Spontaneous data collection and variable frequency of patient visits may lead to gaps in the available data, consistent with most registries.

INTRODUCTION

Pyruvate kinase (PK) deficiency is a rare, hereditary, chronic haemolytic anaemia, which leads to associated long-term complications, such as bone fractures, pulmonary hypertension, iron overload, gallbladder disease and extramedullary haematopoiesis.[1 2] The diagnosed prevalence of PK deficiency in Western populations is estimated as 3.2–8.5 individuals per million; however, as the disease is under-recognised by healthcare practitioners, patients are often misdiagnosed or have a delayed diagnosis and the true prevalence may be higher.[3]

PK deficiency is an autosomal recessive disease caused by either homozygous or compound heterozygous mutations in the

PK liver and red blood cell (RBC)-specific (*PKLR*) gene. The *PKLR* gene encodes PKR, the enzyme responsible for the final step in glycolysis in RBCs, and more than 300 different mutations have been described with varying impact on this glycolytic activity.[4 5] As mature RBCs lack both a nucleus and mitochondria, they are critically dependent on glycolysis for ATP production,[4] and disruption of PKR can reduce their total ATP production by up to 50%.[6] ATP is essential for maintaining Na+/K+ ATPase activity and cell morphology. Due to the deficiency in ATP, RBCs from patients with PK deficiency have a shortened life span, leading to chronic haemolysis.[1 6]

The heterogenous haematological and clinical manifestations of PK deficiency reflect the symptoms and complications of lifelong chronic haemolysis,[1 5 6] and can be unpredictable throughout the course of the disease.[7 8] In non-transfused children with intact spleens, the median haemoglobin is 91 g/L (range 60–125), whereas in non-transfused adults the median haemoglobin is slightly higher, but with a wide range (median value 113 g/L (range 76–142).[8] Most patients have an indirect hyperbilirubinaemia (adult median value 4.1 mg/dL (range 0.9–17.6)), increased reticulocytes (adult median reticulocyte % 18.9 (range 2.5–76.0)) and hyperferritinaemia (adult median ferritin value 594 ng/mL (range 32–8220)).[8] Patients also commonly experience exertional dyspnoea, fatigue, jaundice, gallstones, iron overload and splenomegaly.[1 2 9] The fatigue associated with PK deficiency can restrict activities of daily living, cause cognitive and emotional deficiencies, disturb sleep, and negatively impact health-related quality of life (HRQoL).[9 10] Jaundice may also have a significant impact on self-esteem.[9]

Historically, management of PK deficiency has been supportive only. Blood transfusions, splenectomy and cholecystectomy are commonly used to address the sequelae of PK deficiency, but all carry long-term risks, and none address the underlying metabolic defect of the disease.[8] Curative therapy with stem cell transplant has been reported in a small cohort of patients,[11 12] but the high risk of death and morbidity associated with this procedure, in addition to the difficulty of clinical diagnosis before the onset of iron overload, precludes its use as standard treatment for PK deficiency.[12] Furthermore, there are no evidence-based guidelines for the monitoring and management of patients with PK deficiency, leading to wide variability in practice.[2 7] There is, therefore, a significant unmet need for acceptable new treatments that address the underlying basis for PK deficiency. Disease-modifying strategies that target the metabolic cause of PK deficiency include lentiviral-mediated gene therapy and small-molecule allosteric activators of PKR. The feasibility and safety of the lentiviral-mediated gene therapy RP-L301 (Rocket Pharmaceuticals, Cranbury, New Jersey, USA) is being evaluated in a phase I study (NCT04105166) of adults and paediatric patients with severe PK deficiency. Preliminary results from the first two patients receiving treatment show one patient had no transfusion requirements at 6 months post-treatment and both patients demonstrated increases in haemoglobin levels (from 74 g/L at baseline to 139 g/L at 6 months post-treatment in patient 1 and from ~70 g/L at baseline to 138 g/L at 3 months post-treatment in patient 2). Markers of haemolysis were normalised in both patients and no serious safety issues or infusion-related complications were observed.[13] Mitapivat (Agios Pharmaceuticals, Cambridge, Massachusetts, USA) is a first-in-class, oral, small-molecule activator of PK that is approved by the US Food and Drug Administration for the treatment of haemolytic anaemia in adults with PK deficiency.[14] In the phase III ACTIVATE study in adults with PK deficiency who were not regularly transfused, 40% (16/40) of patients receiving mitapivat achieved a sustained ≥15 g/L increase in haemoglobin concentration from baseline, compared with 0/40 receiving placebo (p<0.0001).[15] In the phase III ACTIVATE-T study, 37% (10/27) of adult patients with PK deficiency receiving regular transfusions dosed with mitapivat achieved a ≥33% reduction in transfusion burden compared with patient's historical transfusion burden (one-sided p=0.0002).[16] In addition, no treatment-emergent adverse events led to discontinuation of mitapivat during either ACTIVATE or ACTIVATE-T.[15 16]

As a result of its rarity and clinical heterogeneity, information on the natural history of PK deficiency, its clinical burden and long-term clinical course is limited. This represents a major challenge in the effort to develop new therapies and establish disease-specific recommendations for diagnosis and patient care.[6 17] Patient registries can help to address these gaps in clinical knowledge by enabling the monitoring of patient and treatment outcomes over time, as well as how these may change with the approval of mitapivat, with the aim to improve standards of care.[17] In particular, registry data are useful to study heterogeneous populations with rare diseases and can be used to investigate the level of effectiveness of treatments in different patient subgroups,[18] as well as to support peer networks for clinicians and patients.[19] To assist with understanding PK deficiency and the development of novel treatments for the disease, two patient registries were sequentially created: the PK Deficiency Natural History Study (NHS; ClinicalTrials.gov identifier: NCT02053480) and the Pyruvate Kinase Deficiency Global Longitudinal Registry, also known as the Peak Registry (ClinicalTrials.gov identifier: NCT03481738).[1 20] The NHS was developed in 2013 as an international, observational, retrospective and prospective registry for adult and paediatric patients with PK deficiency.[1 21] Patients were enrolled from 2014 to 2017 and followed for 2 years. During this period, data on medical history,[1 5 21 22] treatment patterns[1 2 23] and quality of life[10] were collected from 254 patients at 31 sites in 6 countries. The Peak Registry was initiated in 2018 to build on the NHS and develop an understanding of the longitudinal clinical implications of PK deficiency using a larger number of patients and geographical reach, broader data collection and longer patient follow-up.[20]

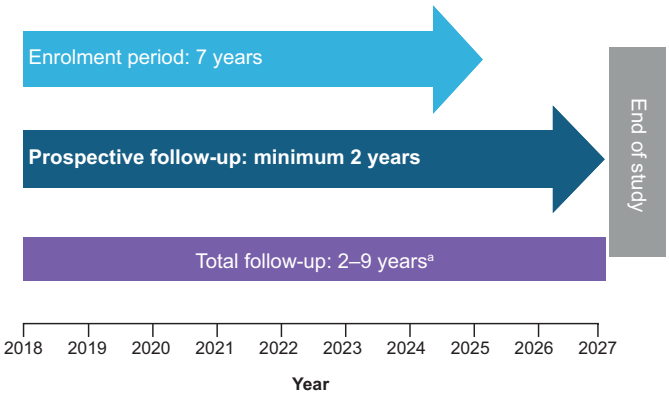

Figure 1 Study duration. [a]Participants in the Peak Registry who were originally included in the Natural History Study, conducted by Boston Children's Hospital, from 2014 to 2017 and for whom data are integrated within the Peak Registry may have a cumulative follow-up exceeding 11 years.

Here, we describe the study design and methodology for the Peak Registry, including the governance, data being collected for evaluation, general methods for data integration with the NHS and the potential insights it will provide to clinicians and patients.

METHODS AND ANALYSIS

Study design and objectives

The Peak Registry is an observational, longitudinal, multicentre, global registry of patients with a genetically confirmed diagnosis of PK deficiency. The registry aims to enrol approximately 500 adult and paediatric patients from approximately 60 study centres across 20 countries and will be open for enrolment for 7 years with all participants to be followed prospectively for at least 2 years and for up to 9 years (figure 1). Participants in the Peak Registry who were originally included in the PK Deficiency NHS from 2014 to 2017 and for whom data are integrated within the Peak Registry may have a cumulative follow-up exceeding 11 years. This provides an appropriate length of follow-up for a longitudinal study, while balancing the burden of data collection, which could result in reduced data entry and quality over time. Enrolment for the Peak Registry began on 23 April 2018 and will end on 30 April 2025. The study will end on 30 April 2027.

The primary objective of the Peak Registry is to develop an understanding of the longitudinal clinical implications of PK deficiency, including the natural history of the disease, treatments and outcomes, and the variability in clinical care and disease burden. Secondary objectives include evaluating outcomes associated with pregnancy and examining a possible correlation between the *PKLR* genotype and the PK deficiency clinical phenotype. Substudies within the registry, including the HRQoL (NCT04964323) and cognition (NCT04995315) studies, will characterise patient-reported HRQoL and disease burden in patients with PK deficiency and evaluate if PK deficiency has an impact on cognitive performance, respectively. Both substudies are prospective, observational cohort studies that are managed via a decentralised model using a web-based portal. Participating Peak Registry sites can invite eligible patients (patients ≥18 years of age in select countries) to participate in the substudies through the online Peak Patient Community Portal and begin the informed consent form process.

Registry governance

The Peak Registry is overseen by a Scientific Steering Committee, composed of international experts in PK deficiency who are involved in research, diagnosis, and clinical practice, patient representation, and sponsor representatives. The Peak Scientific Steering Committee currently includes 11 external clinicians from 10 countries (Canada, Czech Republic, Denmark, Italy, Japan, the Netherlands, Spain, Thailand, the UK, and the USA), a patient representative and representatives from the sponsor (Agios Pharmaceuticals). Activities for the Committee include defining the objectives and scientific direction of the registry, advising on clinical data to be captured, and providing insight and oversight on planned analyses and dissemination of the data.

Site selection and patient enrolment

Site selection began in 2017, with the first site active in 2018, initially targeting centres with experience in managing patients with PK deficiency, including the top enrolling sites in the NHS in the USA, the Netherlands, Italy, Germany, Czech Republic and Canada. Additional sites were recruited through expanded outreach in 2019 and 2020, including sites in countries that did not participate in the NHS (Denmark, France, Ireland, Portugal, South Korea, Spain, Switzerland, Thailand, Turkey and the UK) and sites where patients with confirmed PK deficiency had expressed an interest in being included. Additional sites may be considered for inclusion if they are in countries that are not currently represented and they are able to recruit sufficient numbers of patients. Most future enrolment is expected to be driven primarily through existing sites and through remote enrolment of patients treated at non-participating sites (provided that a medical

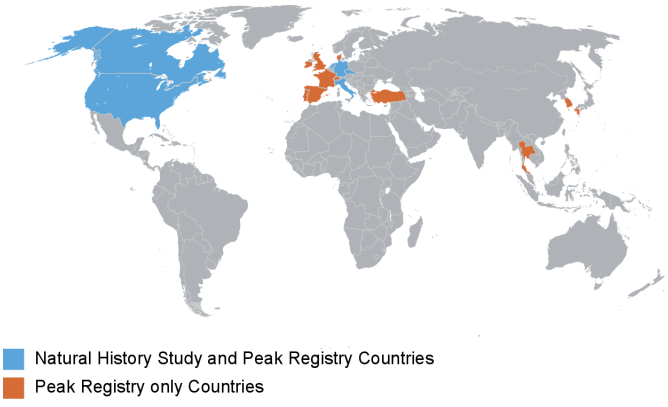

Figure 2 Countries with Peak Registry and Natural History Study sites.

Table 1 Data collected to assess management of the clinical course of PK deficiency

Data parameter*	Examples of variables to be collected†	Collected at enrollment	Collected at follow-up visits‡
Demographics	► Date of birth	✓	
	► Sex	✓	
	► Race/ethnicity	✓	
	► Birth country/birth country of parents	✓	
	► Parental consanguinity (per country-specific regulations)	✓	
Diagnosis	► Date of first symptoms	✓	
	► Date of clinical diagnosis	✓	
	► Dates of enzymatic diagnostic tests	✓	
	► Enzyme test results	✓	
	► Dates of genetic testing	✓	
	► Genetic test result	✓	
Current and prior medications§	► Relevant medications, vitamins, and supplements	✓	✓
	► Reason for use of each medication, vitamin, and supplement	✓	✓
Physical examination	► Blood pressure, height, weight, smoking status	✓	✓
Key laboratory tests¶	► Haematocrit, haemoglobin, RBC count, absolute reticulocyte count, percent reticulocyte count, reticulocyte age distribution/index, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, red cell distribution width, nucleated RBC count, white cell count, absolute neutrophil count, absolute lymphocyte count, absolute eosinophil count and platelet count	✓	✓
	► Iron, total iron-binding capacity, transferrin saturation and ferritin	✓	✓
	► Haptoglobin	✓	✓
	► Lipids	✓	✓
	► Liver function tests: aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase with isozyme profile, total and indirect bilirubin, alkaline phosphatase	✓	✓
	► Hormones: total testosterone, free testosterone, estradiol, estrone, vitamin D	✓	✓
	► Urine glycoalbumin	✓	✓
Chelation therapy	► Types and timing of each chelation treatment	✓	✓
Treatment patterns and reasons for decisions	► Transfusion history	✓	✓
	► Splenectomy	✓	✓
	► Chelation	✓	✓
	► Stem cell transplant	✓	✓
	► Cholecystectomy	✓	✓
Pregnancy and other health outcomes	► Full-term healthy, pre-term delivery, neonatal death, elective termination, stillbirth (≥20 weeks gestation), ectopic pregnancy, spontaneous miscarriage (<20 weeks gestation), molar pregnancy	✓	✓
Healthcare resource utilisation	► Hospitalisations: all causes and PK deficiency related		✓
	► Emergency room visits		✓

Continued

Table 1 Continued

Data parameter*	Examples of variables to be collected†	Collected at enrollment	Collected at follow-up visits‡

*On registry enrolment, all known historical diagnostic and demographic information for the patient will be entered in the eCRF.
†No specific laboratory or imaging tests (aside from genetic testing to confirm diagnosis for registry eligibility purposes) are required from investigators; investigators are asked to provide only the data they collect as part of routine care.
‡Any variable collected at follow-up is collected at all follow-up visits. The frequency of follow-up visits varies by patient, and patients have visits in accordance with their own or their physician's standard clinical practice.
§Ongoing medications will be recorded at the time of enrolment.
¶At enrolment, the most recent test results ≤3 months prior to enrolment, or test results from assessments that were conducted at the enrolment visit.
eCRF, electronic case report form; PK, pyruvate kinase; RBC, red blood cell.

record release authorisation is supplied by the patient, their electronic medical records are accessible and local regulations and site policies permit this). Figure 2 shows the countries with participating sites for the Peak Registry and for the NHS.

Peak Registry population

Patients of any age, with a diagnosis of PK deficiency confirmed via clinical genetic testing, are eligible for enrolment in the Peak Registry. Genetic diagnosis includes the presence of biallelic *PKLR* mutations (either compound heterozygous or homozygous state), including newly described variants. Participants carrying novel *PKLR* variants classified as variants of unknown significance will be deemed eligible if, in the opinion of the investigator, there is a reduction in PK activity and patients' clinical and laboratory data are sufficient to support a diagnosis of PK deficiency. Participation in the registry is voluntary, and patients may decline to participate or withdraw consent at any time. The registry includes both participants who were previously enrolled in the NHS and opted to continue in the Peak Registry and newly identified participants for enrolment in the Peak Registry.

Data collection

The Peak Registry involves both retrospective and prospective data collection, including relevant data from routine clinical care or assessments associated with a clinical event (tables 1 and 2), in order to assess the burden and management of the disease.

Data collected at enrolment include demographics, diagnosis history, *PKLR* genotyping, PK deficiency-related medical history, transfusion history, and laboratory and imaging assessments. Prospectively defined follow-up data capture includes relevant clinical events, targeted medical therapy, complications, procedures, transfusions, laboratory/imaging assessments, medication changes and emergency room visits or hospitalisations since the previous visit. Data are collected from participating registry physicians, participants, and, where appropriate, parents/guardians. All data are submitted to the registry via electronic case-report forms (eCRFs). Chart review and follow-up visit data entry is encouraged to take place at least annually to promote a longitudinal understanding of PK deficiency; however, no specific schedule of assessments is prescribed, as visits are expected to align with standard-of-care practices in the real-world setting.

Data quality and management

To ensure compliance with good clinical practice and all applicable regulatory requirements, processes and procedures for reviewing, querying and resolving data quality issues with study sites are governed by a data monitoring and management plan. In brief, the plan stipulates that all data for enrolled patients are entered into the eCRFs via an electronic data capture system provided by the registry physician or authorised study site staff. Only authorised staff are permitted to enter data into the eCRFs. Data are reviewed remotely for completeness, query resolution and edit checks based on the data validation specification document. Overall ~15%–20% of eCRFs' critical data are checked for accuracy versus source document data by the monitor assigned by the study sponsor or its contract research organisation. If any entries into the eCRF are incorrect or incomplete, the monitor asks the registry physician or authorised study site staff to make appropriate corrections, and the corrected eCRF is reviewed again for completeness and consistency.

Integration of NHS and Peak Registry data

Data from the NHS and from the Peak Registry will be integrated, generating three cohorts of patients (figure 3).

- NHS-only cohort: Patients who were enrolled in the NHS (2014–2017) but are not enrolled in the Peak Registry.
- Peak-only cohort: Patients who enrolled in the Peak Registry only (2018–2026).
- NHS+Peak cohort: Patients enrolled in the NHS who subsequently enrolled in the Peak Registry (2014–2026).

The comparability of data collected from the two studies will be assessed prior to data integration. Data from the two studies will be assessed, and results will be combined/integrated if statistically feasible, with adjustments (eg, conversion of units) where necessary. Baseline will be determined by the enrolment date of the NHS for each participant in the NHS-only and NHS+Peak cohorts. For patients enrolled in the Peak Registry only, baseline

Table 2 PK deficiency-related medical history, complications and comorbidities

Data parameter*	Examples of variables to be collected†, ‡	Collected at enrollment	Collected at follow-up visits§
Biliary events	► Cholecystitis	✓	✓
	► Cholangitis	✓	✓
	► Asymptomatic gallstones	✓	✓
	► Bile duct stones	✓	✓
Cardiac health	► Arrhythmia	✓	✓
	► Pulmonary hypertension	✓	✓
	► Congestive heart failure	✓	✓
Thromboembolic events	► Date of thrombotic event	✓	✓
	► Platelet count at time of thrombotic event	✓	✓
	► Type: DVT, pulmonary embolism, venous embolism, cerebral venous thrombosis, portal vein thrombosis, ischaemic stroke, other	✓	✓
	► Methods of evaluation: ultrasound on abdomen and legs	✓	
	► Prior prophylactic anticoagulation or anti-platelet therapy	✓	✓
Endocrine complications	► Growth hormone deficiency	✓	✓
	► Hypoparathyroidism	✓	✓
	► Thyroid disease	✓	✓
	► Hypogonadal hypogonadism	✓	✓
	► Diabetes	✓	✓
	► Nocturia	✓	✓
	► Microalbuminuria	✓	✓
Bone health	► DXA scan findings	✓	✓
	► Fractures	✓	✓
	► Osteoporosis/osteopenia	✓	✓
	► Bone pain	✓	✓
	► Bone enlargement/bony expansion	✓	✓
Haematological complications	► Extramedullary haematopoiesis	✓	✓
	► Aplastic crisis	✓	✓
	► Haemolytic crisis	✓	✓
	► Jaundice	✓	✓
Hepatic and cardiac iron load¶	► Dates of tests	✓	✓
	► T2* MRI, cardiac T2* MRI, FerriScan	✓	✓
	► Liver: iron/g dry weight	✓	✓
	► Heart: T2* MRI measurement in ms	✓	✓
Liver complications	► NASH	✓	✓
	► NAFLD	✓	✓
	► Cirrhosis	✓	✓
	► Hepatomegaly	✓	✓
Stem cell transplant	► Date of transplant	✓	✓
	► Type of transplant	✓	✓
Vascular complications	► Leg ulcers	✓	✓

Continued

Table 2 Continued

Data parameter*	Examples of variables to be collected†, ‡	Collected at enrollment	Collected at follow-up visits§
Infection history	► Hepatitis B or C	✓	✓
	► HIV	✓	✓
	► Infections with encapsulated bacteria post-splenectomy	✓	✓
	► Sepsis	✓	✓
Prenatal/neonatal complications	► *In utero* growth retardation	✓	✓
	► Hydrops fetalis	✓	✓
	► Preterm delivery	✓	✓
	► Blueberry muffin rash	✓	✓
	► Neonatal coronary artery disease	✓	✓
	► Neonatal pulmonary hypertension	✓	✓
	► Neonatal hepatomegaly or splenomegaly	✓	✓
	► Neonatal hyperferritinaemia	✓	✓
	► Neonatal thrombocytopenia	✓	✓
	► Exchange transfusion in neonatal period	✓	✓
	► Neonatal jaundice	✓	✓
	► Neonatal anaemia	✓	✓
Mental health conditions	► Anxiety	✓	✓
	► Depression	✓	✓

*At enrolment, all known historical diagnostic and demographic information for the patient is entered in the eCRF.
†Specific definitions for the conditions listed are not required as part of medical history; these are instead dependent on the investigator's assessment.
‡No specific laboratory or imaging tests (aside from genetic testing to confirm diagnosis for registry eligibility purposes) are required from investigators; investigators are asked to provide only the data they collect as part of routine care.
§Any variable collected at follow-up is collected at all follow-up visits. The frequency of follow-up visits varies by patient, and patients have visits in accordance with their own or their physician's standard clinical practice.
¶At enrolment, the most recent test results ≤3 months prior to enrolment, or test results from assessments that were conducted at the enrolment visit.
DVT, deep vein thrombosis; DXA, dual-energy X-ray absorptiometry; eCRF, electronic case-report form; MRI, magnetic resonance imaging; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PK, pyruvate kinase.

is determined based on the date of enrolment of each participant into the Peak Registry. Follow-up year is determined based on duration from baseline to follow-up visits. The integrated data will be summarised by cohort using the same statistical methods as outlined below. As data mature in Peak, a separate detailed data integration plan will be developed.

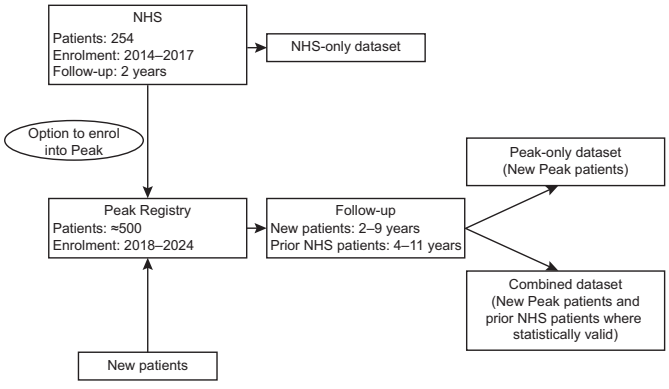

Figure 3 Data integration between the NHS and Peak Registry. NHS, Natural History Study.

Data analysis

Two data analysis sets are defined for Peak: the all participants set (APS) includes patients who have signed informed consent, and the full-analysis set (FAS) includes patients who meet inclusion criteria and are enrolled in the Peak Registry. The FAS is used to summarise all data and perform all analyses. The reason for screen failure will be summarised for all participants in the APS who are later found to be ineligible for the study. Data will be summarised at baseline and by follow-up year. Due to the nature of the observational study, data analysis will mainly be descriptive. Continuous variables will be summarised using descriptive statistics, that is, number of non-missing values, mean, SD, median, quartiles, minimum and maximum. Categorical variables will be summarised

by frequency distributions (number and percentage of patients within a given category in the analysis dataset). Count data will be summarised in patient-years, calculated as the sum of the follow-up years of all participants. For summaries by visit, percentages will be based on the number of patients with data available for that visit, unless otherwise specified.

All data will be analysed as collected in the Peak Registry database. Generally, missing data will not be imputed and will be summarised as a separate 'missing' category. If a patient withdraws from the registry, previously collected data may be excluded from the database and analyses if this is required by country-specific privacy laws.

If sample sizes permit, subgroup analyses may also be conducted for subgroups of interest, for example, by age (paediatric and adult patients), genotype, transfusion status, splenectomy status and disease complications.

Data sharing

Agios Pharmaceuticals and the Peak Registry Steering Committee will seek to share data where appropriate while maintaining appropriate legal, regulatory and Peak Registry protocol guidelines, and the privacy of all patients who participate. Data may be used for purposes such as longitudinal study of disease and understanding treatment patterns, quality of life, and clinical outcomes. Participating Peak Registry research sites retain research rights to their own patients' data and are permitted to use these data for such activities as site-level analyses, individual patients' disease management, case studies, posters or presentations.

A digital platform (hosted on Digital Infuzion's N of 1 Health Research software as a service Platform) has been developed to allow participating physicians to view individual clinical data for each of their patients entered into the Peak Registry, as well as reports of aggregated data across all registry participants. Physicians will have access to these data and reports through a principal investigator portal, as a benefit of participating in the registry. Similarly, a patient portal will allow participating patients to view reports of aggregate data entered into the registry and to obtain information about and enrol in registry substudies, on topics such as quality of life and cognition, they may wish to join.

Requests for registry-wide or subset analyses of registry data can be made by submitting a form found on the Peak Registry website (https://peakregistry.com). Raw data will not be shared. Data analysis and publication requests are subject to review and approval by the Peak Steering Committee and Agios Pharmaceuticals. On approval, analyses will be conducted by Agios, and aggregated results will be shared with the requester in the form of tables, listings, figures and/or study reports. All data included in such analyses will be deidentified.

Ethics and dissemination

The registry protocol and informed consent form are approved by institutional review boards/independent ethics committees at each study site. The full list of ethics committees that have approved the Peak Registry can be found in online supplemental table 1. The study is being conducted in accordance with the ethical principles of the Declaration of Helsinki. Informed consent and assent, when appropriate, are obtained from all enrolled patients and/or their guardian.

Dissemination of registry data will be facilitated by the Peak Steering Committee and will be published in peer-reviewed journal articles and conference publications and proceedings. Publication of registry data will be subject to review from the Peak Steering Committee.

Patient and public involvement

A patient representative has been included as a member of the Peak Steering Committee, adding a patient's perspective and input into steering committee activities and the scientific direction of the registry. These activities include defining the objectives of the registry, providing insight on how to optimally disseminate data to the PK deficiency patient community, and advising on patient recruitment to the study.

As mentioned above, a patient portal will also allow patients to access reports of aggregate registry data and to participate in substudies on patient-reported topics such as quality of life and cognitive function.

Current status

The first patient in the Peak Registry was enrolled in April 2018 and a total of 56 sites in 16 countries are currently active. Patient enrolment as of September 30, 2022 is displayed in figure 4, showing patients enrolled directly onto the Peak Registry and those enrolled from the NHS. As of the latest data cut, 251 patients both met criteria for the study and were enrolled in the Peak Registry. Analyses on all patients enrolled to date are in progress and will be detailed in future publications focused on baseline characteristics, patient management, molecular characterisation/genotype–phenotype, disease spectrum

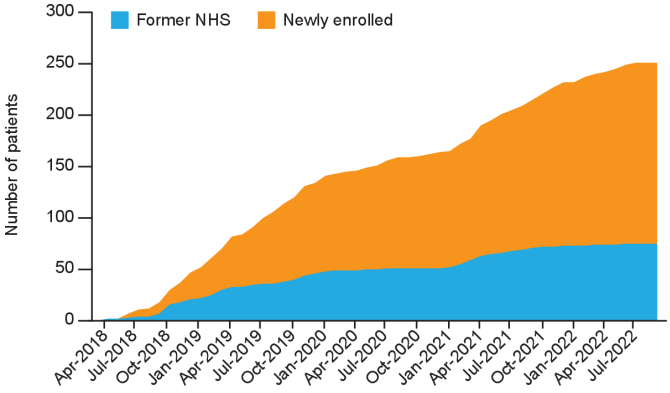

Figure 4 Patient enrolment into the Peak Registry, as of 30 September 2022. Patients enrolled in the Peak Registry only are shown in orange. Patients who had previously also participated in the NHS are shown in blue. NHS, Natural History Study.

and progression, cognitive state, and patient-reported outcomes, among other topics.

DISCUSSION

Globally, there are approximately 7000 rare disease conditions of which 95% do not have effective treatments,[24] constituting substantial unmet medical needs. Developing new therapies for rare diseases can be particularly challenging as there are few cases to evaluate and there is often considerable phenotypic heterogeneity among patients.[25] In general, information on the natural history of PK deficiency has been limited, leading to gaps in knowledge about the diagnostic pathway, clinical implications of the disease, disease burden and definitions of severity, as well as questions about optimal supportive care strategies.

Patient registries are key to help overcome the barriers to successful research into rare diseases, such as PK deficiency.[17] Data collected from registries can enhance understanding of disease global prevalence and natural history, as well as patient management and outcomes, ultimately leading to improved standards of care.[17] In addition, registries enable the monitoring of treatments and patient outcomes to facilitate the recruitment of patients for clinical trials and can help provide data that support the establishment of disease-specific recommendations. Importantly, registries with extended follow-up provide an opportunity to evaluate current and future interventions and treatments.

The Peak Registry will provide real-world longitudinal data on the range and incidence of symptoms, treatments and complications related to PK deficiency.[20] The registry will provide an understanding of the longer-term health outcomes in patients with the condition.[26 27] Another benefit of the Peak Registry will be the establishment of a PK deficiency community for collaboration among healthcare professionals and patients around a common registry.[27]

There are limitations to the Peak Registry, including the variation in routine care between centres and countries, access to tests among centres, potential gaps in the available data and the fact that screening for patients with PK deficiency may be more likely to occur in patients with more severe symptoms, leading to a registry population that is less diverse than in the real world. In addition, since many participating sites are centres with experience in managing patients with PK deficiency, their associated patterns of testing, screening for complications and disease management may not be representative of the entire PK deficiency healthcare treatment community. Some patients with PK deficiency may be excluded because genetic diagnosis is not available to all patients or in certain countries. Furthermore, country regulations and specific study site policies may prevent patients from enrolling remotely if an investigational site is not located in the country where they reside. It should also be noted that the registry does not capture follow-up data at prespecified, regular intervals. Instead, it is recommended that patients are seen and data are entered at least annually, and therefore, regularity of data collection is not guaranteed, as visit frequency may vary across patients and centres. However, this approach was chosen, in part, to reduce the burden on sites and patients and to maintain the registry as a non-interventional study. It is anticipated that this strategy will encourage enrolment and participation over the long term.

A key feature of the Peak Registry is that it will provide data to improve understanding of PK deficiency, with the inclusion of patients from a broad geographical distribution and long follow-up through 2026. The integration of selected data from the NHS into the Peak Registry will allow monitoring over an 11-year period for some patients, increasing the understanding of the natural history of this disease and interpatient and intrapatient variability over time, as well as the disease burden and treatment outcomes. It is hoped that the data and insights generated from the Peak Registry will ultimately support guideline recommendations for the care of patients with PK deficiency in the future.

Further information about the Peak Registry is available at www.clinicaltrials.gov (NCT03481738), https://peakregistry.com and medinfo@agios.com.

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