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Evaluating change in diet with pegvaliase treatment in adults with phenylketonuria: Results from phase 2 and 3 clinical trials

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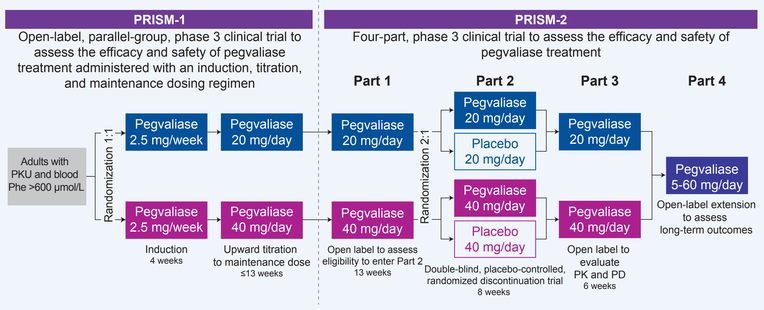
Background

- Phenylketonuria (PKU) is caused by deficiency of the enzyme phenylalanine hydroxylase, resulting in phenylalanine (Phe) accumulation[1]
- Pegvaliase (Palynziq®), PEGylated recombinant *Anabaena variabilis* phenylalanine ammonia lyase (PAL), converts Phe to *trans*-cinnamic acid and ammonia[2-4]
- Pegvaliase is an enzyme substitution therapy indicated in the United States to reduce blood Phe in adults with PKU who have uncontrolled blood-Phe concentrations >600 µmol/L with existing management[5]

Methods

- The ability of subcutaneous pegvaliase to lower plasma Phe in adults with PKU using an induction, titration, and maintenance (ITM) dosing schedule in phase 2 (165-205, NCT01560286; PAL-003, NCT00924703) and 3 (PRISM) studies with doses up to 60 mg/day was evaluated (see **Figure 1** for phase 3 design)
  - In PRISM-1 (165-301, NCT01819727), subjects were randomized 1:1 to titrate upward to a maintenance dose of pegvaliase 20 or 40 mg/day
  - PRISM-1 subjects could enroll into PRISM-2 (165-302, NCT01889862), which included an ongoing long-term extension that allowed pegvaliase dosing of 5–60 mg/day
- Subjects were instructed to maintain consistent protein intake from medical food and intact food, with increases allowed if blood Phe was <30 µmol/L
  - Participants recorded dietary intake fzor 3 consecutive days prior to each clinic visit
  - Dietary intakes were analyzed by dietitians using MetabolicPro® (Genetic Metabolic Dietitians International, Decatur, GA)
- Final study results are reported from the last study visit on February 5, 2019

Figure 1. Study design of PRISM-1 and PRISM-2



Subjects were asked to take tyrosine supplementation 3 times daily throughout both PRISM studies.
Subjects with <20% blood Phe reduction from pre-treatment baseline entered Part 4 (data cut: February 5, 2019).
PD: pharmacodynamics; PK: pharmacokinetics.

Results

Table 1. Baseline demographics and characteristics

	Total Population (N=285, unless otherwise indicated)
Age at enrollment, mean (SD), years	29.2 (9.0)
Female sex, n (%)	143 (50.2%)
White race, n (%)	278 (97.5%)
Weight, n=283	
Mean (SD), kg	80.2 (21.0)
Min, max	42, 139
Body mass index, n=281	
Mean (SD), kg/m^2	28.3 (6.7)
Min, max	17, 47
Dietary Phe intake, mg/day, n=270	
Mean (SD)	1696.2 (1182.8)
Median	1355.0
Dietary intact food intake, g/day, n=250	
Mean (SD)	38.5 (27.7)
Median	29.9
Receiving protein from medical food, n (%)	149 (57.1%)
>75% of protein intake from medical food, n (%)	**41 (15.7%)**
Blood Phe, µmol/L	
Mean (SD)	**1227.3 (379.3)**
Median	1201.0
Min, max	285, 2330
Duration of treatment, mean (SD), months	33.42 (21.63)

Exposure

- For the 285 subjects enrolled in the studies, the mean pegvaliase treatment duration was 33.42 (21.63) months; 80.4% had ≥6 months of pegvaliase treatment (≥12 months, 70.3%; ≥24 months, 63.5%; ≥36 months, 56.1%; ≥48 months, 39.5%)

Disposition

Table 2. Disposition summary

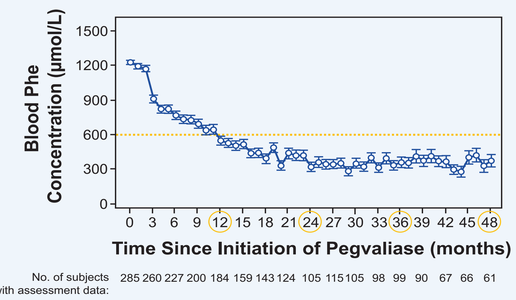
Discontinuations, n (%)	N=285
Reason for study drug discontinuation	
AE*	44 (41.1%)
Subject withdrawal	31 (29.0%)
Physician decision	11 (10.3%)
Lost to follow-up	9 (8.4%)
Protocol deviation	3 (2.8%)
Pregnancy	2 (1.9%)
Other	7 (6.5%)

*The most common AEs by preferred term leading to study drug discontinuation were anaphylactic reaction (n=9), arthralgia (n=9), and rash generalized (n=2). AE: adverse event.

Blood Phe

- Substantial and sustained reduction in blood Phe was observed (**Figure 2**). In the Total Population, mean (SD) blood Phe decreased from a pre-treatment baseline of 1227.3 (379.3) µmol/L to 372.6 (422.9) µmol/L at Month 48 (n=61)
  - This reduction was maintained throughout the follow-up period

Figure 2. Reductions in blood Phe levels over 48 months of follow-up

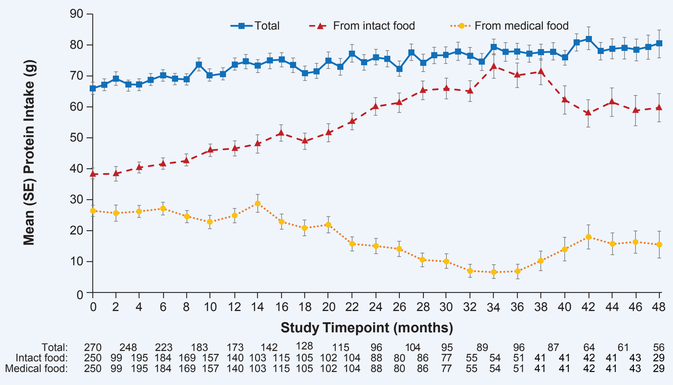


Sample size reflects participants with data available at timepoint and who have reached timepoint at data cut.
Error bars represent standard error (SE).

Dietary measures

- Mean (SD) total protein intake at baseline was 65.0 (32.0) g, and was relatively stable, with a change at Month 48 (n=49) of 7.1 (32.2) g (**Figure 3**)
  - At Month 48, the mean (SD) change from baseline in protein intake from intact food increased by 18.2 (34.7) g, whereas intake from medical food decreased by 6.6 (23.5) g (**Figure 3**)

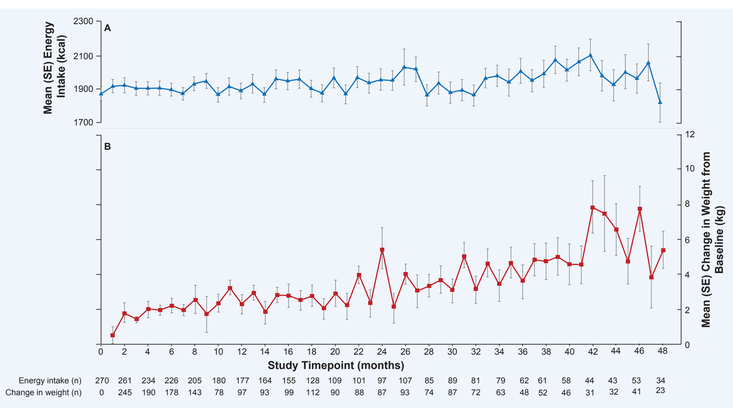
Figure 3. Protein intake over 48 months of follow-up



Analysis based on number of subjects with available data on each visit. SE: standard error.

- Energy intake increased over time, with a mean (SD) change from baseline at Month 48 of 130.2 (645.9) kcal (**Figure 4A**), which was associated with a mean (SD) increase in weight of 5.4 (5.2) kg (**Figure 4B**)

Figure 4. Energy intake (A) and change in weight (B) over 48 months of follow-up



Safety

- Most adverse events (AEs) were mild or moderate (99%) and resolved without dose interruption or reduction (97%)
- In the Total Population, the most common AEs were arthralgia (76.5%), injection site reaction (65.6%), headache (55.1%), and injection site erythema (50.9%) (**Table 3**)
  - 16 subjects had 25 acute systemic hypersensitivity reactions these events were externally adjudicated as being consistent with the clinical anaphylaxis criteria of the National Institute of Allergy and Infectious Diseases and the Food Allergy and Anaphylaxis Network (NIAID/FAAN)
  - None of the events were associated with drug-specific immunoglobulin E at or near the time of the event; all events resolved without sequelae

Table 3. Summary of most common adverse Events (incidence ≥30%) in the Total Population (N=285)

Adverse Event*	Incidence, n (%)	Event Rate per Person-Year (# of events)
Any AE	285 (100%)	22.87 (18,153)
Arthralgia	218 (76.5%)	1.74 (1,380)
Injection site reaction	187 (65.6%)	2.55 (2,022)
Headache	157 (55.1%)	1.33 (1,055)
Injection site erythema	145 (50.9%)	0.93 (737)
Nasopharyngitis	128 (44.9%)	0.45 (358)
Upper respiratory tract infection	115 (40.4%)	0.39 (308)
Rash	113 (39.6%)	0.54 (426)
Injection site bruising	108 (37.9%)	0.52 (410)
Nausea	101 (35.4%)	0.26 (209)
Injection site pruritus	100 (35.1%)	0.53 (423)
Pain in extremity	94 (33.0%)	0.27 (215)
Pruritus	94 (33.0%)	0.66 (526)
Back pain	92 (32.3%)	0.23 (180)
Urticaria	90 (31.6%)	0.84 (667)
Cough	89 (31.2%)	0.17 (133)
Vomiting	88 (30.9%)	0.24 (192)
Oropharyngeal pain	87 (30.5%)	0.19 (153)
Injection site pain	86 (30.2%)	0.37 (290)

Table includes AEs with onset after the initiation of study drug in the parent study to 30 days after the last dose administered across all studies in which the subject was enrolled.
*MedDRA preferred terms. AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities.

Conclusions

- Substantial and sustained reduction in blood Phe was observed even with increases in protein intake from intact food and decreases in medical food intake
- Due to the changes in nutritional needs during pegvaliase treatment, patients receiving pegvaliase require careful monitoring of protein and energy intake to ensure adequate nutrition
- Pegvaliase had a manageable safety profile for most subjects who continued on long-term treatment, with arthralgia and injection site reactions being the most common AEs

References

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Disclosures

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