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Dietary intakes and adverse events in pegvaliase-treated phenylketonuria adults who had low blood phenylalanine concentrations

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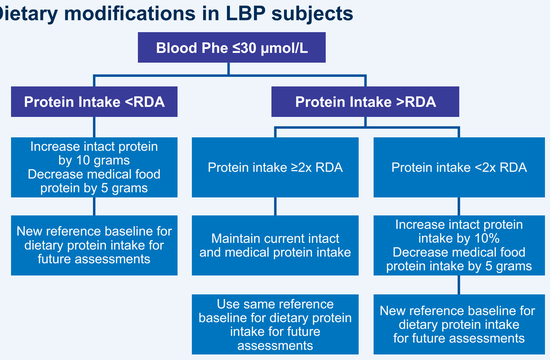
Background

- Phenylketonuria (PKU) is an inherited metabolic disorder caused by a deficiency in phenylalanine hydroxylase activity that results in phenylalanine (Phe) accumulation in the blood and tissues; high levels of Phe may be toxic in the brain[1]
- Pegvaliase (Palynziq®), PEGylated recombinant *Anabaena variabilis* phenylalanine ammonia lyase (PAL), is an injectable enzyme substitution therapy that converts Phe to trans-cinnamic acid and ammonia[2-4]
- Pegvaliase is approved for PKU patients with uncontrolled blood Phe concentrations >600 µmol/L on existing management in the US for adults at doses of up to 40 mg once daily[5] and by the European Commission for patients ≥16 years at doses of up to 60 mg once daily[6]
- The objective of this analysis was to characterize the long-term safety and efficacy of pegvaliase in clinical trial participants who experienced low blood Phe (LBP) events and describe the impact of the per protocol dietary modification made in LBP subjects

Methods

- Pegvaliase was administered by subcutaneous injection to adults with PKU in phase 2 (165-205, NCT01560286; PAL-003, NCT00924703) and phase 3 (PRISM-1 [165-301], NCT01819727; PRISM-2 [165-302], NCT01889862) studies using an induction, titration, and maintenance (ITM) dosing regimen with doses up to 60 mg/day
- In PRISM-1, subjects were randomized to receive pegvaliase doses of 20 or 40 mg/day that were continued into PRISM-2, which included a randomized discontinuation trial and an extension study, in which the dose of pegvaliase could be adjusted between 5–60 mg/day, based on efficacy and safety
- Subjects were instructed to maintain consistent dietary protein intake throughout the study (from medical food and natural intact protein sources). Modifications to dietary protein intake up to 2 times the US Recommended Dietary Allowance (RDA) were allowed if a subject experienced a LBP event, as shown in **Figure 1**
- Final study results are reported from the last study visit on February 5, 2019

Figure 1. Dietary modifications in LBP subjects



LBP was defined as ≥2 consecutive blood Phe levels <30 µmol/L, in which the start of the event is defined as the first blood Phe assessment with <30 µmol/L, and the end of the event is the day prior to the first blood Phe assessment ≥30 µmol/L. Total protein RDA for adults is 0.8 g/kg per day.

Results

- 285 subjects (**Table 1**) received pegvaliase treatment for mean (SD) duration of 33.4 (21.6) months, with median of 38.4 months
- 130 (45.6%) subjects experienced ≥1 event of LBP
  - 53 (18.6%) experienced 1 LBP event and 77 (27%) experienced >1 LBP event
  - Event rates were similar across all dose ranges (**Table 2**)

Table 1. Baseline characteristics

	LBP (N=130)	Non-LBP (N=155)
Age		
Mean (SD), years	29.7 (8.9)	28.7 (9.1)
Median (min, max), years	28 (16, 56)	27 (16, 55)
Sex		
Female, N (%)	65 (50.0%)	78 (50.3%)
Race		
White, N (%)	128 (98.5%)	150 (96.8%)
Ethnicity		
Non-Hispanic or Latino, N (%)	127 (97.7%)	150 (96.8%)
Baseline blood Phe		
Mean (SD), µmol/L	1239.7 (373.7)	1216.9 (385.6)
Median (min, max), µmol/L	1247 (510, 2229)	1171 (285, 2330)
Weight		
Mean (SD), kg	77.2 (19.6)	82.6 (21.8)
Median (min, max), kg	74 (42, 136)	80.4 (45, 139)
Body mass index		
Mean (SD), kg/m^2	27.4 (6.2)	29 (7.1)
Median (min, max), kg/m^2	26.9 (17, 47)	28 (17, 47)
Baseline total protein intake[a]		
Mean (SD), g/day	69.1 (30.8)	61.4 (32.6)
Median, g/day	70.3 (9, 181)	59.3 (4, 264)
Baseline intact protein intake[b]		
Mean (SD), g/day	40 (27.8)	37.4 (27.7)
Median, g/day	31 (5, 155)	29.3 (4, 156)
Baseline medical food protein intake[b]		
Mean (SD), g/day	29.9 (30.4)	23.5 (26.7)
Median (min, max), g/day	20 (0, 120)	13.3 (0, 108)
On a Phe-restricted diet[a]		
N (%)	16 (12.3%)	25 (16.1%)

[a]Subjects were considered on restricted diet if >75% of total protein intake was from medical food. Total protein intake was the sum of the protein from medical food and intact food. Protein intakes were calculated from taking the average of daily protein intake over 3 days prior to assessment point. [b]Data were only collected for subjects with parent study of Study 165-301. Baseline was defined as the last measurement prior to first dose of pegvaliase. SD, standard deviation.

- Total treatment duration with pegvaliase for subjects with LBP was a mean (SD) of 47.3 (12.8) months compared with 21.8 (20.7) months in subjects who did not have an LBP event (non-LBP) **(Table 2)**

Table 2. Pegvaliase treatment exposure and dose

	LBP (N=130)	Non-LBP (N=155)
Duration of treatment with pegvaliase		
Mean (SD), months	47.3 (12.8)	21.8 (20.7)
Average pegvaliase daily dose[a], mg/day		
Mean (SD)	29.9 (12.1)	28.3 (16.2)
Median	30.4	30.8
Min, Max	9, 61	3, 60
Pegvaliase dose at LBP event[b], number of events (%)		
0 – <20 mg/day	10 (3.5%)	N/A
20 – <40 mg/day	25 (8.8%)	N/A
40 – <60 mg/day	76 (26.7%)	N/A
≥60 mg/day	19 (6.7%)	N/A

[a]Average daily dose calculated by the total amount of study drug received/the total number of days dosed. [b]Dose at start of first event. Duration includes time from the first dose to last dose across all studies in which a subject was enrolled. Intervals of missing doses >28 days were excluded from the duration. N/A: not applicable.

- Early discontinuation and discontinuation due to an adverse event (AE) were more common in non-LBP subjects (**Table 3**)

Table 3. Subject disposition

	LBP (N=130)	Non-LBP (N=155)
Continuing study drug in ongoing studies[a], N (%)	121 (93.1%)	57 (36.8%)
Reason for early discontinuation[b], N (%):		
Adverse event	2 (1.5%)	42 (27.1%)
Lost to follow-up	2 (1.5%)	7 (4.5%)
Physician decision	0	11 (7.1%)
Pregnancy	1 (0.8%)	1 (0.6%)
Protocol deviation	1 (0.8%)	2 (1.3%)
Withdrawal by subject	3 (2.3%)	28 (18.1%)
Other	0	7 (4.5%)

[a]Phase 2 and 3 extension studies ongoing. [b]Percentage calculated based on the total number of subjects in LBP and non-LBP groups.

- LBP events were not associated with an increase in any adverse events (**Table 4**), with the exception of amino acid level decrease (MedDRA code mapping to hypophenylalaninemia) and alopecia, which was more commonly observed in LBP subjects vs. non-LBP subjects (21.5% of 130 LBP subjects and 5.2% of 155 non-LBP subjects)
  - Alopecia resolved in 84.8% of the subjects in the LBP group. For 69.0% of subjects experiencing alopecia, their symptoms resolved during the LBP event
  - No subjects discontinued pegvaliase due to alopecia

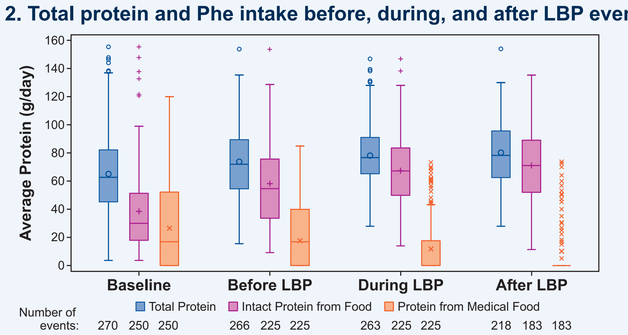
Table 4. AEs and safety profile of LBP and non-LBP subjects

Number of subjects with event (%) Number of events (event rate per person-year)	LBP (N=130)	Non-LBP (N=155)
Total treatment exposure, person-years[a]	181	281.2
AEs	125 (96.2%) 3639 (20.1)	155 (100.0%) 7052 (25.1)
AEs assessed by investigator as related to study drug	107 (82.3%) 1497 (8.3)	155 (100.0%) 4962 (17.7)
Serious AEs (SAEs)	10 (7.7%) 16 (0.1)	36 (23.2%) 46 (0.2)
SAEs assessed by investigator as related to study drug	2 (1.5%) 2 (0)	27 (17.4%) 33 (0.1)

[a]Subject incidence only.

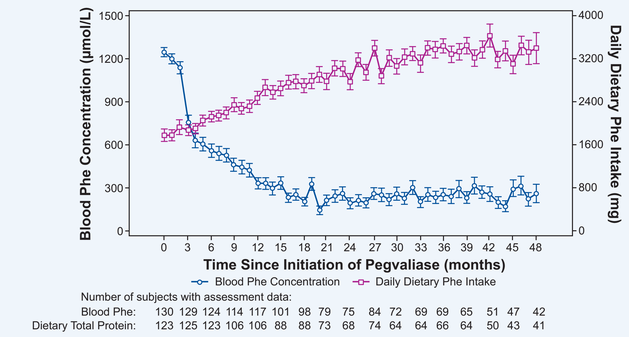
- Total dietary intake of protein and Phe increased in LBP subjects during and after LBP events (**Figure 2**)
- Mean (SD) total Phe intake in LBP subjects was 2564.2 (1278.8) mg/day before LBP events, but increased to 3025.9 (1120.4) mg/day during LBP events and 3242.3 (1190.2) mg/day after LBP events

Figure 2. Total protein and Phe intake before, during, and after LBP event



- Mean (SE) blood Phe in LBP subjects decreased from pre-treatment baseline to month 12 and remained stable through month 48 **(Figure 3)**
- Increase in daily dietary protein intake in LBP subjects was associated with reductions in blood Phe concentrations, while on pegvaliase treatment

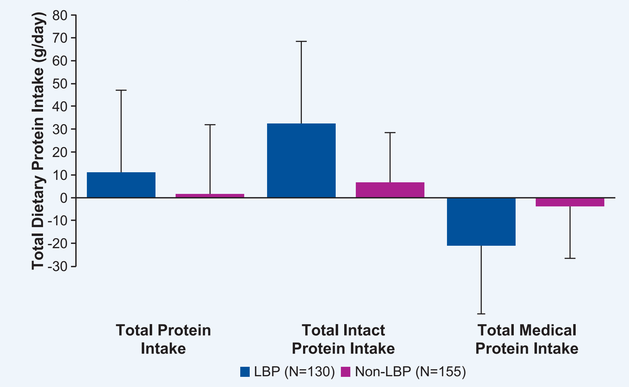
Figure 3. Mean (SE) blood Phe concentration and daily dietary total protein intake over time in LBP subjects



Sample size reflects participants with data available at time point and who reached timepoint at data cut. Error bars represent standard error. SE, standard error.

- Total protein intake and intact protein intake increased from baseline to last study visit in LBP subjects; mean (SD) total protein intake increased from baseline of 69.1 (30.8) to 80.2 (30.8) g/day and intact protein intake increased from 40.0 (27.8) to 72.4 (29.7) g/day (**Figure 4**)
- Mean (SD) total medical protein intake decreased from baseline of 29.9 (30.4) to 8.7 (18.9) g/day in LBP subjects. Total dietary protein intakes were similar from baseline to last study visit in non-LBP subjects

Figure 4. Change in total dietary protein intake from baseline to last study visit in LBP and non-LBP subjects



Conclusions

- LBP events in pegvaliase-treated subjects were observed at all doses
- LBP events were not associated with an increase in AEs, except for alopecia, which resolved in the majority of subjects, was manageable, and did not result in discontinuation of pegvaliase in any subjects
- Overall, discontinuation of pegvaliase due to AEs was lower in the LBP group
- Dietary intake of total protein, intact protein, and Phe increased in LBP subjects from baseline to during and after LBP events, allowing for a decreased protein intake from medical food
- While on treatment with pegvaliase, daily dietary protein intake increased over time in LBP subjects, while substantial and sustained reductions in blood Phe levels were observed
- Overall, LBP events appeared to be well tolerated, manageable, and allowed for greater dietary intake of intact protein and Phe in subjects treated with pegvaliase

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