

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

Longo N¹, Clague GE², Decker C², Hunt J², Sazova O³

¹University of Utah, Salt Lake City, UT, USA; ²BioMarin Pharmaceutical Inc., Novato, CA, USA; ³BioMarin Europe Ltd., London, UK

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 levels¹
- 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 retardation⁴; it is hence recommended that blood Phe levels be maintained between 120–360 µmol/L during the entire pregnancy⁵⁻⁷
- 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 management⁸⁻¹²
- 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 Germany, Italy, and the US
- 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

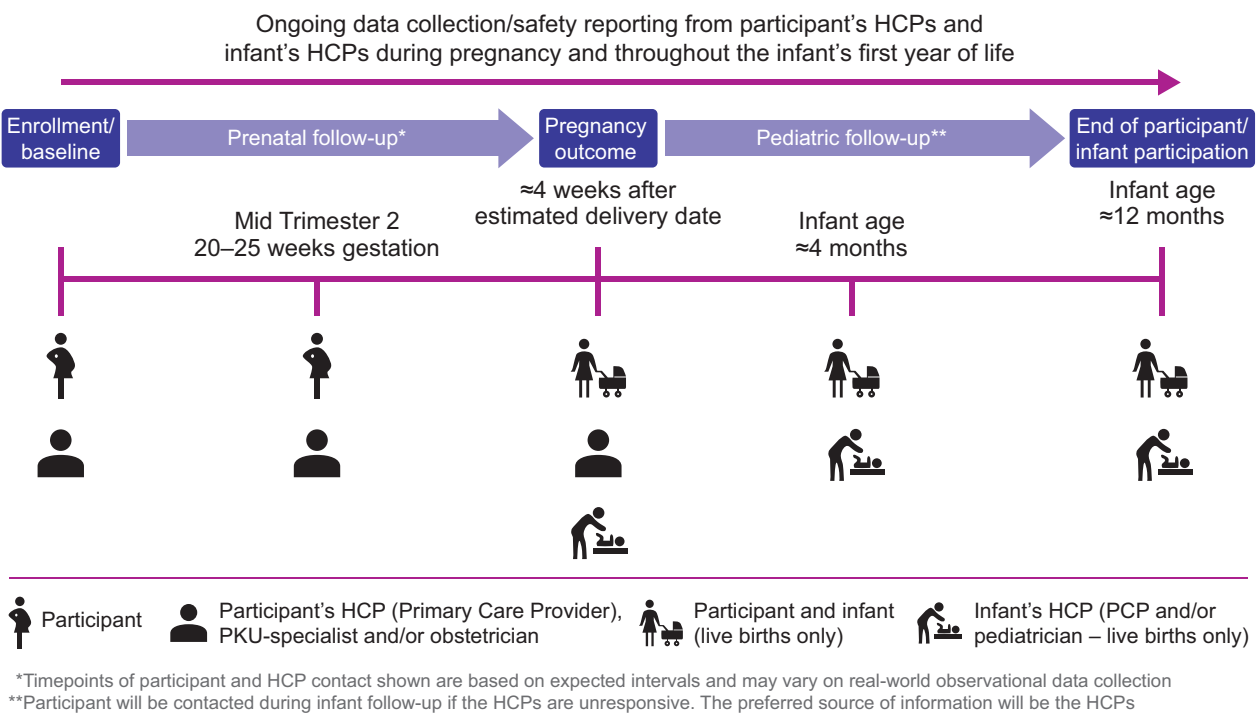


Table 2. PALomino key inclusion and exclusion criteria

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

- Blau N, et al. *Lancet*. 2010;376(9750):1417-1427.
- Lenke RR & Levy HL. *New Eng J Med*. 1980;303(21):1202-1208.
- Rouse B, et al. *Am J Med Genet*. 1997;69(1):89-95.
- Teissier R, et al. *J Inherit Metab Dis*. 2012;35(6):993-999.
- Vockley J, et al. *Genet Med*. 2014;16(2):188–200.
- Platt LD, et al. *Am J Obstet Gynecol*. 2000;182(2):326-333.
- van Wegberg AMJ, et al. *Orphanet J Rare Dis*. 2017;12(1):162.
- Palynziq (pegvaliase-pqz) [US Prescribing Information]. BioMarin Pharmaceutical Inc.; 2020.
- Palynziq (pegvaliase) [EU Product Information]. BioMarin International Ltd.; 2019.
- Palynziq (pegvaliase) [Australia Product Information]. BioMarin Pharmaceutical Australia Pty Ltd.; 2023.
- Palynziq (pegvaliase) [Japan Package Insert]. BioMarin Pharmaceutical Japan K.K.; 2023.
- Palynziq (pegvaliase) [Taiwan Product Information]. BioMarin Pharmaceutical Inc.; 2023.

Conflict of interest

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