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TWO-YEAR INTERIM SAFETY AND EFFICACY OF PEGVALIASE IN JAPANESE ADULTS WITH PHENYLKETONURIA

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（BioMarin）

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[8]. However, only approximately 20% to 56% of patients with PKU respond to sapropterin treatment[9,10,11], and many adults struggle to maintain guideline-recommended levels of Phe control[12]
- Pegvaliase, PEGylated recombinant *Anabaena variabilis* phenylalanine ammonia lyase (PAL), converts Phe to trans-cinnamic acid and ammonia[13-15]
- 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[16-19]

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.; 2021. **9.** Burton BK et al. *J Inherit Metab Dis*. 2007;30:700-707. **10.** Levy HL et al. *Lancet* 2007;370:504-510. **11.** Trefz FK et al. *J Pediatr*. 2009;154:700-707. **12.** Jurecki ER et al. *Mol Genet Metab*. 2017;120(3):190-197. **13.** Bell SM et al. *PLoS One*. 2017;12:e0173269. **14.** Longo N et al. *Lancet*. 2014;384:37-44. **15.** Sarkissian CN et al. *Proc Natl Acad Sci USA*. **16.** Palynziq [package insert]. BioMarin Pharmaceutical Inc.; 2018. **17.** Palynziq (pegvaliase) [EU Product Information]. Shanbally, Ireland: BioMarin International Ltd.; 2019. **18.** Palynziq (pegvaliase-pqpz) [US Prescribing Information]. Novato, CA: BioMarin Pharmaceutical Inc.; 2020. **19.** Palynziq (pegvaliase) [TGA Product Information]. BioMarin Pharmaceutical Australia Pty Ltd.; 2021.

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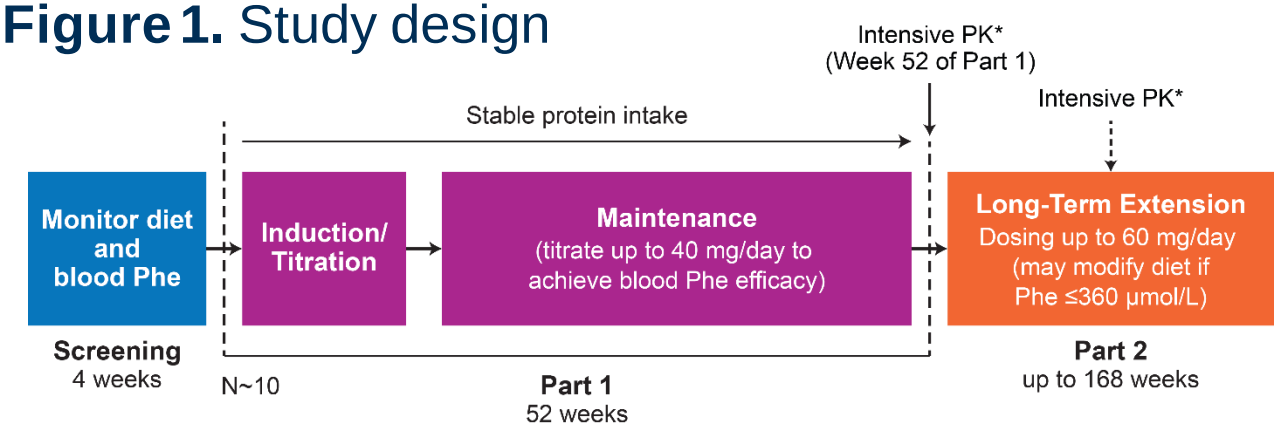
Methods

- 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
- During Part 2, participants with blood Phe ≤360 µmol/L may adjust dietary protein intake based on individual subject response to pegvaliase and guidance from the investigator
- Results reported here are from Part 2 as of March 31, 2022

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.

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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)	1032.3 (166.2)	1025.9 (172.7)
Median	1107.8	1112.0
Daily protein from intact food, g		
Mean (SD)	34.5 (20.5)	33.3 (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 participants (safety population) were enrolled into the study and received at least two doses of pegvaliase from 3 clinical sites in Japan
- 10/12 were evaluated for the 104-week interim efficacy endpoint
- At interim data cut-off, 9 subjects had 104–144 weeks of exposure
- Mean (SD) pegvaliase treatment duration was 117.2 (38.4) weeks

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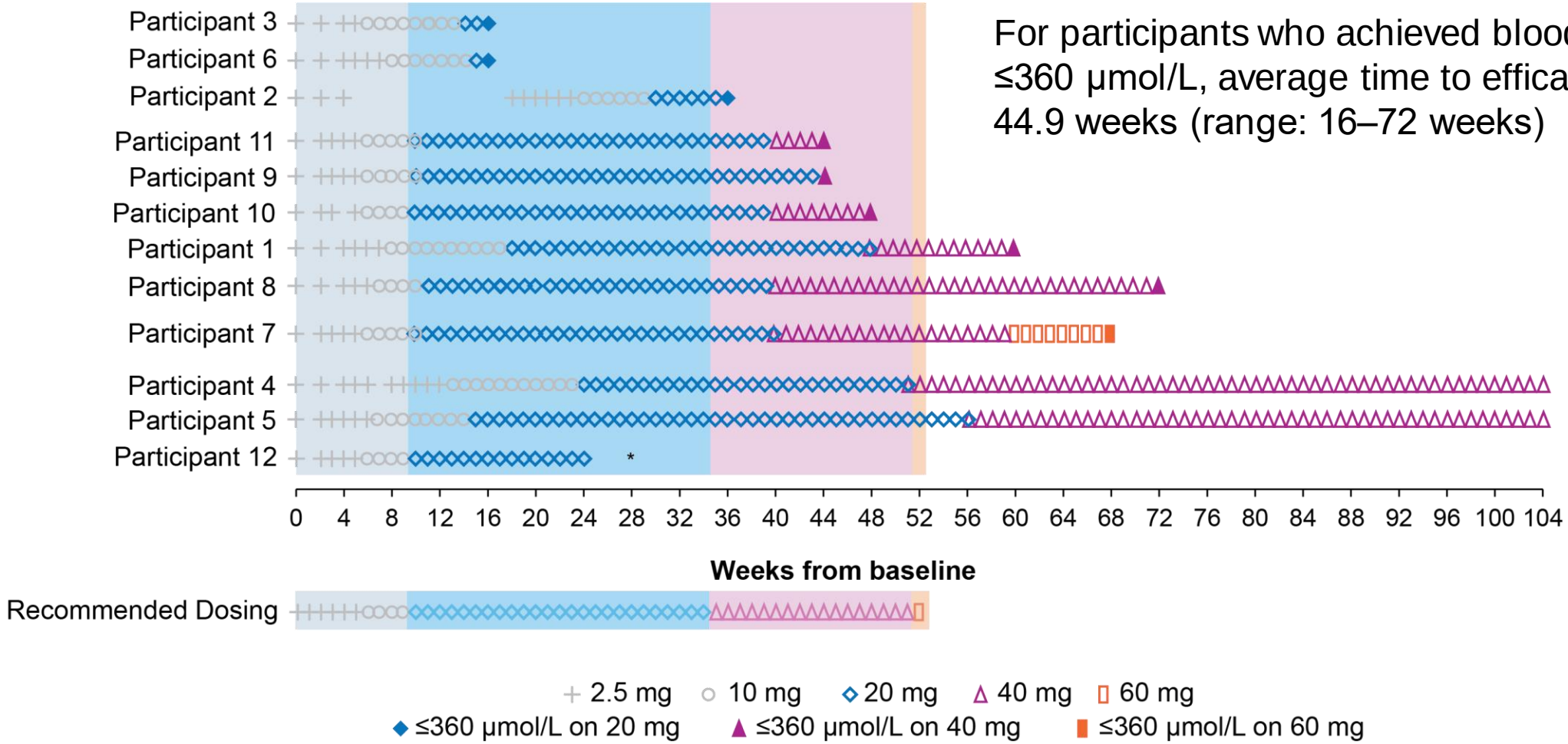
Dosing Patterns

Figure 2. First achievement of blood Phe ≤360 µmol/L



For participants who achieved blood Phe ≤360 µmol/L, average time to efficacy was 44.9 weeks (range: 16–72 weeks)

*Participant 12 discontinued during Part 1

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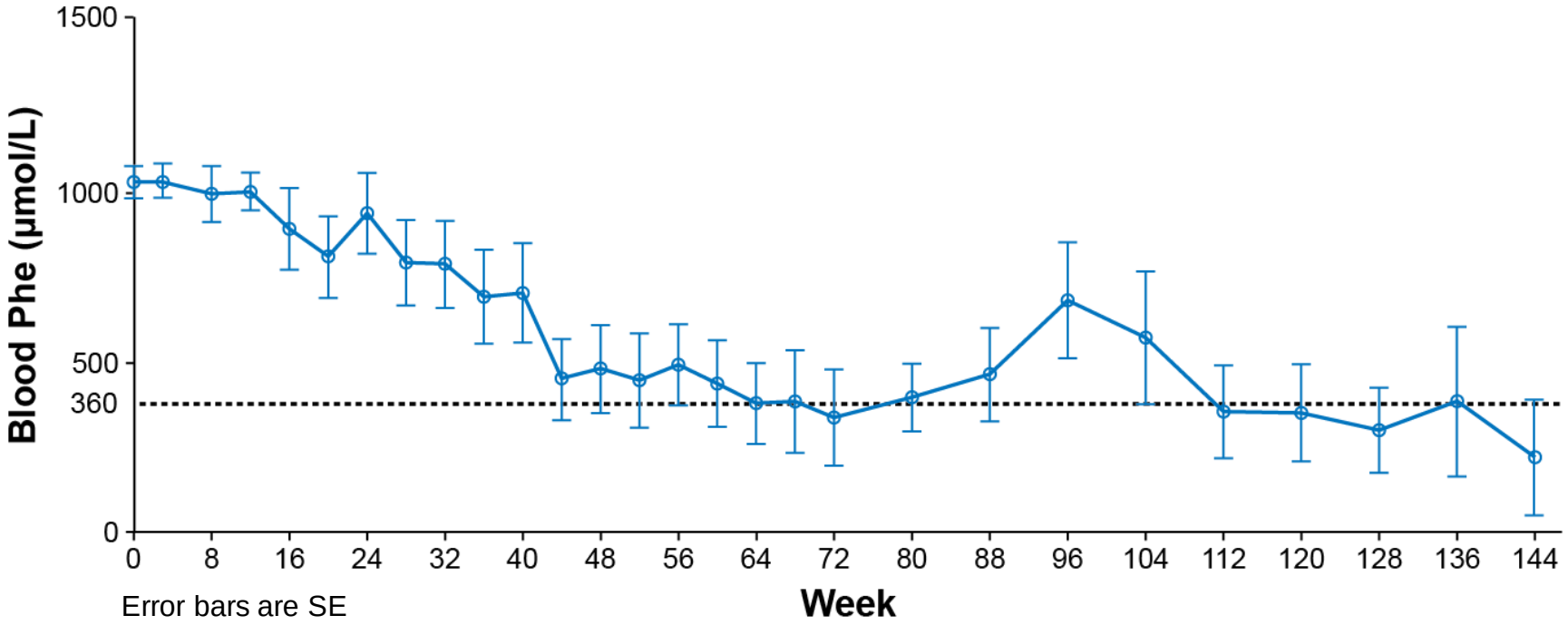
Blood Phe

Figure 3. Mean blood Phe over time



- Blood Phe data are available for 144 weeks of follow-up
- Mean (SD) blood Phe was 573.8 (617.8) µmol/L at 104 weeks, a decrease of 42.9% (68.4%) from baseline

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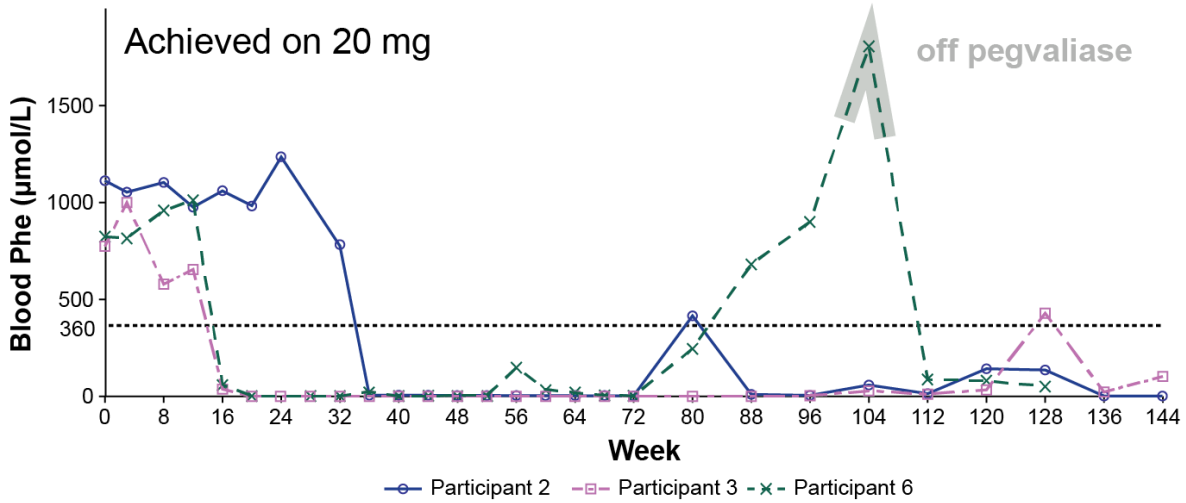
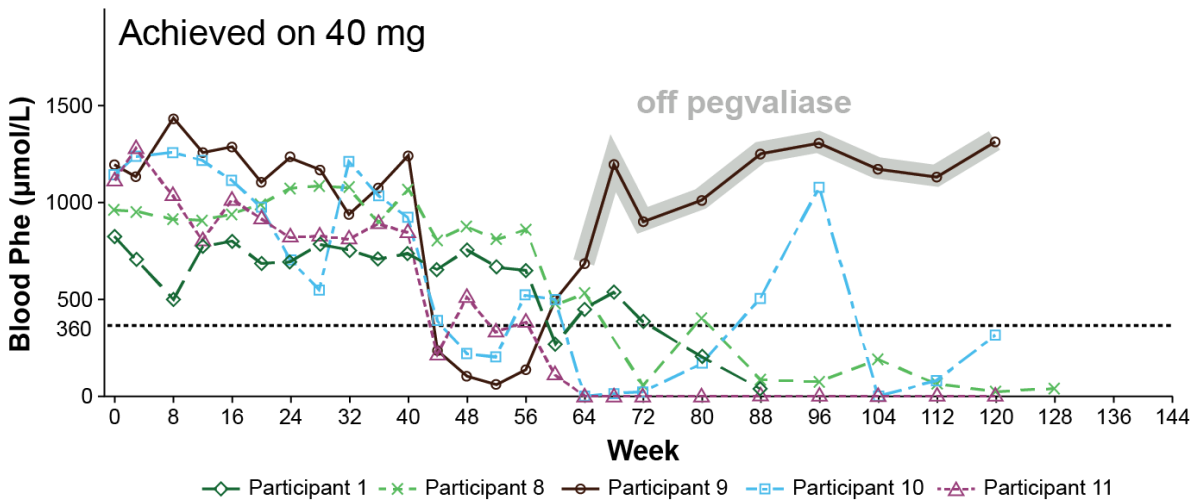
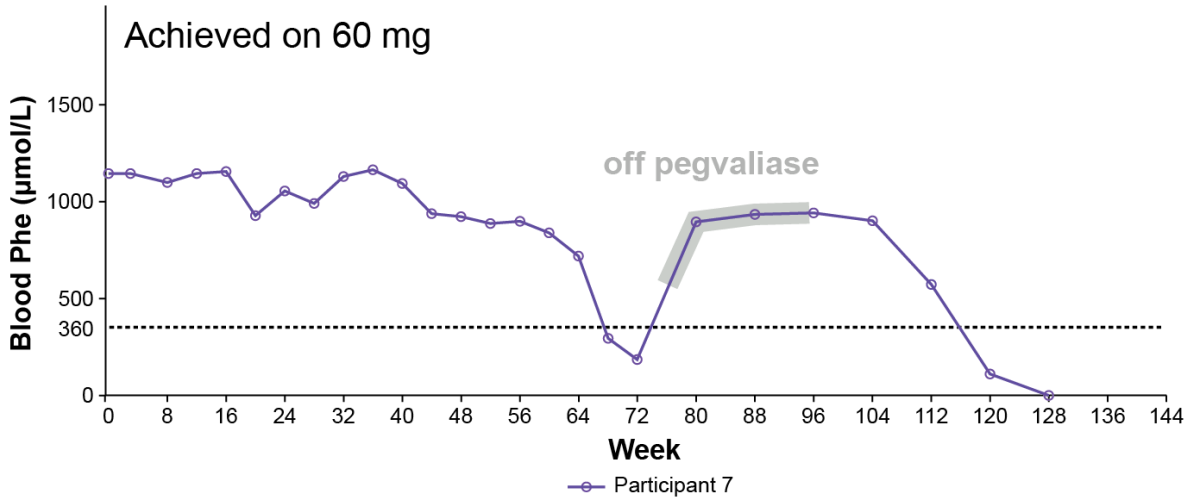
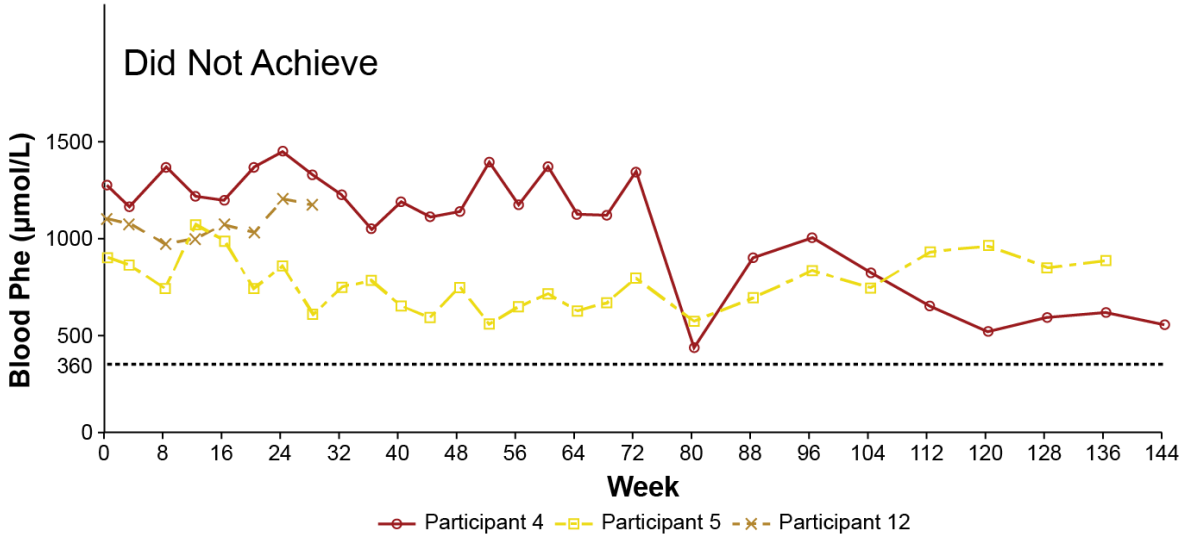
Blood Phe

Figure 4. Individual participant's blood Phe levels over time



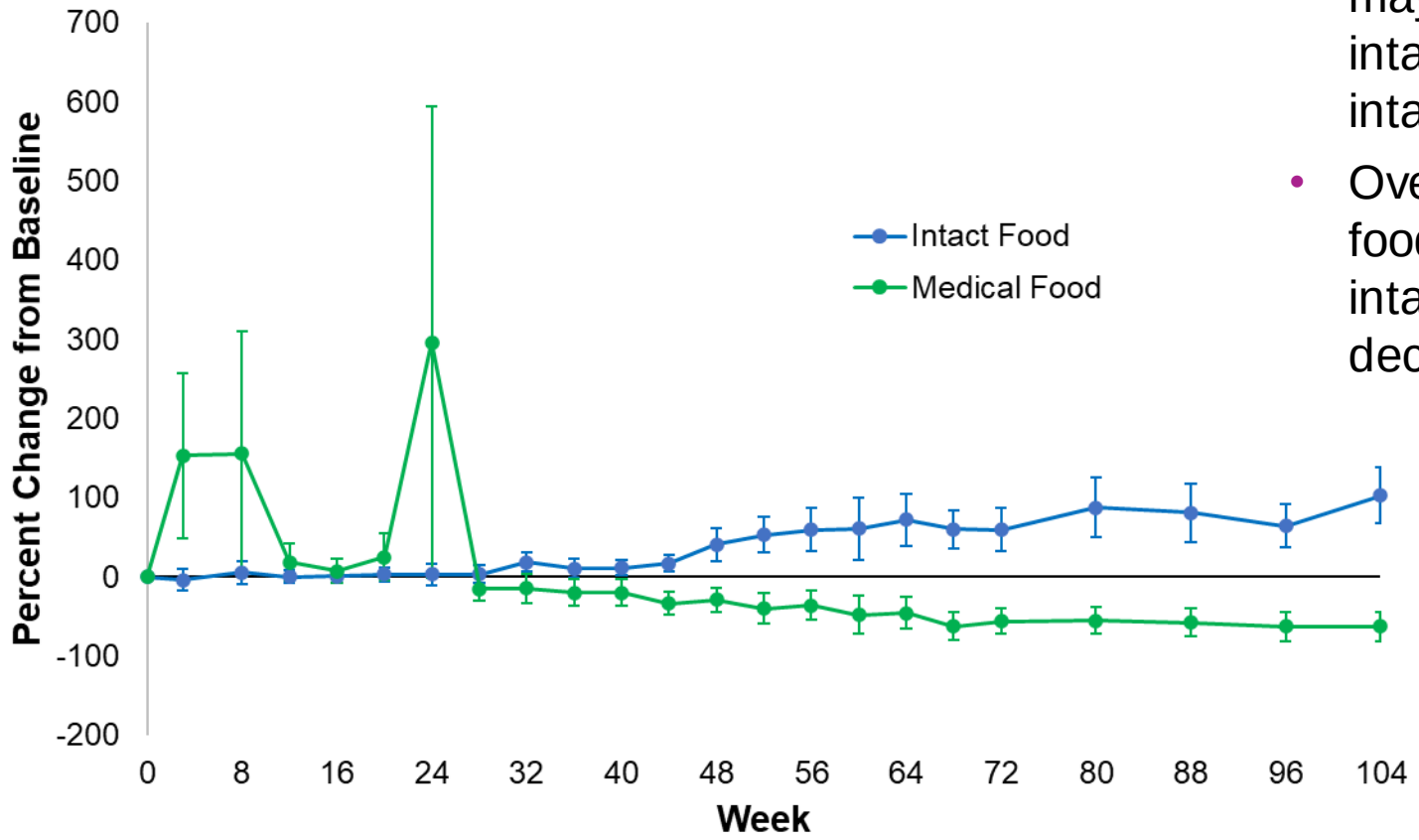






Dietary Intake

Figure 5. Dietary protein intake up to Week 104



Error bars are SE

- Participants reaching blood Phe ≤360 µmol/L during Part 2 may adjust dietary protein intake from medical food and intact food per protocol
- Overall, Phe intake from intact food increased and protein intake from medical food decreased over time

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Safety Overview

- All 12 participants (100%) experienced 1 or more treatment emergent adverse events (TEAEs)
  - The most common AEs were injection site erythema and injection site swelling (83.3% each); arthralgia (75.0%); nasopharyngitis (66.7%); malaise (58.3%); allergic dermatitis, injection site pruritus and urticaria (50.0% each); and injection site pain, pyrexia, headache, decreased complement factor C3 and decreased complement factor C4 (41.7% each)
- 2 participants (16.7%) had AEs of Common Terminology Criteria for Adverse Events (CTCAE) severity Grade ≥3
  - Hemorrhagic intestinal diverticulitis – assessed as unrelated to pegvaliase by the investigator
  - Allergic arthritis – assessed as possibly related to pegvaliase by the investigator
- None of the participants (0%) had anaphylaxis; 6 participants (50%) 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), increased aspartate aminotransferase and increased alanine aminotransferase (both in 1 participant)
- Six participants (50%) had AEs leading to dose interruption
- No participants (0%) withdrew from the study due to an AE. Two participants (16.7%) withdrew due to: ‘Withdrawal by subject’

Safety Events by Treatment Phase

Table 2. Adverse events by treatment phase

	Induction/Titration (N=12)	Maintenance (N=10)	Overall (N=12)
Total treatment exposure, person-years	11.0	15.5	28.3
AEs, n (rate per person-years) [a]	503 (45.5)	313 (20.2)	816 (28.8)
AEs leading to dose reduction	0	4 (0.3)	4 (0.1)
AEs leading to dose interruption	27 (2.4)	3 (0.2)	30 (1.1)
AEs leading to study drug discontinuation	0	0	0
AEs leading to study discontinuation	0	0	0
SAEs, n (rate per person-years) [a]	1 (0.1)	3 (0.2)	4 (0.1)
SAEs leading to dose reduction	0	0	0
SAEs leading to dose interruption	0	2 (0.1)	2 (0.1)
SAEs leading to study drug discontinuation	0	0	0
SAEs leading to study discontinuation	0	0	0
Treatment-related AEs, n (rate per person-years) [a, b]	455 (41.2)	209 (13.5)	664 (23.5)
Treatment-related SAEs	0	1 (0.1)	1 (0.0)
AEs of CTCAE Grade ≥3, n (rate per person-years) [a]	0	4 (0.3)	4 (0.1)
Death, n (rate per person-years) [a]	0	0	0
AESI, n (rate per person-years) [a]			
Anaphylaxis	0	0	0
Skin reactions	9 (0.8)	10 (0.6)	19 (0.7)
Hypersensitivity AE	66 (6.0)	48 (3.1)	114 (4.0)

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] Event Rate = Number of events/Person Year.

[b] Relationship to study drug was as 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.

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Conclusions

- Analysis of the interim results up to Week 104 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 throughout the study duration

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