Design of a global, multicenter study to assess maternal, fetal, and infant outcomes of pegvaliase exposure during pregnancy and breastfeeding

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Introduction

- Phenylketonuria (PKU) is an inherited disorder caused by deficiency of phenylalanine hydroxylase that converts phenylalanine (Phe) into tyrosine, thus resulting in elevated blood Phe levels[1]
- In pregnant women with PKU, high Phe levels can severely affect intrauterine fetal growth and development, increasing the risk of congenital abnormalities[2,3], while Phe values below 120 µmol/L (hypophenylalaninemia) and/or inadequate protein intake during pregnancy may increase the risk of intrauterine growth retardation[4]; it is hence recommended that blood Phe levels be maintained between 120–360 µmol/L during the entire pregnancy[5-7]
- Pegvaliase (Palynziq®) is an enzyme substitution therapy approved for the treatment of adults with PKU who have uncontrolled blood Phe ≥600 µmol/L on existing management[8-10]
- Although pegvaliase clinical trials have demonstrated an acceptable benefit-risk profile, there are no well-controlled studies on the effects on pregnancy and offspring associated with pegvaliase exposure during pregnancy and breastfeeding
- PALomino (NCT05579548) is a global, multicenter study to assess the impact of pegvaliase treatment in pregnant women with PKU and on their offspring who were exposed to pegvaliase at any time during pregnancy and breastfeeding

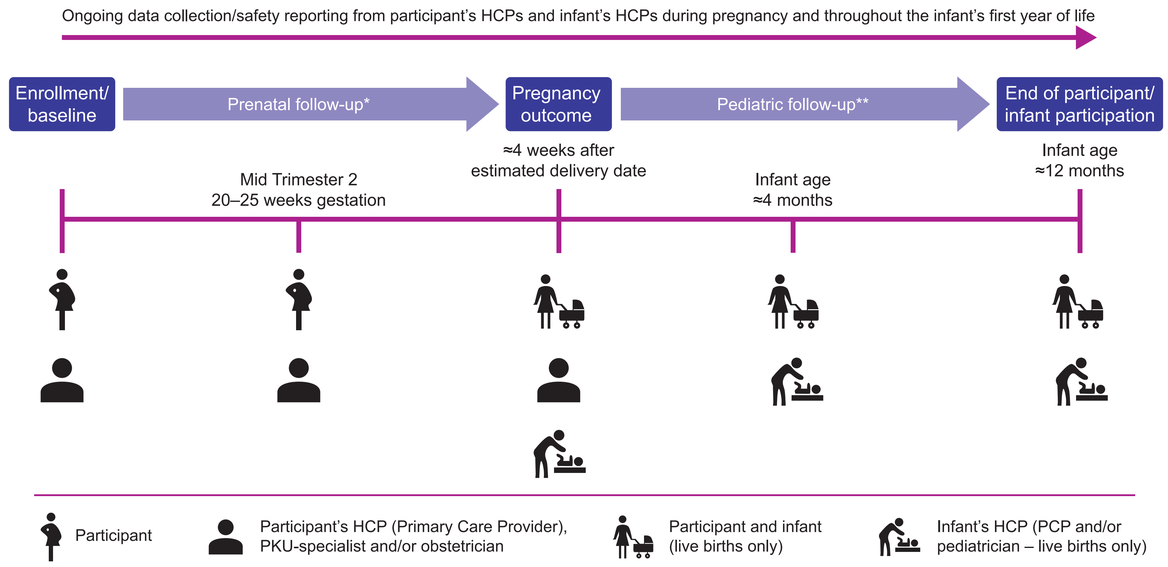
Study Design

- This observational, prospective, multicenter study is currently open to enrollment in the US and is planned to open to enrollment in Europe in 2023
- The objective of this study is to assess the frequency of pregnancy outcomes (e.g., spontaneous abortion, stillbirth, live birth, and termination) among women with PKU treated with pegvaliase during pregnancy and also fetal/infant outcomes (all major congenital malformations [MCMs] and specifically microcephaly and congenital heart defects), intrauterine growth, preterm birth, failure to thrive, and developmental delays in their offspring **(Table 1)**
- This study is enrolling pregnant women diagnosed with PKU who have been treated with pegvaliase from 2 weeks prior to last menstrual period (LMP) or at any time during pregnancy **(Figure 1)**; continuation of pegvaliase treatment throughout the pregnancy is not required to enroll
- Upon consent, data will be collected from the participant's HCPs retrospectively for at least 3 months prior to LMP; data including pegvaliase exposure (as applicable) will also be recorded during pregnancy and breastfeeding
- Duration of individual participation will be up to 21 months

Table 1. PALomino objectives

Primary objectives	Secondary objectives
Assess the frequency of pregnancy outcomes (spontaneous abortion, stillbirth, live birth, and termination) among participants with PKU treated with pegvaliase during pregnancy	Compare the frequency of pregnancy outcomes and fetal/infant outcomes among participants with PKU treated with pegvaliase during pregnancy and their offspring to information on those same outcomes in non-pegvaliase exposed, pregnant women with PKU as described in reference literature
Assess the frequency of fetal/infant outcomes (all MCMs and specifically microcephaly and congenital heart defects, intrauterine growth, preterm birth, failure to thrive, and developmental delays) among the offspring of participants with PKU exposed to pegvaliase during pregnancy	Examine differences in the frequency of pregnancy outcomes and fetal/infant outcomes among participants with PKU treated with pegvaliase during pregnancy and their offspring by maternal blood Phe levels
	Estimate the frequency of SAEs other than CMs in infants exposed to pegvaliase during pregnancy through their first year of life
	Estimate the frequency of selected outcomes in participants with PKU treated with pegvaliase during breastfeeding (low milk supply) and their infants (failure to thrive and SAEs in infants) through their first year of life

Figure 1. Study design



*Timepoints of participant and HCP contact shown are based on expected intervals and may vary on real-world observational data collection
**Participant will be contacted during infant follow-up if the HCPs are unresponsive. The preferred source of information will be the HCPs

Table 2. PALomino key inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Participant (or a legally authorized representative) consent obtained prior to enrollment. Consent will be obtained in compliance with any country-specific regulations or requirements	Currently participating in a BioMarin-sponsored interventional study of any investigational product, device, or procedure
Confirmation of ongoing pregnancy. Participants who have undergone prenatal testing (e.g., targeted ultrasound, amniocentesis) may enroll; these will be classified as retrospective pregnancies (regardless of test findings). Participants enrolling prior to prenatal testing will be classified as prospective pregnancies; the primary analysis will include both categories	
Diagnosed with PKU per local standard of care	
Documentation that the participant was treated with pegvaliase at any point starting from 2 weeks prior to the date of LMP	
Agrees to permit the investigator (e.g., CCA, CRP, PI) to contact the participant's HCPs (e.g., PCP, OB) and the infant's HCP (e.g., pediatrician, neonatologist) for medical information	

CCA, coordinating center associate; CRP, coordinating registry physician; HCP, healthcare professional; OB, obstetrician; PCP, primary care provider; PI, principal investigator

Summary

- Pegvaliase is an enzyme substitution therapy approved to treat adults with PKU who have blood Phe ≥600 µmol/L on existing management
- The results from this study will increase knowledge about the safety of pegvaliase during pregnancy and breastfeeding

Find out more about PALomino at PALominoStudy.com

References

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Conflict of interest

NL has participated on the Scientific Advisory Committee for the PALomino study and has received consulting fees from BioMarin. EB, GEC, CD, JH, and OS are employees and stockholders of BioMarin.

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