Final safety and efficacy of pegvaliase in Japanese adults with phenylketonuria

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(BioMarin)

Background

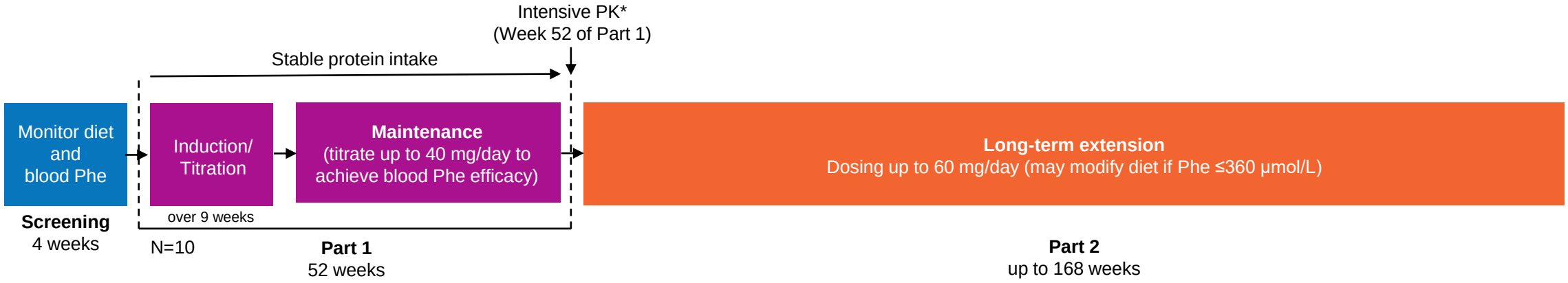
- PKU is caused by deficiency of phenylalanine hydroxylase, leading to elevated Phe levels in the blood and brain, which negatively impacts neurocognitive function in adults with PKU[1-3]
- The Japanese clinical guidelines recommend maintaining blood Phe below 360 µmol/L[4]
- Alongside diet therapy, Biopten® (sapropterin hydrochloride) is available in Japan,[5] but only ~20–56% of patients with PKU respond to sapropterin,[6-7] and many adults struggle to maintain recommended blood Phe levels[8]
- Pegvaliase, a PEGylated recombinant *Anabaena variabilis* PAL, converts Phe to trans-cinnamic acid and ammonia[9]
- This study aimed to evaluate the efficacy and safety of pegvaliase in Japanese patients aged ≥18 years with PKU (blood Phe >600 µmol/L) using an Induction/Titration/Maintenance (I/T/M) dosing regimen similar to the pivotal phase 3 trials that supported its approval in other countries[10-11]

PAL, phenylalanine ammonia lyase; Phe, phenylalanine; PKU, phenylketonuria

1. Moyle JJ et al. *J Clin Exp Neuropsychol*. 2007;29(4):436-441. **2.** Gassió R et al. *Acta Paediatr.* 2003;92(12):1474-1478. **3.** ten Hoedt AE et al. *J Inherit Metab Dis.* 2011;34(1):165-171. **4.** Japanese Society for Inherited Metabolic Diseases. Guidelines for the Treatment of Diseases Targeted for Newborn Mass Screening. 2019. **5.** Biopten® (sapropterin hydrochloride) [Japanese package insert]. Daiichi Sankyo Company, Limited; 2021. **6.** Levy HL et al. *Lancet.* 2007;370(9586):504-510. **7.** Trefz FK et al. *J Pediatr.* 2009;154(5):700-707. **8.** Jurecki ER et al. *Mol Genet Metab.* 2017;120(3):190-197. **9.** Longo N et al. *Lancet.* 2014;384(9937):37-44. **10.** Palynziq® (pegvaliase-pqpz) [US prescribing information]. BioMarin Pharmaceutical Inc.; 2020. **11.** Palynziq® (pegvaliase) [Japan package insert]. BioMarin Pharmaceutical Japan K.K.; 2023.

Methods

- The study included a low-dose induction period followed by sequential titration to a maintenance dose (see Figure)
- During Part 1, participants were instructed to maintain a stable diet, assessed using data from 3-day diet diaries; however, diet modifications could be made if blood Phe levels were <30 µmol/L
- During Part 2, participants with blood Phe ≤360 µmol/L could adjust dietary protein intake based on response to pegvaliase and investigator guidance
- The study concluded in August 2023, with the final results reported up to the last follow-up



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

Phe, phenylalanine; PK, pharmacokinetics

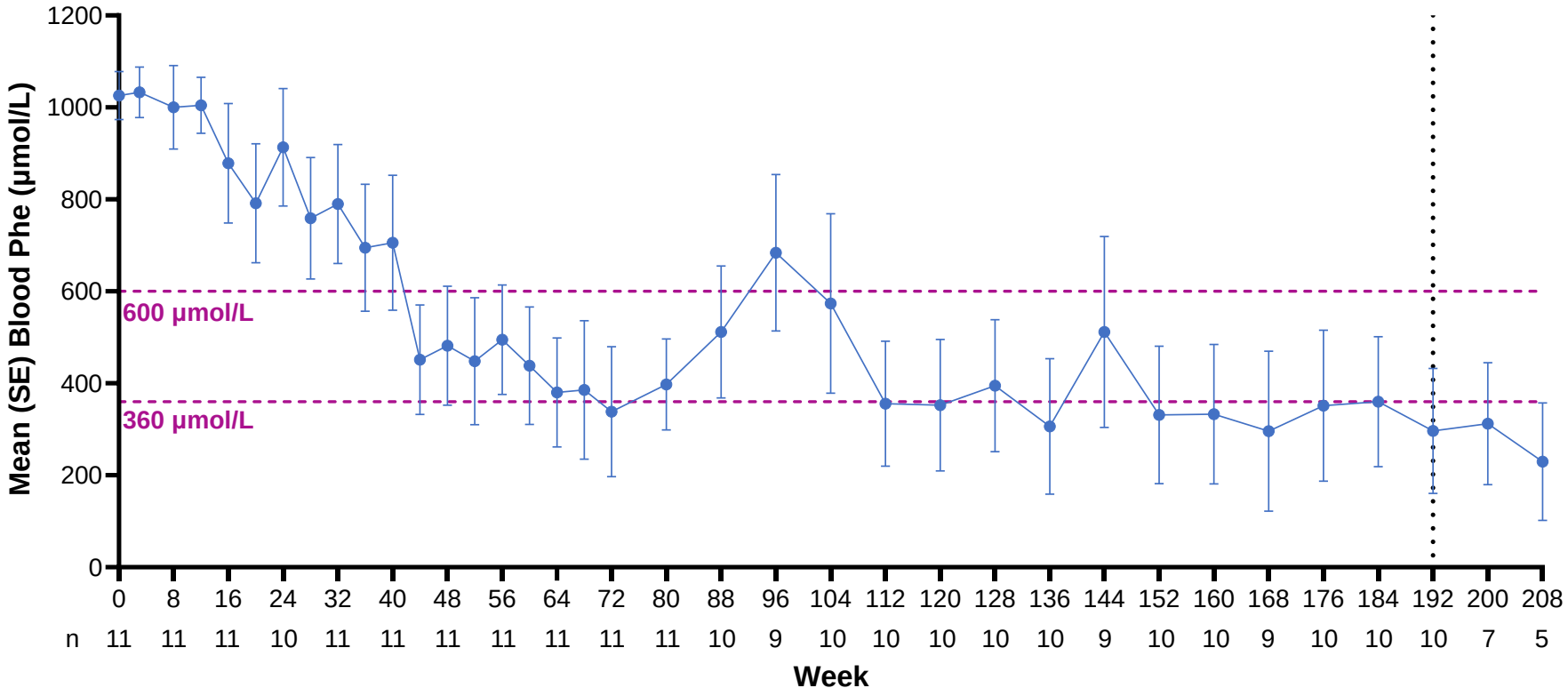
Baseline demographics and characteristics

Characteristic	All participants* (N=12)
Age, years	
Mean (SD)	29.4 (8.1)
Sex, n (%)	
Female	4 (33.3)
Weight, kg	
Mean (SD)	64.4 (15.2)
Median	59.0
BMI, kg/m^2	
Mean (SD)	23.5 (5.3)
Median	22.4
Blood Phe, µmol/L	
Mean (SD)	1032.3 (166.2)
Median	1107.8
Average daily protein intake from intact food, g	
Mean (SD)	34.5 (20.5)
Median	33.4
Average daily protein intake from medical food, g	
Mean (SD)	22.2 (19.6)
Median	19.6

- A total of 12 participants were enrolled into the study from 3 clinical sites in Japan
- Mean pegvaliase treatment duration was 166.4 weeks (range: 24–212 weeks)
- At baseline, the mean (SD) daily protein intake was 34.5 (20.5) g from intact food and 22.2 (19.6) g from medical food

*Total number of participants in the efficacy evaluable population was 11
BMI, body mass index; Phe, phenylalanine; SD, standard deviation

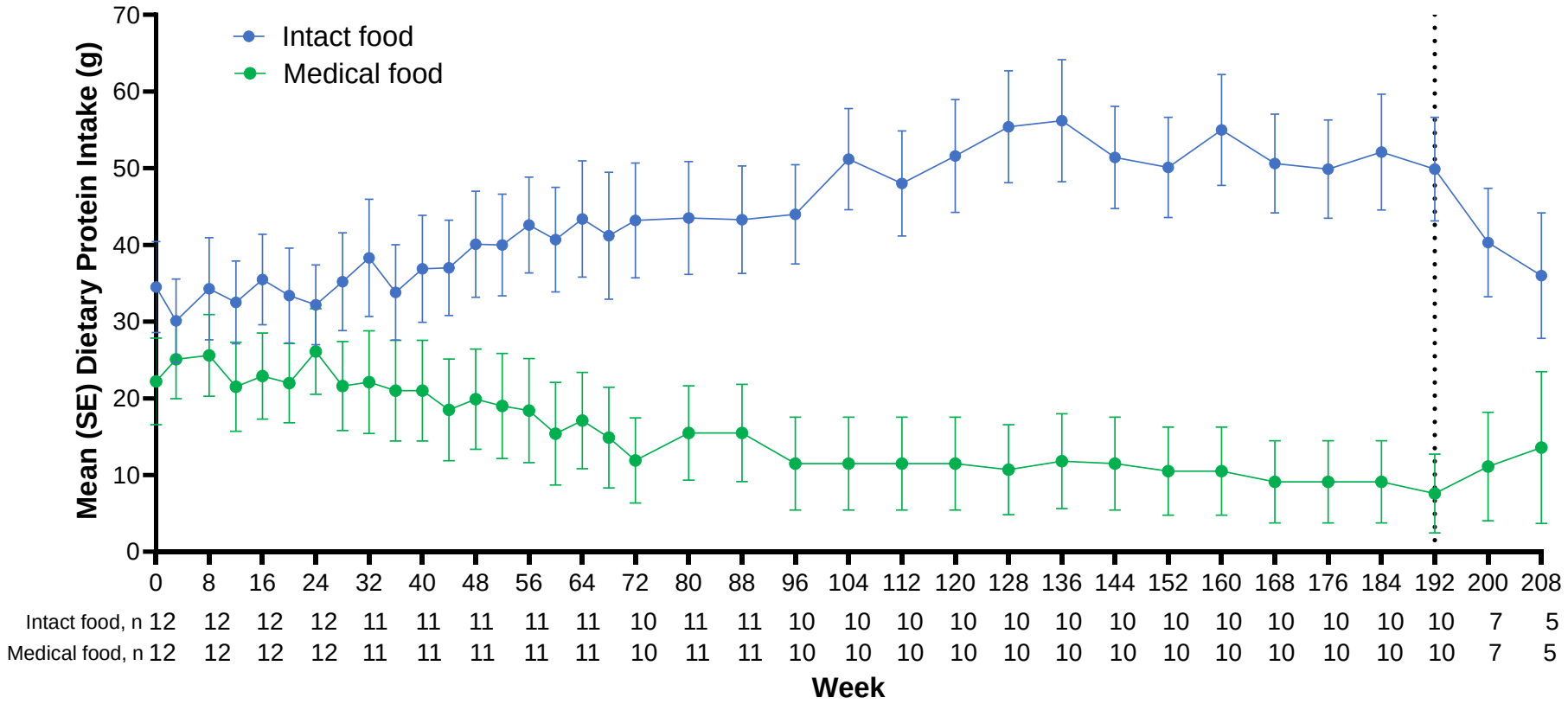
Mean blood Phe over time in the efficacy evaluable population*



- Blood Phe data are available for 208 weeks of follow-up
- Mean (SD) blood Phe was 229.4 (285.6) µmol/L at 208 weeks, a decrease of 77.0% (32.0%) from pegvaliase-naïve baseline

*n=11; the efficacy evaluable population consisted of a subset of participants in the efficacy population who completed 52 weeks of treatment and had blood Phe concentration measures at week 52
Phe, phenylalanine; SD, standard deviation; SE, standard error

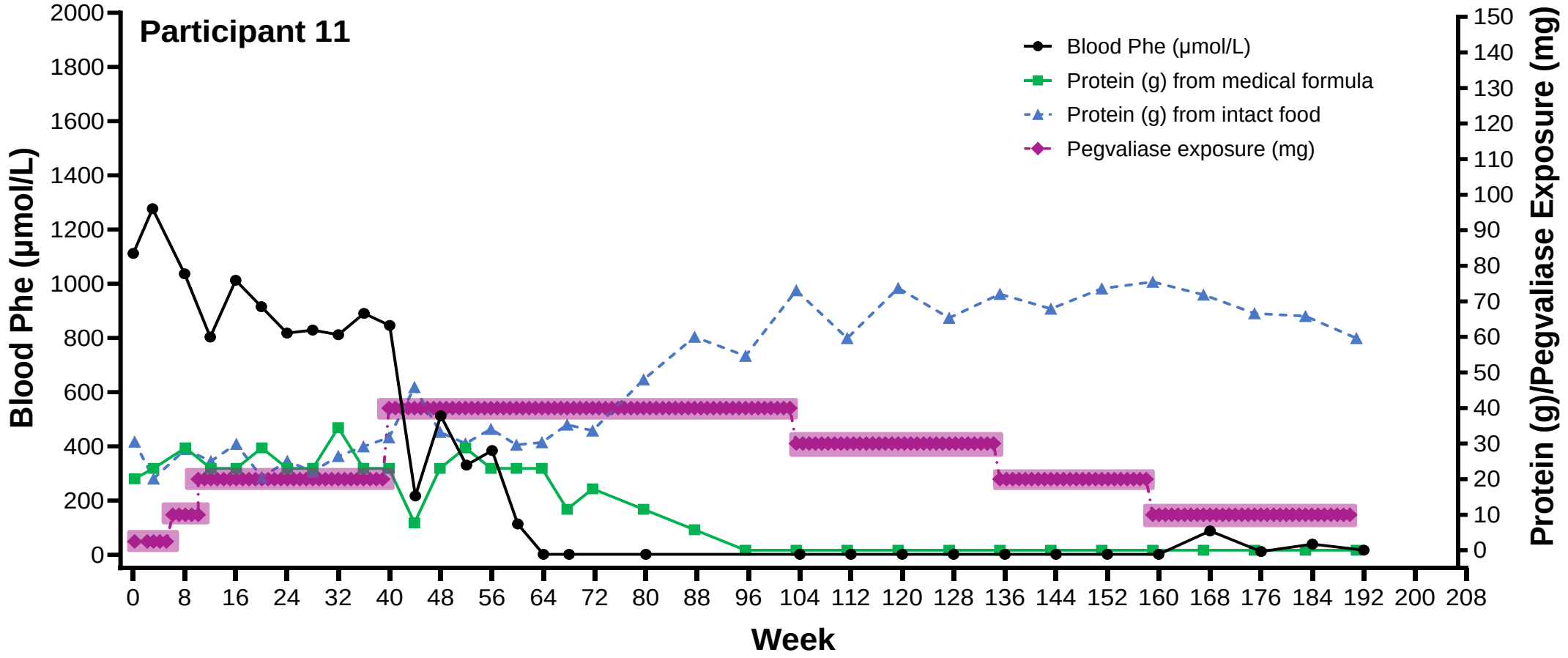
Dietary protein intake up to week 208



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

Phe, phenylalanine; SE, standard error

Example participant profile showing blood Phe, protein intake, and pegvaliase exposure over time



Phe, phenylalanine

Summary of outcomes by participant

Participant details				Blood Phe (µmol/L)		First achievement of ≤360 µmol/L		Pegvaliase administration			Protein intake			
									At last exposure		BL		Last follow-up*	
ID	Age (years)	Sex	Weight (kg)	BL	Final	Daily dose (mg)	Time to reach (weeks)	Duration (weeks)	Dose (mg)	Frequency	Total (g)	Medical food (%)	Total (g)	Medical food (%)
3	31	F	54	774	4	20	16	216	10	2x/week	69	71.3	75	23.9
6	46	F	54	828	719	20	16	200	10	4x/week	55	34.4	60	0
2	22	M	56	1113	186	20	36	208	10	2x/week	35	48.0	45	0
9	32	M	69	1196	683†	20	44	64	40	daily	80	0	72	0
10	22	M	64	1142	207	40	48	192	40	daily	39	3.4	48	0
11	38	F	49	1112	17	40	52	192	10	daily	51	39.7	60	0
1	21	M	59	823	40†	40	60	96	40	daily	63	74.5	58	82.0
7	37	M	78	1149	23	60	68	208	20	daily	51	0	38	0
8	23	F	54	964	<2	40	72	200	20	daily	60	54.7	44	21.7
4	31	M	104	1278	227	40	168	208	40	daily	49	2.7	38	0
5	20	M	75	904	709	-	-	208	40	daily	53	95.4	56	90.2
12	30	M	59	1104	1178	-	-	28	20	2x/week	76	36.6	67	27.8

*Final diet status was calculated as the mean of the daily protein intake from intact food and medical food at early termination/study completion; †Blood Phe at last pegvaliase exposure
BL, baseline; F, female; M, male; Phe, phenylalanine

Safety overview

- All 12 participants (100%) experienced ≥1 treatment-emergent AE
  - The most common AEs were injection site erythema and injection site swelling (83.3% each), arthralgia (75.0%), malaise and nasopharyngitis (66.7% each), allergic dermatitis (58.3%), and injection site pruritus and urticaria (50.0% each)
  - 1 participant had an anaphylactic reaction deemed unrelated to pegvaliase by the investigator
- 2 participants experienced an SAE that led to dose interruption in the maintenance phase
  - SAE #1: Allergic arthritis, assessed as related, dose interrupted but not discontinued
  - SAE #2: Fall, assessed as not related, dose interrupted due to fracture surgery
- 6 participants (50%) had an AE of special interest of skin reactions lasting ≥14 days without improvement, and all 12 experienced hypersensitivity AEs during induction/titration (80% affected during maintenance)
- 1 participant discontinued pegvaliase due to hypersensitivity reactions
- 7 of 11 participants (63.6%) experienced hypoPhe (≥2 blood Phe levels <30 µmol/L), with 3 of these cases occurring during maintenance and no clinically significant AEs except for temporary hair loss in 1 participant associated with hypoPhe

AE, adverse event; hypoPhe, hypophenylalaninemia; Phe, phenylalanine; SAE, serious adverse event

Conclusions

- Administration of pegvaliase in Japanese adults with PKU with blood Phe concentrations >600 µmol/L **effectively reduced blood Phe levels to within, and often below, guideline-recommended ranges**
- Treatment was generally well tolerated with **no new safety issues identified**
- **Hypersensitivity-related AEs** were more frequent during early treatment phases but **declined over time** as immune responses matured
- Long-term treatment often allows for **dose reduction and diet liberalization** as immune responses stabilize and blood Phe concentrations are controlled[1]

AE, adverse event; Phe, phenylalanine; PKU, phenylketonuria

1. Rohr F et al. *Mol Genet Metab*. 2024;141(3):108122.

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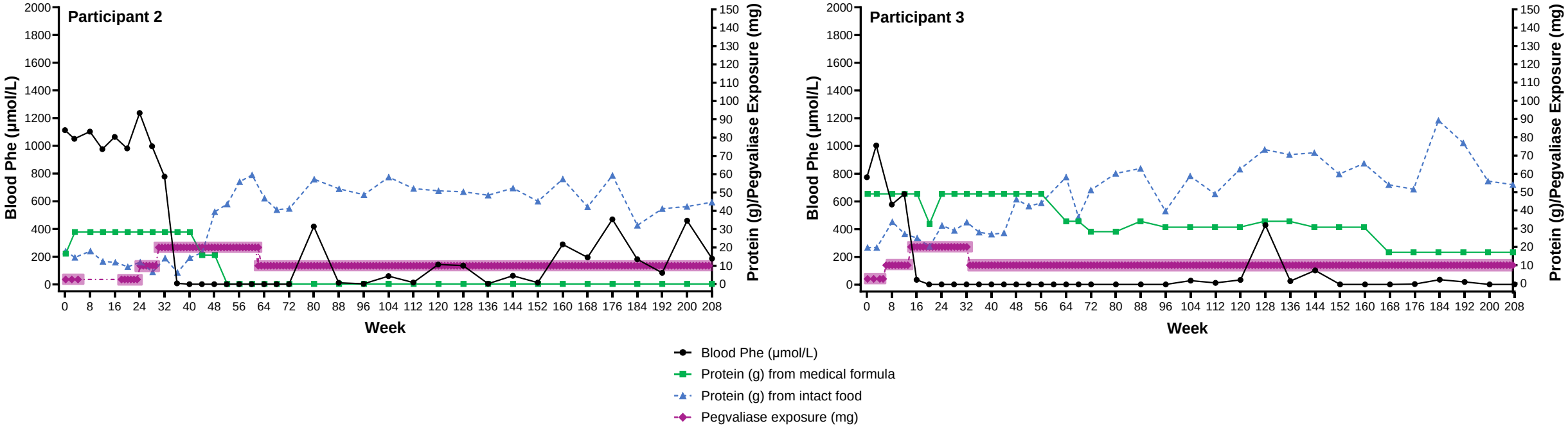
Example participant profiles showing blood Phe, protein intake, and pegvaliase exposure over time



Phe, phenylalanine

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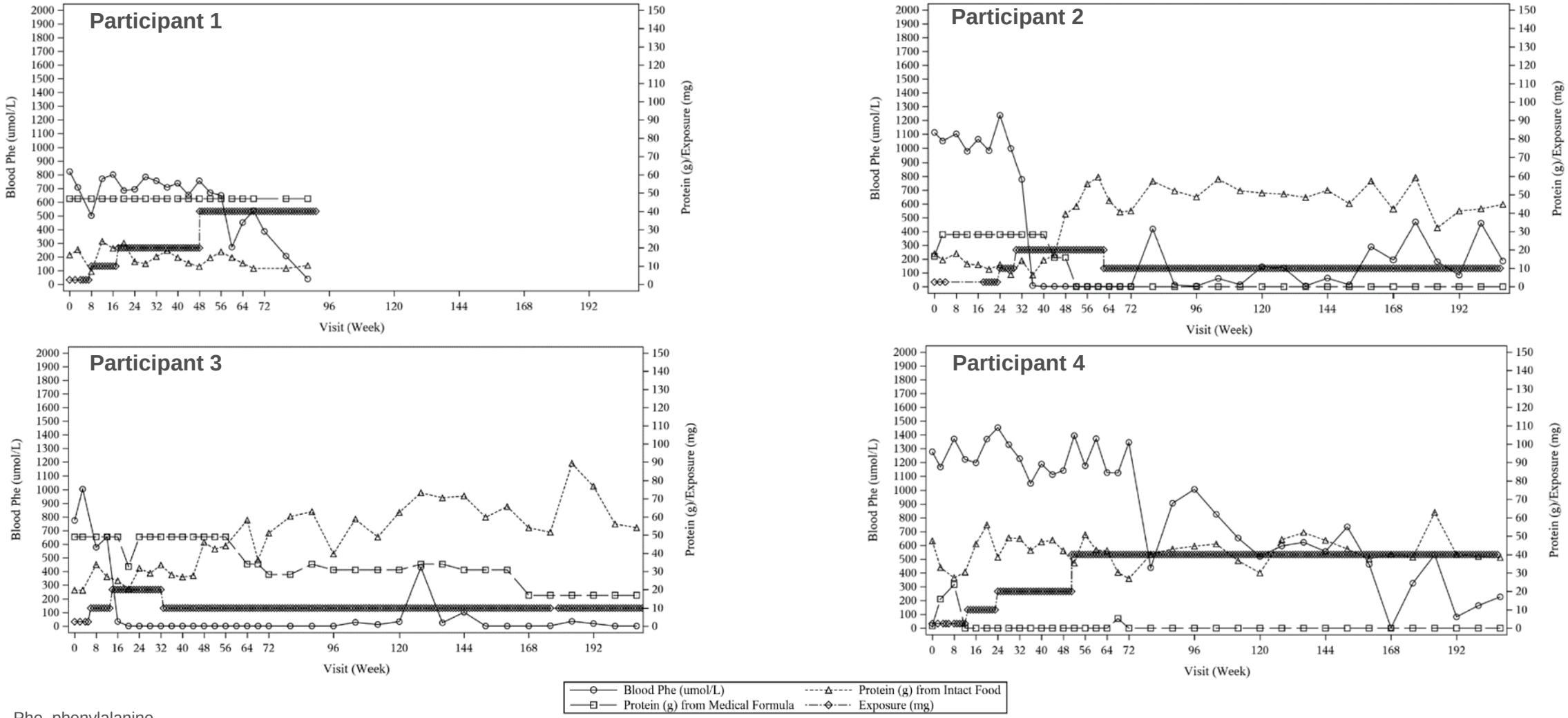

Phe, phenylalanine

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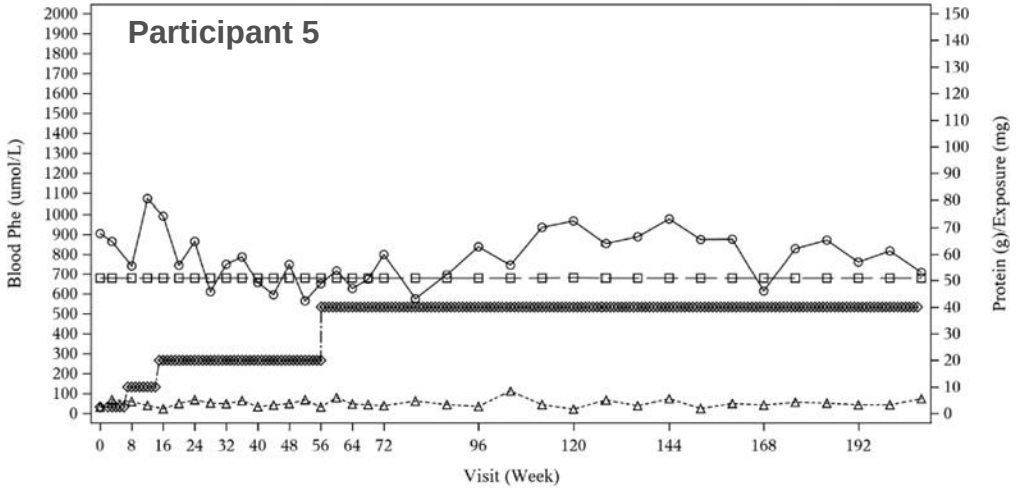

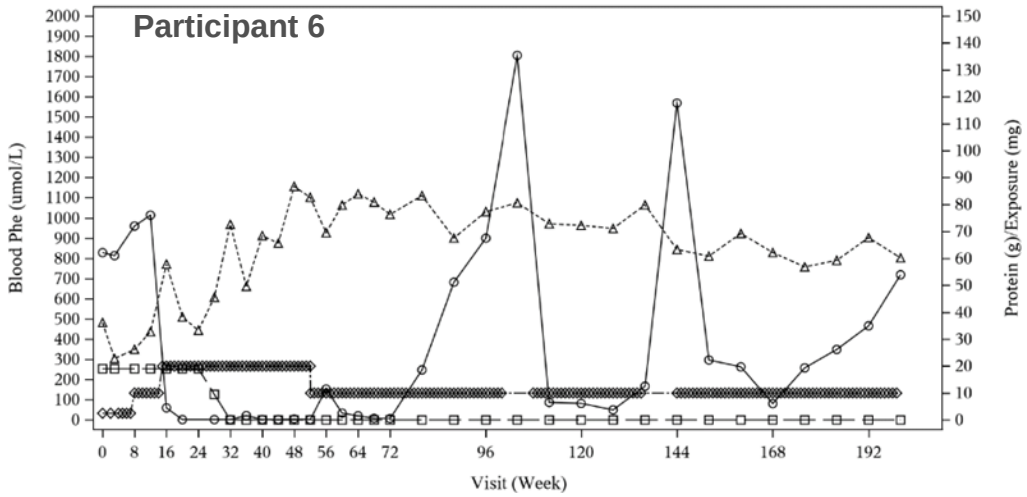

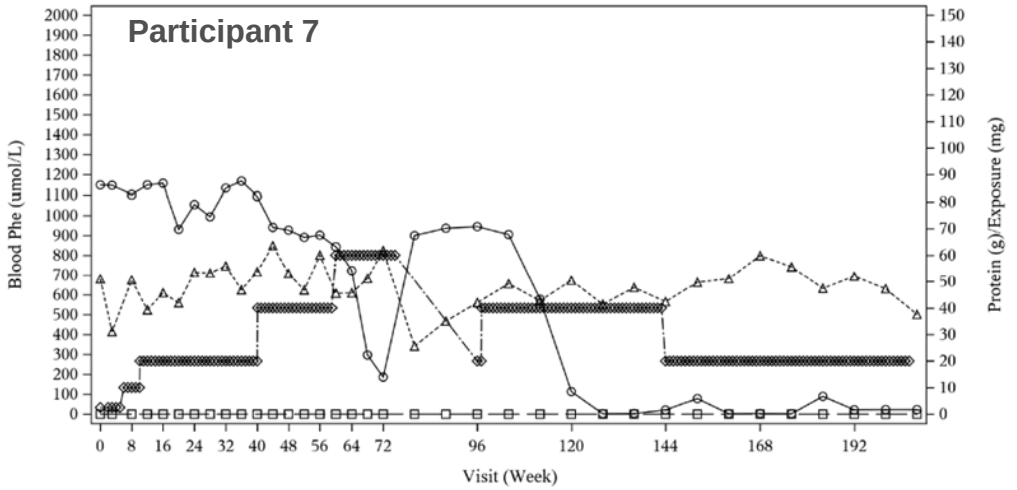

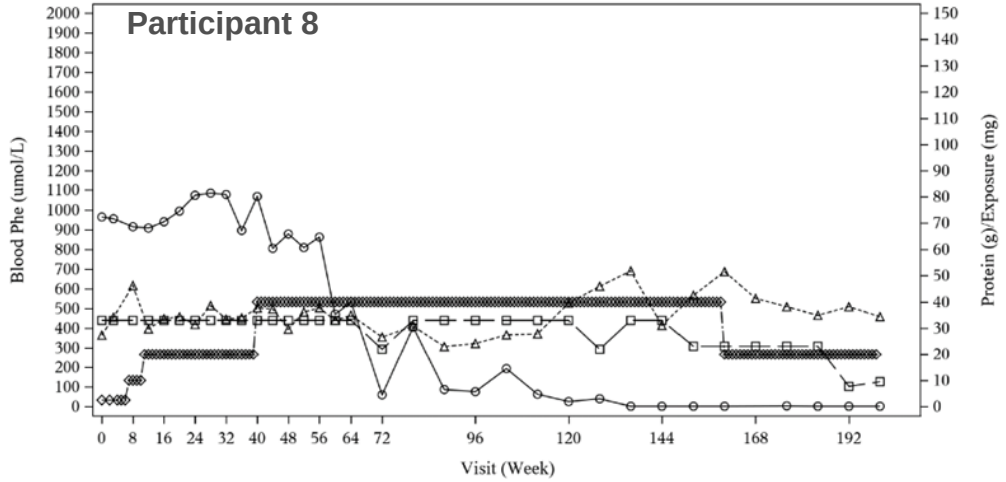

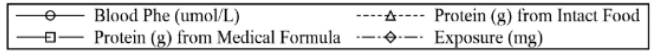

Phe, phenylalanine

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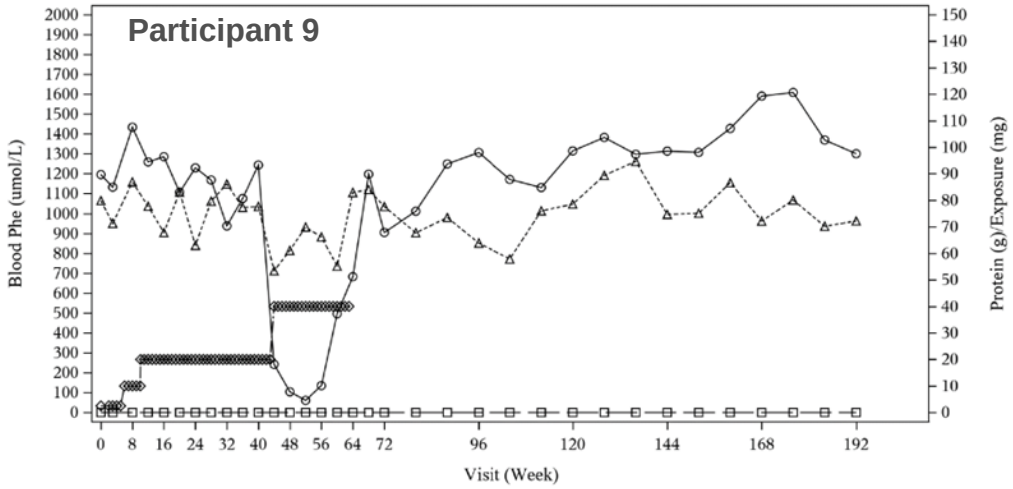

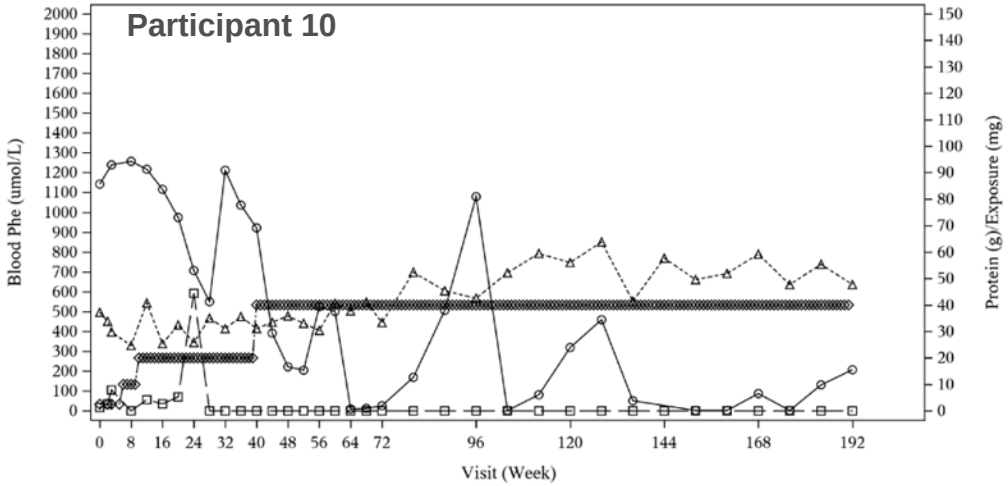

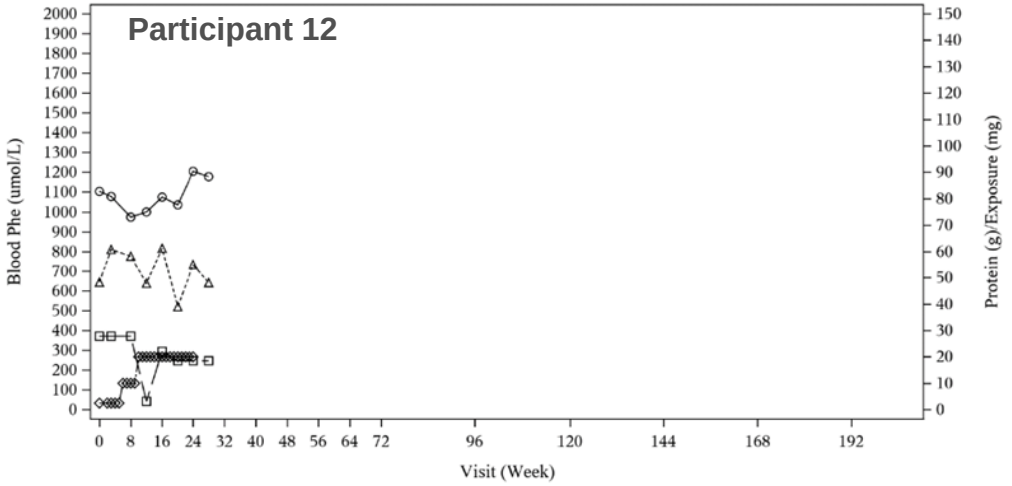

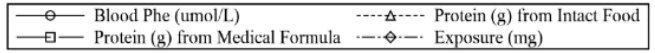

Phe, phenylalanine