Study 165-305: Interim safety and efficacy of pegvaliase in Japanese adults with phenylketonuria

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Background

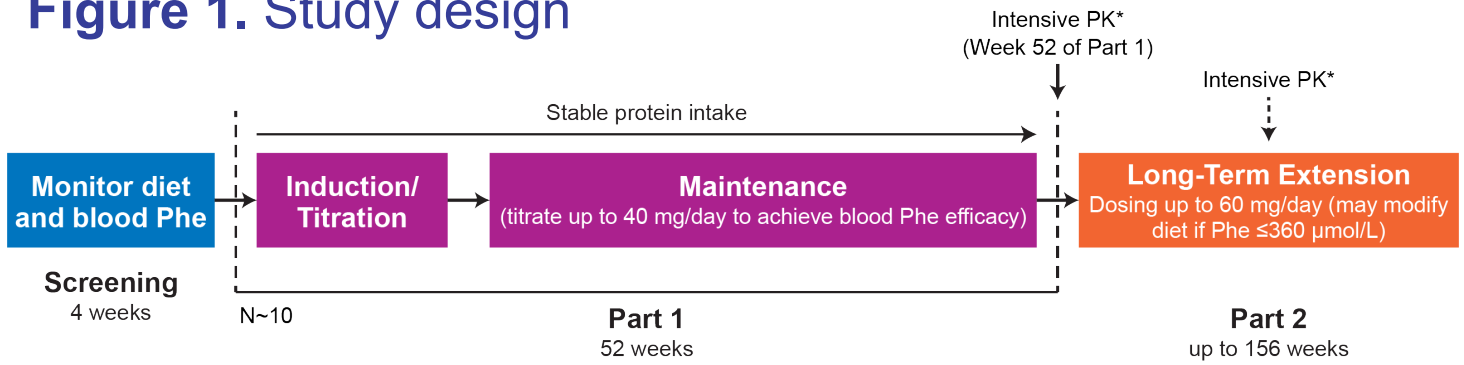
- Phenylketonuria (PKU) is caused by deficiency of the phenylalanine hydroxylase enzyme, resulting in abnormally high concentrations of phenylalanine (Phe) in the blood and brain. High Phe levels are associated with significant negative effects on neurocognitive function in adults with PKU[1-5]
- The Japan clinical guidelines[6] and the American College of Medical Genetics and Genomics (ACMG) practice guidelines[7] for PKU recommend a blood Phe concentration upper limit of 360 µmol/L
- In addition to diet therapy, Biopten® (sapropterin dihydrochloride) is currently available in Japan for patients with PKU. However, approximately 25% to 80% of patients with PKU do not reach a 30% reduction[8] and many adults struggle to maintain guideline-recommended levels of Phe control
- Pegvaliase, PEGylated recombinant *Anabaena variabilis* phenylalanine ammonia lyase (PAL), converts Phe to trans-cinnamic acid and ammonia[9-11]
- The primary objective of this study is to evaluate the efficacy and safety of pegvaliase in Japanese patients ≥18 years of age with PKU (blood Phe >600 µmol/L) using an Induction/Titration/Maintenance (I/T/M) dosing regimen, similar to the regimen used in Phase 3 trials that supported pegvaliase (Palynziq®, pegvaliase-pqpz) approval in multiple geographic regions[12-15]

1. Moyle JJ et al. *J Clin Exp Neuropsychol*. 2007;29(4):436-441. **2.** Pietz J et al. *Pediatrics*. 1997;99(3):345-350. **3.** Waisbren SE et al. *Acta Paediatr Suppl.* 1994;407:98-103. **4.** Gassio R et al. *Acta Paediatr.* 2003;92(12):1474-1478. **5.** ten Hoedt AE et al. *J Inherit Metab Dis.* 2011;34(1):165-171. **6.** Japanese Society for Inherited Metabolic Diseases Guidance. 2019. **7.** Vockley J et al. *Genet Med.* 2014;16(2):188-200. **8.** Biopten (sapropterin hydrochloride [package insert]. Daiichi Sankyo Co. Ltd.; 2013. **9.** Bell SM et al. *PLoS One.* 2017;12:e0173269. **10.** Longo N et al. *Lancet.* 2014;384:37-44. **11.** Sarkissian CN et al. *Proc Natl Acad Sci USA*. **12.** Palynziq [package insert]. BioMarin Pharmaceutical Inc.; 2018. **13.** Palynziq (pegvaliase) [EU Product Information]. Shanbally, Ireland: BioMarin International Ltd.; 2019. **14.** Palynziq (pegvaliase-pqpz) [US Prescribing Information]. Novato, CA: BioMarin Pharmaceutical Inc.; 2020. **15.** Palynziq (pegvaliase) [TGA Product Information]. BioMarin Pharmaceutical Australia Pty Ltd.; 2021.

Methods

- Figure 1 provides an overview of the study design
- Participants were instructed to maintain a stable diet throughout Part 1 of the study, assessed using data from 3-day diet diaries; however, modifications to a participant's diet could be made if blood Phe levels were confirmed to be <30 µmol/L
- Results reported here are from Part 1 as of April 21, 2021

Figure 1. Study design



*Intensive PK sampling taken at pre-dose, 2, 4, 8, 12, and 24 hours post dose. The 24-hour sample will be taken prior to the next daily dose. Intensive PK samples will be taken in all subjects at Week 52 of Part 1. In Part 2, intensive PK samples will be taken only in subjects receiving 60 mg/day after 8 weeks on 60 mg/day.

Results

Table 1. Baseline demographics and characteristics

Characteristic	Safety Population (N=12)	Efficacy Evaluable Population (N=11)
Age, years		
Mean (SD)	29.4 (8.1)	29.4 (8.5)
Female, n (%) [a]	4 (33.3)	4 (36.4)
Weight, kg		
Mean (SD)	64.4 (15.2)	65.0 (15.9)
Median	59.0	59.4
BMI, kg/m^2		
Mean (SD)	23.5 (5.3)	24.0 (5.2)
Median	22.4	23.2
Blood Phe, µmol/L		
Mean (SD)	1008.6 (161.4)	1001.8 (167.5)
Median	1071.3	1059.0
Daily protein from intact food, g		
Mean (SD)	34.5 (20.5)	33.2 (21.0)
Median	33.4	30.6
Daily protein from medical food, g		
Mean (SD)	22.2 (19.6)	21.7 (20.4)
Median	19.6	19.0
ADHD-RS IV [b]		
Mean (SD)	–	5.0 (4.7)
Median	–	4.0

ADHD-RS IV, Attention Deficit Hyperactivity Disorder Rating Scale (Investigator-rated); BMI, body mass index; SD, standard deviation.
[a]Percentages were calculated using the total number of participants in the Safety Population, or Efficacy Evaluable Population as the denominator, as applicable. [b]Only analyzed for Efficacy Evaluable Population

- A total of 12 patients (safety population) were enrolled into the study and received at least two doses of pegvaliase from 3 clinical sites in Japan
- 11/12 were evaluated for the 52-week interim efficacy endpoint
- Mean pegvaliase treatment duration was 47.8 (8.4) weeks

Exposure

- All 12 participants completed ≥4 weeks induction followed by ≥5 weeks of titration with 10 mg/day; the mean (min, max) time to first 20 mg dose was 14.0 (9.3, 29.1) weeks
- Pegvaliase exposure by dose is shown in Table 2

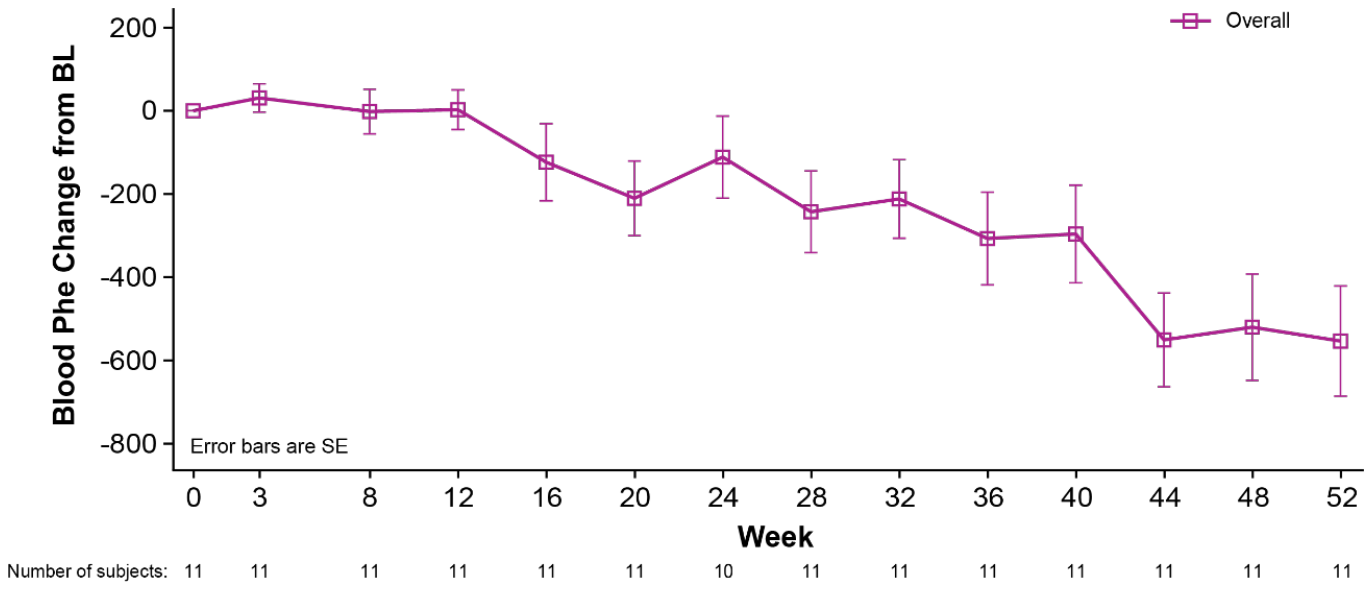
Table 2. Pegvaliase exposure by dose category (N=12)

	<10 mg/day (N=12)	≥10-<20 mg/day (N=12)	≥20-<40 mg/day (N=12)	≥40-<60 mg/day (N=7)	Any Dose Level (N=12)
Duration of treatment with study drug (weeks)					
Mean (SD)	5.8 (1.9)	7.9 (6.8)	28.5 (6.8)	9.6 (4.5)	49.6 (8.1)
Median	5.0	5.0	30.0	12.0	52.0
Min, Max	4, 10	4, 28	15, 38	2, 13	24, 52
Average daily dose received (mg/day)					
Mean (SD)	2.2 (0.8)	14.2 (2.1)	21.3 (2.4)	40.3 (0.5)	15.7 (5.0)
Median	2.1	14.8	20.0	40.0	15.9
Min, Max	1, 5	10, 17	20, 26	40, 41	5, 22

Percentages were calculated using the total number of subjects in the Safety population as the denominator.
Subjects who entered Part 2 are not indicated; interim analysis only includes data from Part 1.

Blood Phe

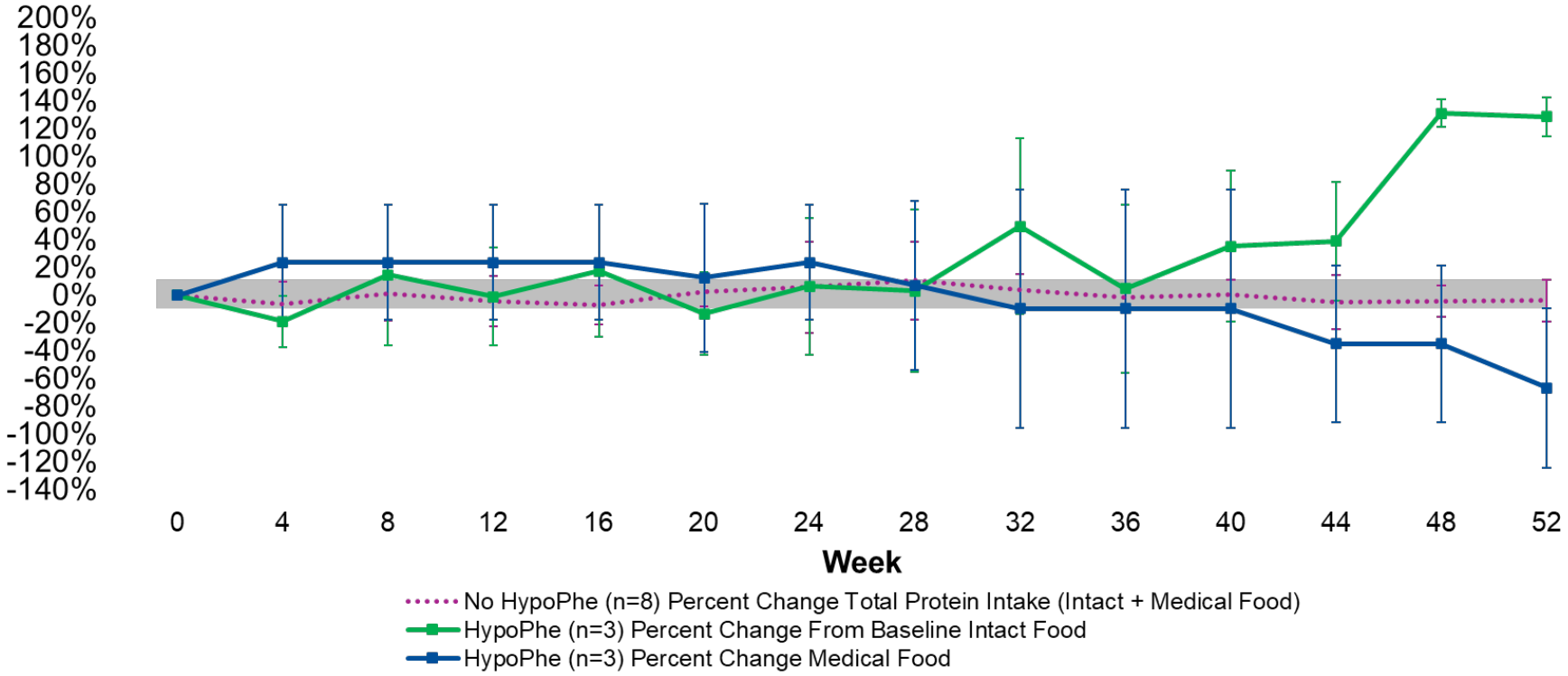
Figure 2. Mean change in blood Phe levels over time from naïve baseline



- At week 52 the mean (SD) blood Phe and percentage change from baseline was 448.3 (458.8) µmol/L and -56.4 (42.3)%, respectively
- By 52 weeks the following proportion of participants had achieved the following thresholds:
  - 72.7% (8/11) were ≤600 µmol/L
  - 54.5% (6/11) were ≤360 µmol/L
  - 36.4% (4/11) were ≤120 µmol/L

Dietary Intake

Figure 3. Dietary intake up to Week 52



- Three participants experienced blood Phe concentrations <30 µmol/L and were permitted per protocol dietary modifications. By Week 52 they had a reduction in medical food and increase in intact protein

Safety Overview

- All 12 participants (100%) experienced 1 or more treatment emergent adverse events (TEAEs), None of the TEAEs had Common Terminology Criteria for Adverse Events (CTCAE) severity Grade ≥3
  - The most commonly injection site erythema and injection site swelling (each 83.3%), arthralgia (75.0%), nasopharyngitis (66.7%), malaise (58.3%), injection site pruritus (50.0%), injection site pain, pyrexia, dermatitis allergic, urticaria, complement factor C3 decreased and complement factor C4 decreased (41.7% for each)
- None of the participants (0%) had anaphylaxis; 1 participant (8.3%) had an AESI of skin reaction, and all 12 participants (100%) experienced hypersensitivity adverse events
- Three participants (25.0%) had AEs leading to dose reduction, including hypophenylalaninemia (2 participants), aspartate aminotransferase increased, and alanine aminotransferase increased (both in 1 participant)
- Five participants (42%) had AEs leading to dose interruption
- No participants (0%) withdrew from the study due to an AE. One participant (8.3%) withdraw due to: ‘Withdrawal by subject’

Safety Events by Treatment Phase

- The occurrence of AEs was higher during the Induction/Titration (I/T) phase as compared to the Maintenance phase (Table 3)
- The most common AEs reported at a ≥10% higher incidence during the I/T phase vs Maintenance phase were injection site erythema, injection site swelling, malaise, dermatitis allergic, pyrexia and arthralgia, nasopharyngitis, injection site pain, complement factor C3 decreased, and complement factor C4 decreased
- 1 participant (8.3%) had a serious adverse event (SAE) (requiring hospitalization) of nasopharyngitis of Grade 2 severity during pegvaliase dosing with <10 mg/day (I/T phase), that was considered unrelated to pegvaliase by the investigator

Table 3. Adverse events by treatment phase

AE Category	Induction/Titration (N=12)	Maintenance (N=5)	Overall (N=12)
Subjects with any AE, n (%) [a]	12 (100.0)	4 (80.0)	12 (100.0)
AEs leading to dose reduction	2 (16.7)	1 (20.0)	3 (25.0)
AEs leading to dose interruption	5 (41.7)	0	5 (41.7)
AEs leading to study drug discontinuation	0	0	0
AEs leading to study discontinuation	0	0	0
Subjects with any SAE, n (%) [a]	1 (8.3)	0	1 (8.3)
SAEs leading to dose reduction	0	0	0
SAEs leading to dose interruption	0	0	0
SAEs leading to study drug discontinuation	0	0	0
SAEs leading to study discontinuation	0	0	0
Subjects with any treatment-related AE, n (%) [a, b]	12 (100.0)	3 (60.0)	12 (100.0)
Treatment-related SAEs	0	0	0
Subjects with any AE of CTCAE Grade ≥3, n (%) [a]	0	0	0
Subjects who died, n (%) [a]	0	0	0
Subjects with any AESI, n (%) [a]			
Anaphylaxis	0	0	0
Skin Reactions	0	1 (20.0)	1 (8.3)
Hypersensitivity AE	12 (100.0)	4 (80.0)	12 (100.0)

AE, adverse event; AESI, adverse event of special interest; CTCAE, common terminology criteria for adverse events; MedDRA, Medical Dictionary for Regulatory Activities; NCI, National Cancer Institute; SAE, serious adverse event; TEAE, treatment-emergent AE. AEs with onset or worsening after the initiation of study drug and up to 30 days after the last dose of study drug were included. AEs were coded using MedDRA version 20.1 and graded for severity using NCI CTCAE version 5.0.[a] Percentages were calculated using the total number of subjects in the safety population (N for each treatment group) as the denominator. Subjects with more than one AE of the same category were counted only once for that category. [b] Relationship to study drug was assessed by the investigator. Maintenance phase is reached when a subject achieves ≤600 µmol/L Phe for at least 26 days with stable dose (≥80% same dose) within the period. Period defined by Phe assessment dates. Induction/Titration occurs at first dose and ends one day before the start of Maintenance phase.

Conclusions

- Analysis of the interim results up to Week 52 support the administration of pegvaliase in Japanese adults with PKU according to an I/T/M dosing regimen
- These results demonstrate the efficacy of pegvaliase in reducing blood Phe concentrations with a manageable safety profile, and are consistent with results of the US Phase 3 program
- The longer-term safety analysis and sustainability of the efficacy results will continue to be evaluated through the study duration