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Three-year interim safety and efficacy of pegvaliase in Japanese adults with phenylketonuria
成人のフェニルケトン尿症患者を対象としたPegvaliase国内治験3年目の報告

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日本先天代謝異常学会
COI開示

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（BioMarin）

Phenylketonuria (PKU)

- Caused by deficiency of phenylalanine hydroxylase (PAH)[1-5]
  - High phenylalanine (Phe) levels in the blood and brain
  - Impaired neurocognitive function
- Management
  - Clinical guidelines: Japan[6] and ACMG[7]
    - Phe <360 µmol/L
  - Sapropterin dihydrochloride is available in Japan[8]
    - Only 20% to 56% of PKU patients respond[9-11] with many unable to maintain guidelines[12]
  - Pegvaliase[13-15]
    - PEGylated recombinant *Anabaena variabilis* phenylalanine ammonia lyase (PAL)
    - Converts Phe to trans-cinnamic acid and ammonia

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.*

GLOBAL MEDICAL AFFAIRS

Objective

- 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 dosing regimen, similar to the regimen used in phase 3 trials that supported pegvaliase approval in multiple geographic regions[1-5]

1. Palynziq (pegvaliase-pqpz) [US Prescribing Information]. BioMarin Pharmaceutical Inc.; 2020. **2.** Palynziq (pegvaliase) [EU Product Information]. BioMarin International Ltd.; 2019.
3. Palynziq (pegvaliase) [Australia Product Information]. BioMarin Pharmaceutical Australia Pty Ltd.; 2023. **4.** Palynziq (pegvaliase) [Japan Package Insert]. BioMarin Pharmaceutical Japan K.K.; 2023.
5. Palynziq (pegvaliase) [Taiwan Product Information]. BioMarin Pharmaceutical Inc.; 2023.

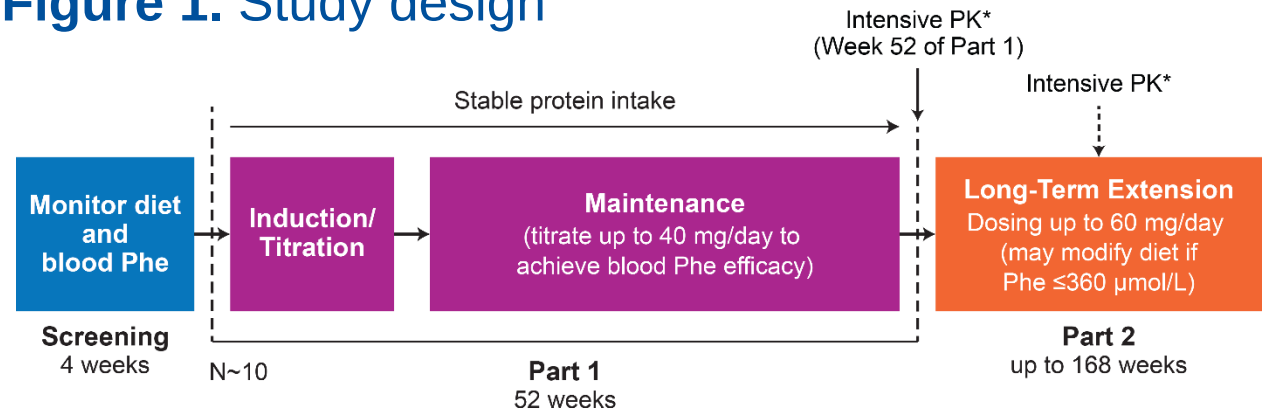
Methods

- **Patients:** PKU, 18 years and older
- **Part 1:**
  - Maintain a stable diet
  - Assessment of diet using 3-day diet diaries
  - Diet modified if blood Phe <30 µmol/L
- **Part 2:**
  - Diet adjustment if blood Phe ≤360 µmol/L
  - Results that will be presented today from Part 2 as of March 24, 2023

Table 1. Recommended dosing

Treatment	Dosage	Duration
Induction	2.5 mg once a week	4 weeks
Titration	2.5 mg twice a week	1 week
	10 mg once a week	1 week
	10 mg twice a week	1 week
	10 mg four times a week	1 week
	10 mg once a day	1 week
Maintenance	20 mg once a day	-

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.

GLOBAL MEDICAL AFFAIRS

Table 2. Demographics and characteristics

Characteristic	Safety Population (N=12)	Efficacy 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 Population as the denominator, as applicable.
[b]Only analyzed for Efficacy Population

- 3 sites in Japan
- 12 participants (Safety Population)
  - At least 2 doses of pegvaliase
- 11 participants (Efficacy Population)
- Mean pegvaliase treatment (range): 153.4 weeks (24–194 weeks)

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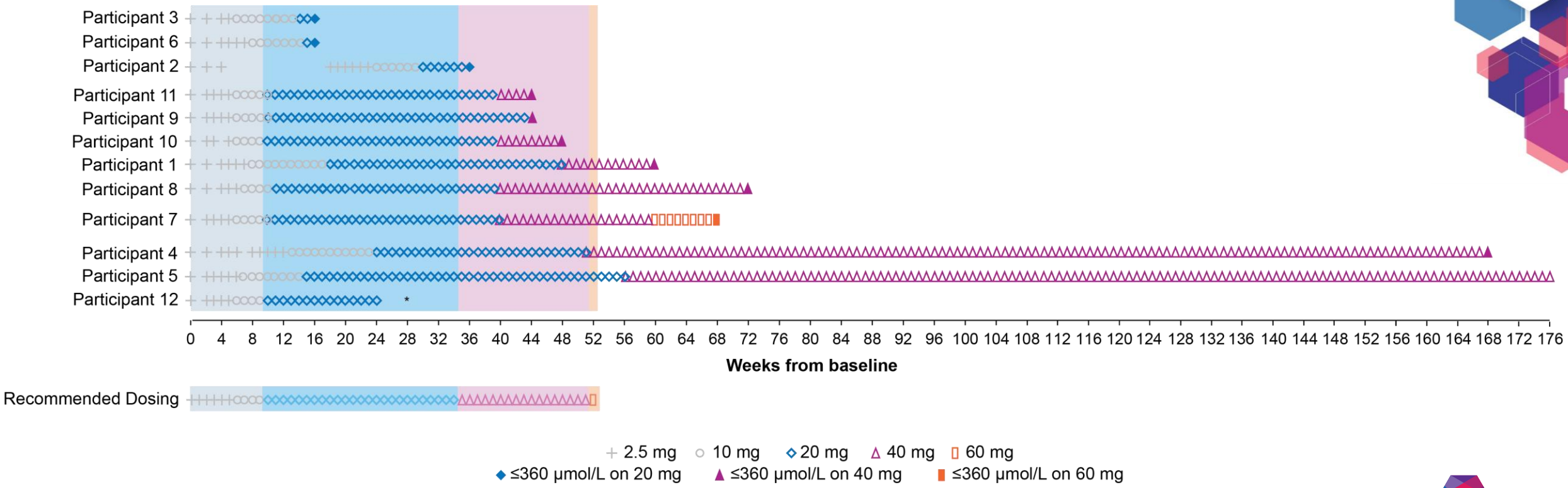
Figure 2. Dosing patterns, first achievement of Phe goal (≤360 µmol/L)

- Participants who achieved blood Phe ≤360 µmol/L:
  - Mean time to efficacy was 63.6 weeks (range: 16–168 weeks)
- Most (70%) achieved goal within 9 weeks of updosing



*Participant 12 discontinued during Part 1

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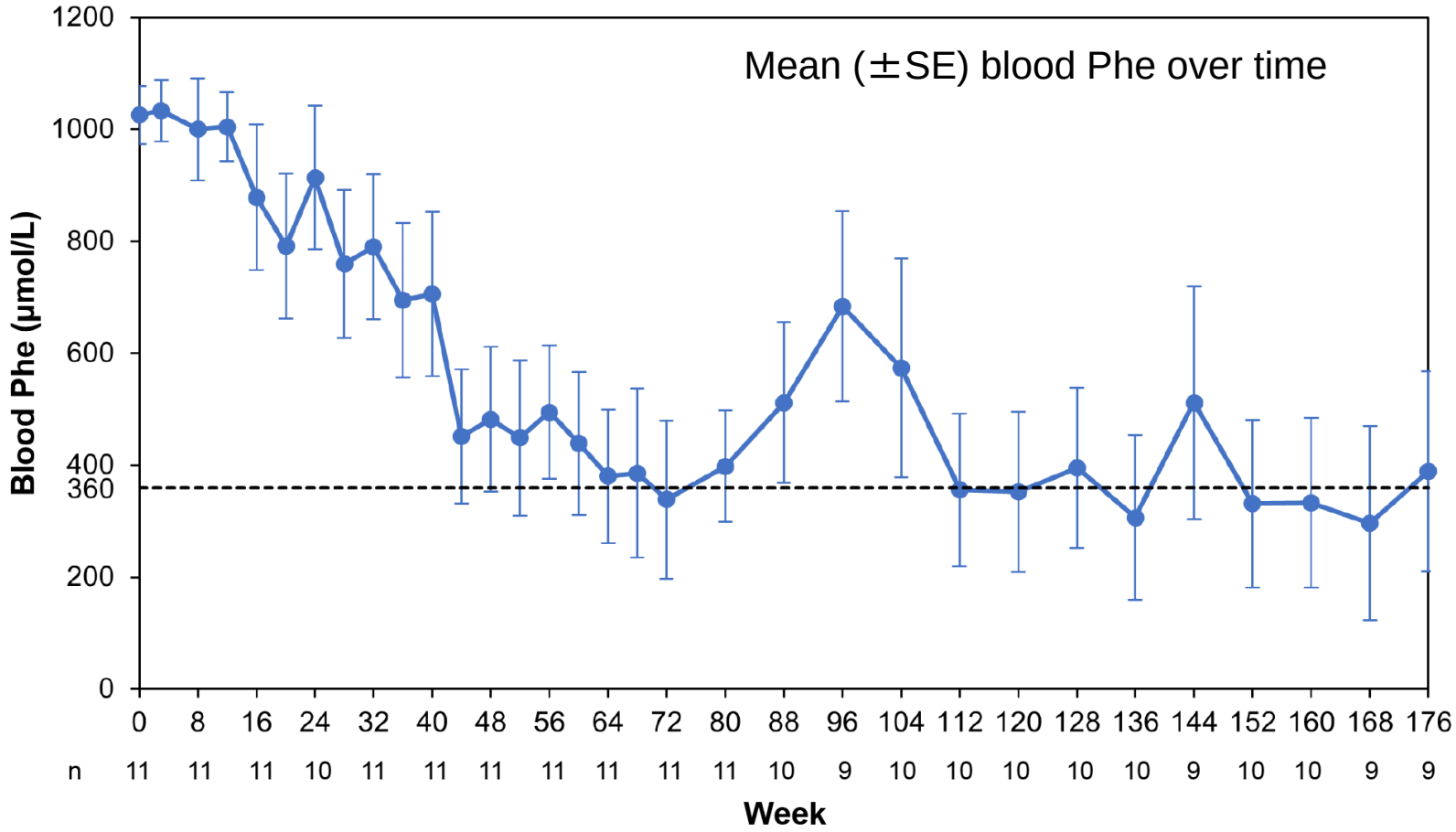
Figure 3. Mean Phe levels up to 176 weeks follow-up



- Mean (SD) Phe level: 389.1 (536.7) µmol/L at 176 weeks
- 63.8% decrease from pegvaliase-naïve baseline

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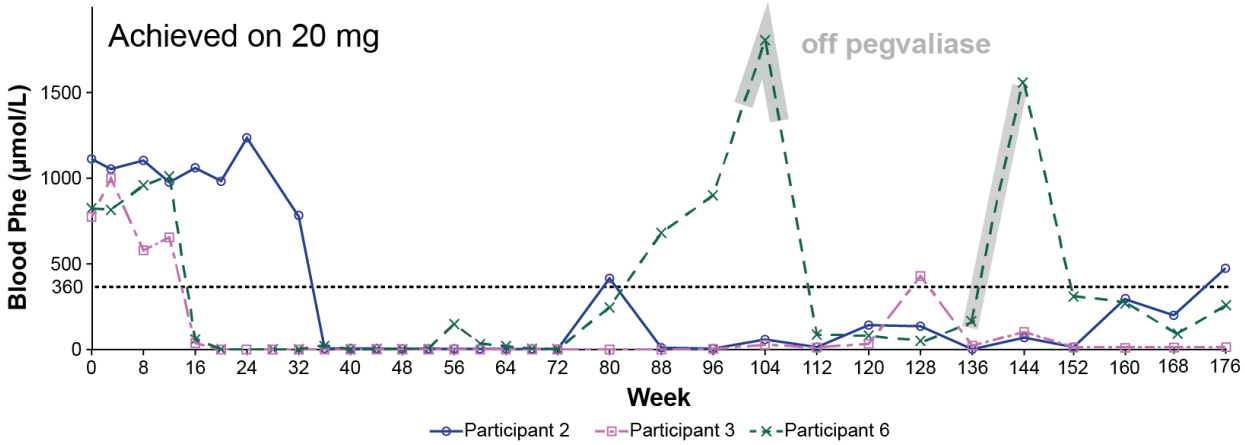
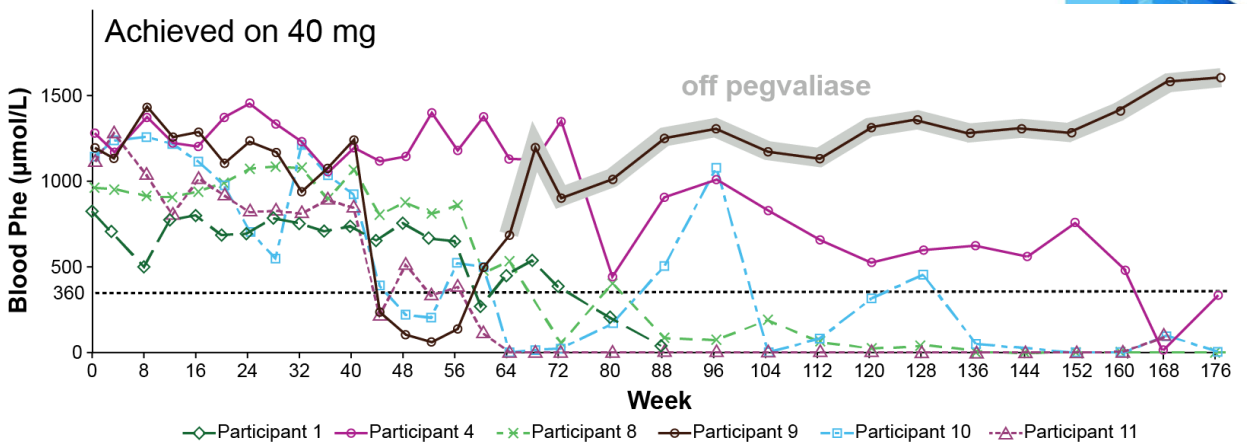
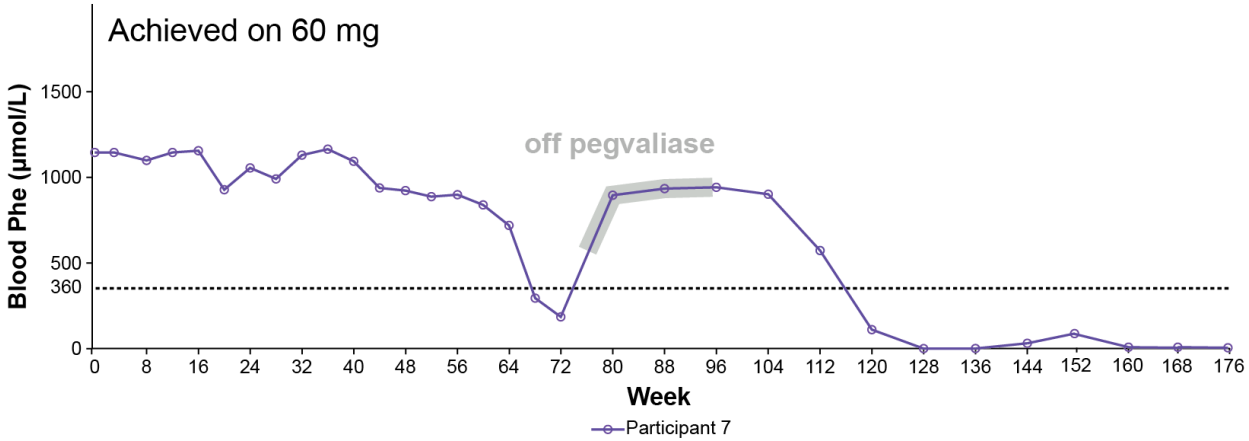
Figure 4. Phe levels of individual participants







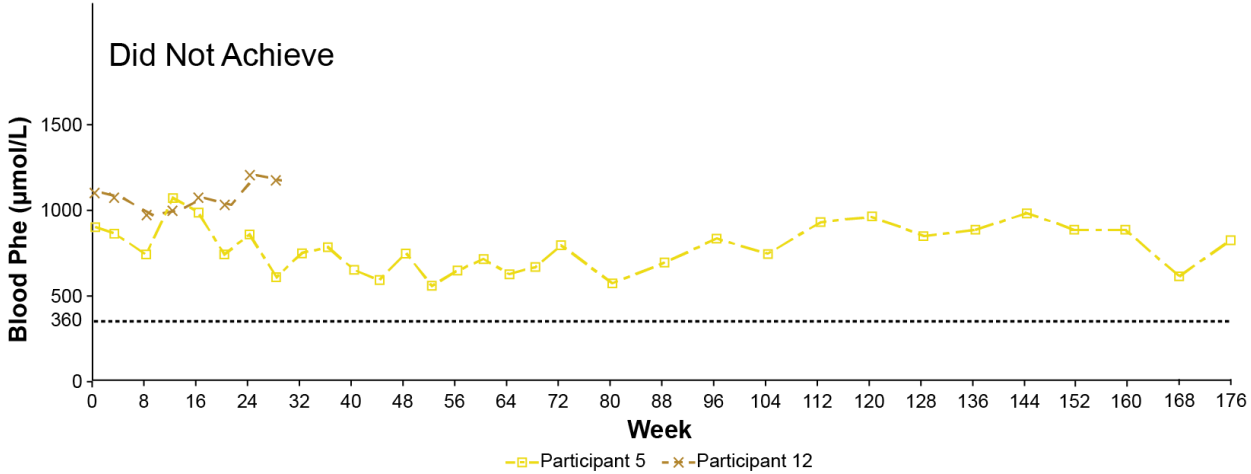


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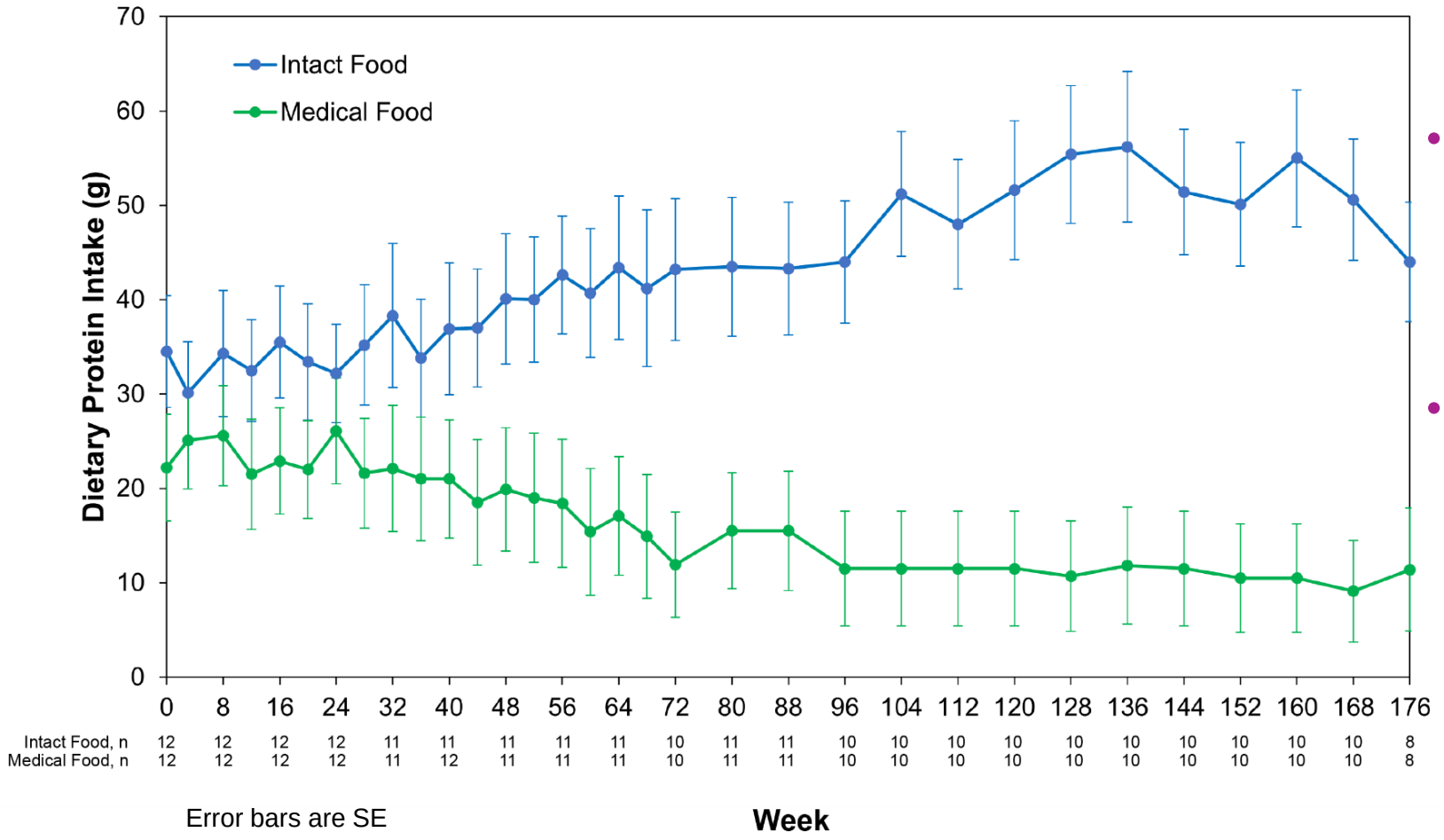
Figure 5. Dietary protein intake up to week 176



Error bars are SE

- Protein intake:
  - adjusted if blood Phe ≤360 µmol/L during Part 2
- Overall
  - Increased intact food intake
  - Decreased medical food

GLOBAL MEDICAL AFFAIRS

Table 3. Hypophenylalaninemia during Maintenance dosing

- Hypophenylalaninemia (hypoPhe: Phe <30 µmol/L)
  - 7/11 participants (63.6%)
- Adverse events (AEs) during hypoPhe
  - No clinically significant AEs
  - Temporary hair loss in one participant

ID	Weeks	Weight (kg) at Start	Intact Protein (g) at Start	Intact Protein (g) at End	HypoPhe Start Dose	Outcome
2	40-72	56.9	14.4	41.2	20 mg/day	10 mg 2 times weekly, blood Phe still low
3	24-112	56.3	31.7	48.9	20 mg/day	20 mg/day, blood Phe fluctuations
6	28-52	57.3	45.5	82.6	20 mg/day	10 mg 4 times weekly, blood Phe fluctuations
7	136-144	72.1	47.7	42.4	40 mg/day	20 mg/day, blood Phe still low
8	144-176	49.8	31.1	38.2	40 mg/day	20 mg/day, blood Phe still low
10	68-72	67.6	41.1	33.4	40 mg/day	40 mg/day, blood Phe fluctuations
11	68-160	48.6	35.3	75.5	40 mg/day	10 mg 4 times weekly, blood Phe still low

Table 4. Adverse events by treatment phase

- All 12 participants at least 1 or more treatment-emergent AEs including hypersensitivity related
- More frequent in the Induction/Titration phase
- Common AEs: Injection site erythema and swelling (83%); arthralgia (75%); malaise and nasopharyngitis (66.7%); allergic dermatitis (58.3%); injection site pruritus and urticaria (50.0%); injection site pain, pyrexia, headache, COVID-19, decreased complement factor C3 and C4 (41.7%)
- 1 participant with a serious AE (SAE) of allergic arthritis, possibly related[b], 1 participant had an anaphylactic reaction, unrelated[b]
- No discontinuations related to AEs

	Induction/Titration (N=12)	Maintenance (N=10)	Overall (N=12)
Participants with any treatment-related AEs, n (%)	**12 (100)**	**5 (50)**	**12 (100)**
Treatment-related SAEs	0	1 (10)	1 (8.3)
Treatment-related AEs, n (rate per person-years)[a]	**455 (41.2)**	**209 (13.5)**	**664 (23.5)**
Treatment-related SAEs	0	1 (0.1)	1 (0.0)
AESI, n (rate per person-years)[a]			
Anaphylaxis	0	1 (0.0)	1 (0.0)
Skin reactions	9 (0.8)	13 (0.5)	22 (0.6)
Hypersensitivity AE	66 (6.0)	76 (3.2)	142 (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.
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 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 176 with pegvaliase

- Patients require individually-based tailored pegvaliase treatment based on their immune response as demonstrated by observed Phe levels over time and AE profile
- Dose adjustments need to be carefully considered for those not responding to the pegvaliase maintenance dose based on each individual's risks and benefits
- Results demonstrate the efficacy of pegvaliase in reducing blood Phe concentrations with a manageable safety profile
- Results are consistent with those of the US phase 3 program

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