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Safety and efficacy of pegvaliase in adolescents with phenylketonuria: Primary results from PEGASUS, a phase 3 open-label randomized controlled study

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Background

Phenylketonuria (PKU)

- PKU is an autosomal recessive disorder caused by deficiency of phenylalanine hydroxylase, resulting in accumulation of phenylalanine (Phe) in the blood and tissues[1]
  - High Phe levels in the brain are associated with neurological, neurocognitive, and psychological symptoms[1]
- Historically, PKU has been managed with medical nutrition therapy (MNT), including a Phe-restricted diet, low-protein foods, and supplements[1]
  - However, individuals with PKU are often unable to achieve and sustain guideline-recommended blood Phe levels of ≤360 µmol/L with MNT alone[2,3]
- Adherence to MNT and blood Phe recommendations worsens during adolescence, influenced by factors such as social pressures, increased independence, and greater responsibility for managing PKU[4,5]
  - Elevated Phe during adolescence may increase risk for neurocognitive symptoms and comorbid conditions like anxiety and depression[5]

MNT, medical nutrition therapy; Phe, phenylalanine; PKU, phenylketonuria

1. van Spronsen FJ et al. *Nat Rev Dis Primers*. 2021;7(1):36. **2.** Burton BK et al. *Mol Genet Metab*. 2024;141(1):108114. **3.** Rocha JC et al. *Nutrients*. 2023;15(18):3940. **4.** Jurecki ER et al. *Mol Genet Metab*. 2017;120(3):190–197. **5.** Burton BK et al. *Mol Genet Metab*. 2022;137(1-2):114–126.

Pegvaliase for the Treatment of PKU

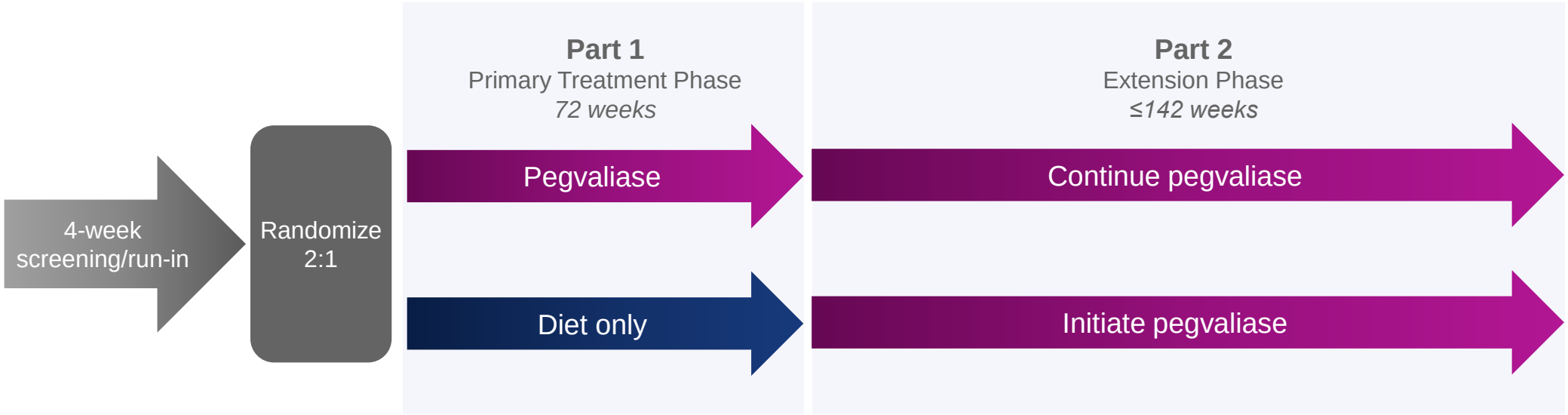
- Pegvaliase is a pegylated recombinant phenylalanine ammonia lyase that metabolizes Phe
- The safety and efficacy of pegvaliase as an enzyme substitution therapy for adults with PKU were demonstrated in the phase 3 PRISM clinical development program[1–3]
- Pegvaliase is approved in multiple geographic regions for the management of PKU in adults (aged ≥15, ≥16, or ≥18 years, depending on region) with blood Phe >600 µmol/L

The phase 3 PEGASUS study aims to evaluate the safety and efficacy of pegvaliase in adolescents (aged 12–17 years) with PKU and blood Phe >600 µmol/L

Phe, phenylalanine; PKU, phenylketonuria

1. Thomas J et al. *Mol Genet Metab*. 2018;124(1):27–38. **2.** Harding CO et al. *Mol Genet Metab*. 2018;124(1):20–26. **3.** Harding CO et al. *Mol Genet Metab Rep*. 2024;39:101084.

PEGASUS Study Design

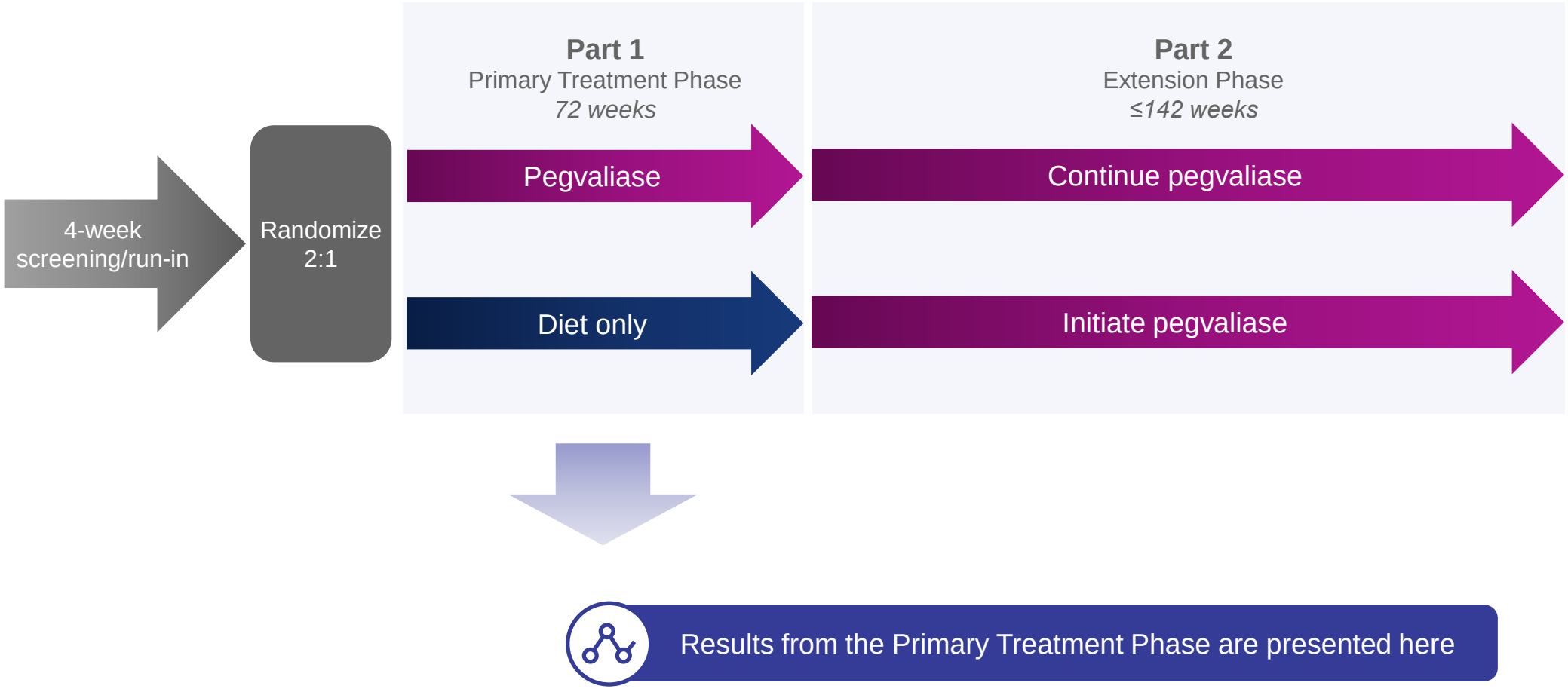


- Phase 3, multicenter, open-label, randomized controlled study *(NCT05270837)*
- Adolescents aged 12–17 (USA) or 12–15 (EU) years with PKU and blood Phe >600 µmol/L
- Pegvaliase induction/titration/maintenance dosing regimen (maximum 60 mg/day) approved for adults

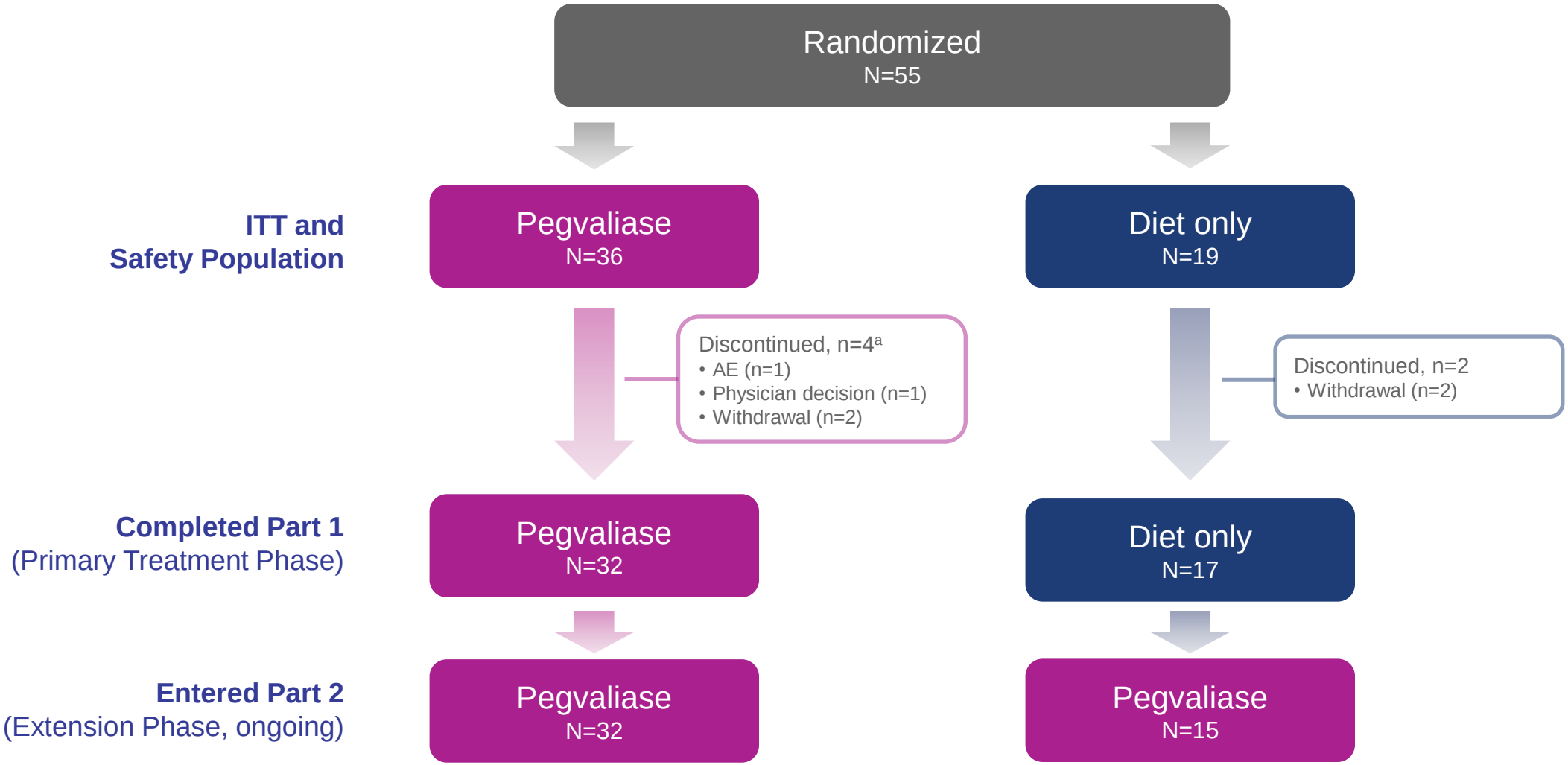
Primary endpoints	• Change from baseline in blood Phe after 72 weeks • Safety
Secondary endpoints	• To characterize total dietary protein intake in adolescent participants with PKU after pegvaliase treatment • Pharmacokinetics
Exploratory endpoints	• Change in neurocognitive outcomes and PKU symptoms and impact • Number (%) of participants in blood Phe target ranges of <600 µmol/L and <360 µmol/L

Phe, phenylalanine; PKU, phenylketonuria

PEGASUS Study Design



Participant Disposition



[a]1 additional participant discontinued treatment (due to an AE) but remained on study in Part 1
AE, adverse event; ITT, intent-to-treat

Baseline Demographics and Clinical Characteristics

	Pegvaliase (N=36)	Diet Only (N=19)	Total (N=55)
Age at baseline, years			
Mean (SD)	14.4 (1.27)	14.1 (1.29)	14.3 (1.27)
12–15	30 (83.3%)	17 (89.5%)	47 (85.5%)
16–17	6 (16.7%)	2 (10.5%)	8 (14.5%)
Gender			
Female	22 (61.1%)	11 (57.9%)	33 (60.0%)
Male	14 (38.9%)	8 (42.1%)	22 (40.0%)
Race			
White	30 (83.3%)	18 (94.7%)	48 (87.3%)
Body mass index, kg/m^2			
Mean (SD)	24.9 (5.43)	24.0 (6.33)	24.6 (5.71)
Blood Phe concentration, µmol/L			
Mean (SD)	1025.3 (254.05)	1028.6 (199.39)	1026.4 (234.70)
Median (min, max)	996.0 (635.3, 1554.7)	1051.0 (686.7, 1414.3)	1045.0 (635.3, 1554.7)
≤1000 µmol/L	18 (50.0%)	10 (52.6%)	28 (50.9%)
>1000 µmol/L	18 (50.0%)	9 (47.4%)	27 (49.1%)

Data are n (%), except where noted
max, maximum; min, minimum; Phe, phenylalanine; SD, standard deviation

Mean age:
14.3 years

Mean blood Phe:
1026.4 µmol/L

Blood Phe >1000 µmol/L:
49.1% of participants

Change from Baseline in Blood Phe Following 72 Weeks on Study

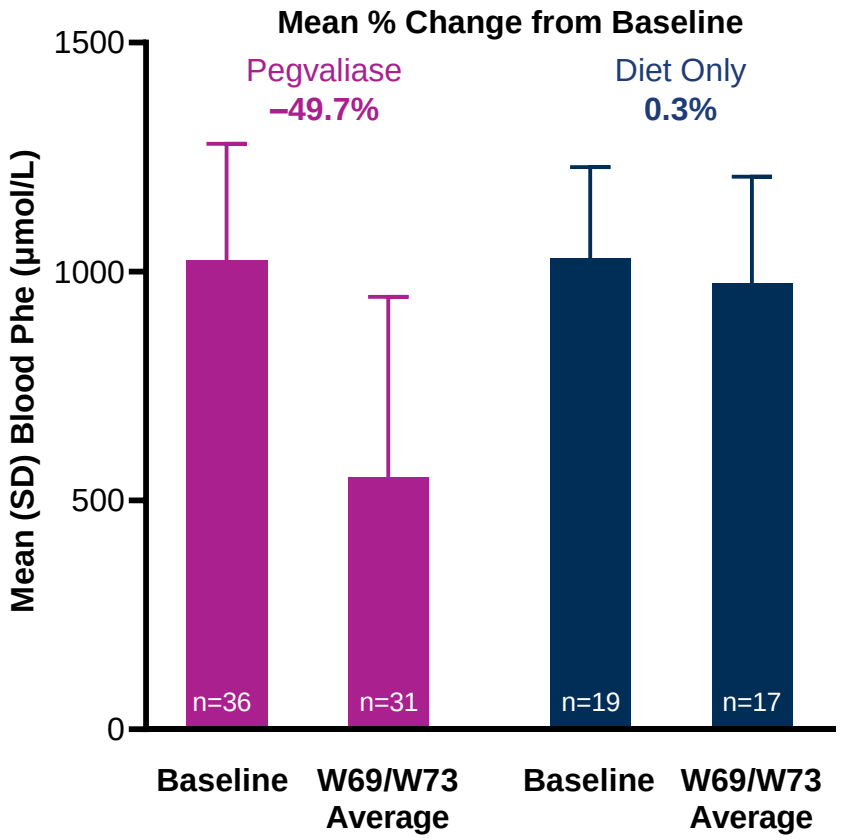
Primary Efficacy Endpoint

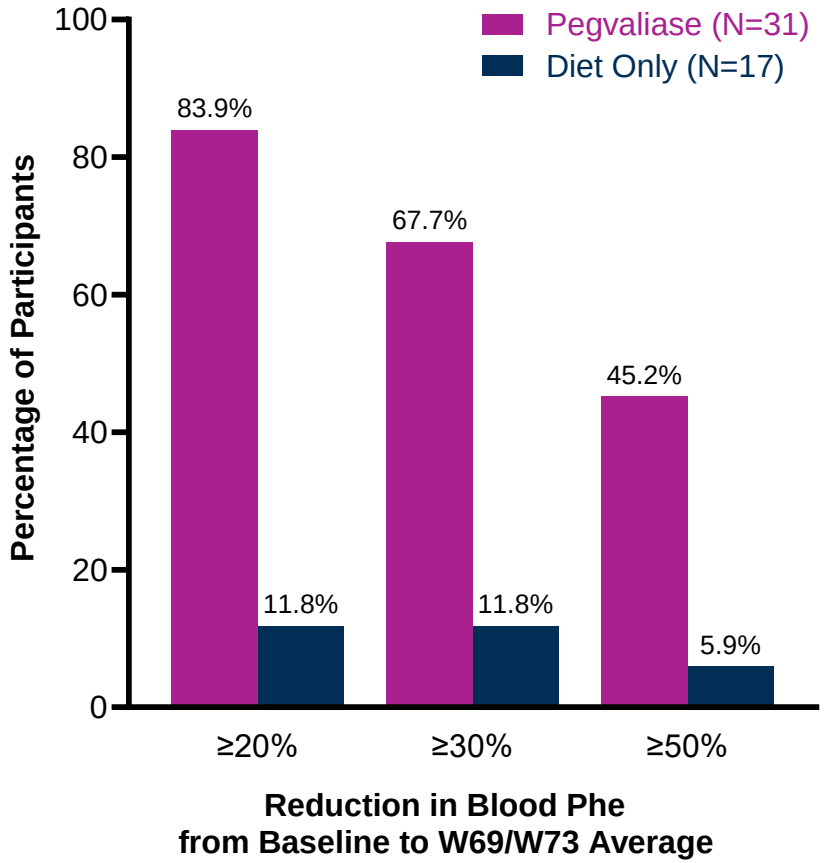
Treatment	N	Baseline Mean (SD), µmol/L	Average of Weeks 69 and 73 Mean (SD), µmol/L	Change from Baseline at Average of Weeks 69 and 73		Difference[a] in LS Mean (95% CI), µmol/L	*P* Value
				Mean (SD), µmol/L	LS Mean (95% CI), µmol/L		
Pegvaliase	36	1025.3 (254.05)	575.4 (388.45)	−449.9 (292.33)	−449.62 (−546.13, −353.11)	**−409.23 (−578.52, −239.94)**	**<0.0001**
Diet Only	19	1028.6 (199.39)	994.1 (263.09)	−34.4 (272.07)	−40.39 (−180.19, 99.41)		

Primary analysis method: ANCOVA using baseline blood Phe, randomization strata (baseline Phe ≤1000 µmol/L or >1000 µmol/L), and treatment group as covariates, with multiple imputation for missing data
[a]Difference calculated as Pegvaliase minus Diet Only
ANCOVA, analysis of covariance; CI, confidence interval; LS, least-squares; Phe, phenylalanine; SD, standard deviation

Pegvaliase-treated participants demonstrated a statistically significant reduction in blood Phe concentration after 72 weeks compared with the diet-only arm (p<0.0001)

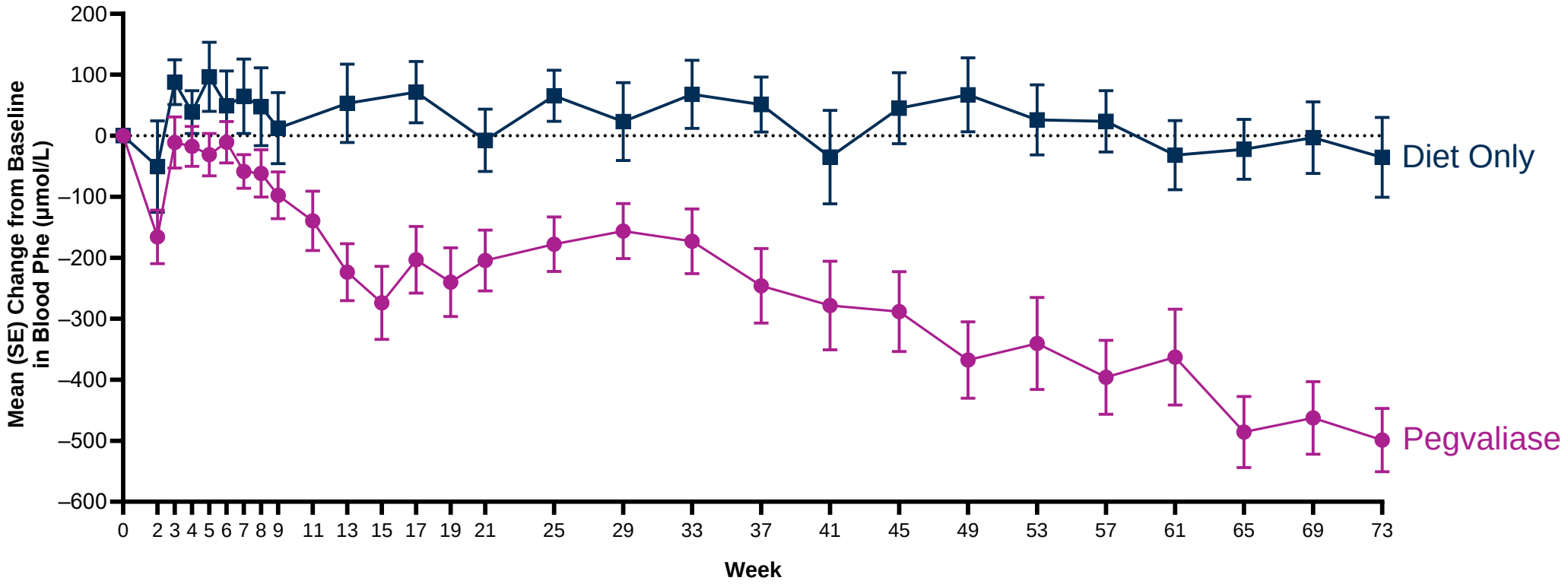
Change from Baseline in Blood Phe Following 72 Weeks on Study





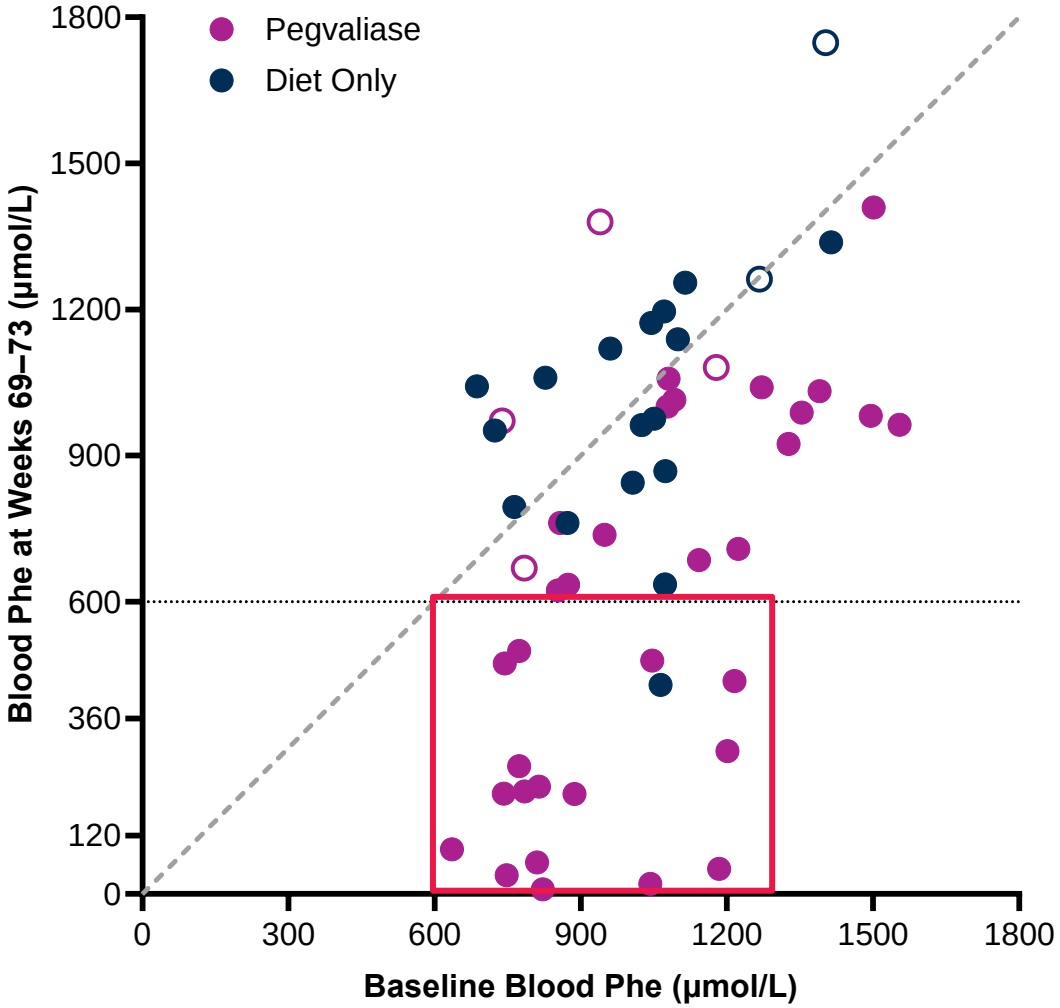
Phe, phenylalanine; W, week

Change from Baseline in Blood Phe Concentration over Time



Phe, phenylalanine; SE, standard error

Change from Baseline in Blood Phe Following 72 Weeks on Study



Blood Phe Levels in Pegvaliase Arm at Average of Weeks 69 and 73[a] (N=31)	n (%)
≤600 µmol/L	16 (51.6%)
≤360 µmol/L	12 (38.7%)
≤120 µmol/L	6 (19.4%)

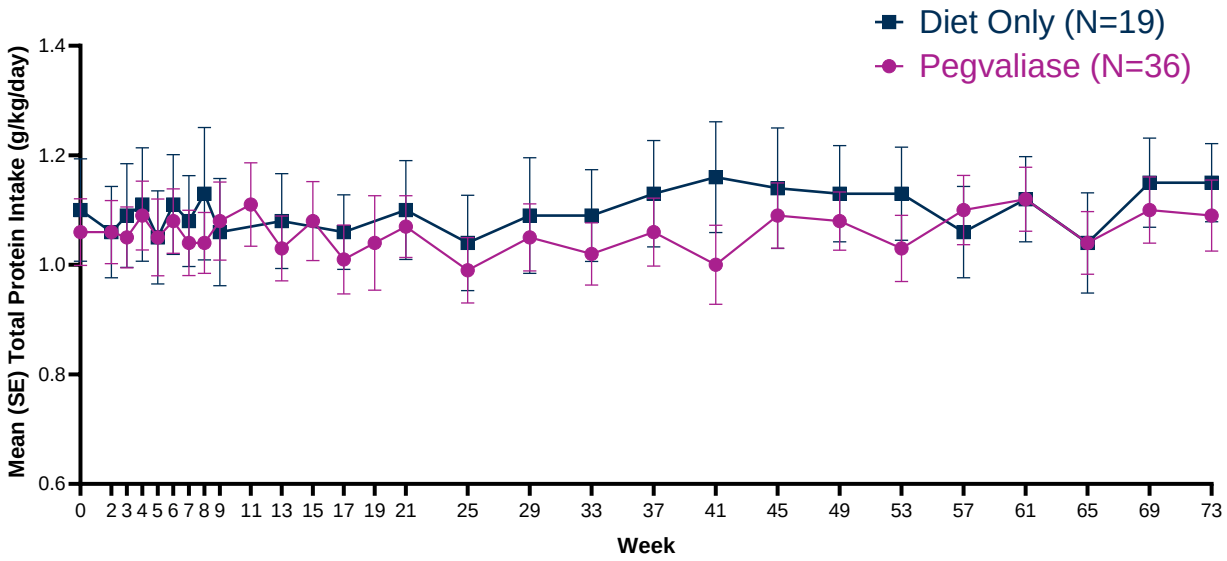
[a]LOCF imputation

Open circles indicate LOCF
LOCF, last observation carried forward; Phe, phenylalanine

Dietary Protein Intake

Secondary Efficacy Endpoint

Total protein intake was relatively stable over time in both groups



Mean	Pegvaliase	Diet Only
Baseline	1.06 g/kg/day	1.10 g/kg/day
Average of weeks 69 and 73[a]	1.09 g/kg/day	1.15 g/kg/day
Change from baseline[a]	0.00 g/kg/day	0.01 g/kg/day
Percent change from baseline[a]	**+6.7%**	**+10.7%**

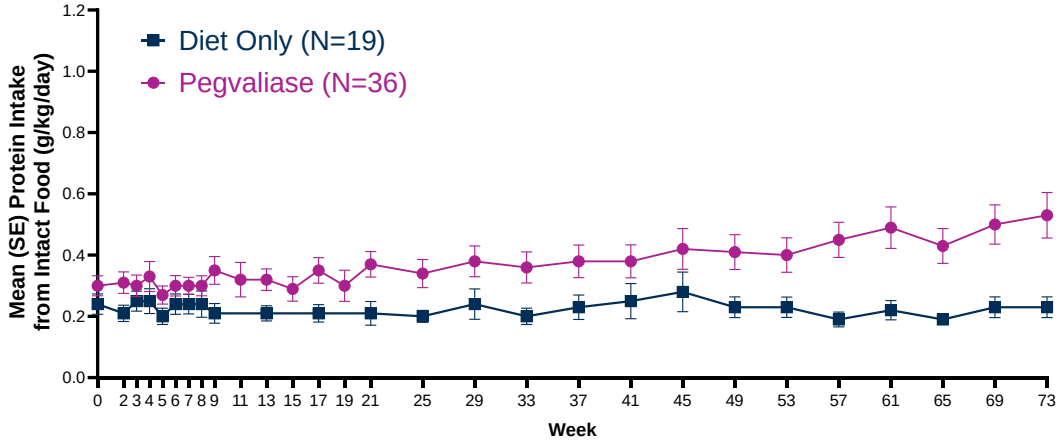
[a]Calculated for participants with data at weeks 69 and 73 (pegvaliase, n=31; diet only, n=17)

Based on observed data. Missing data not imputed
SE, standard error

Dietary Protein Intake

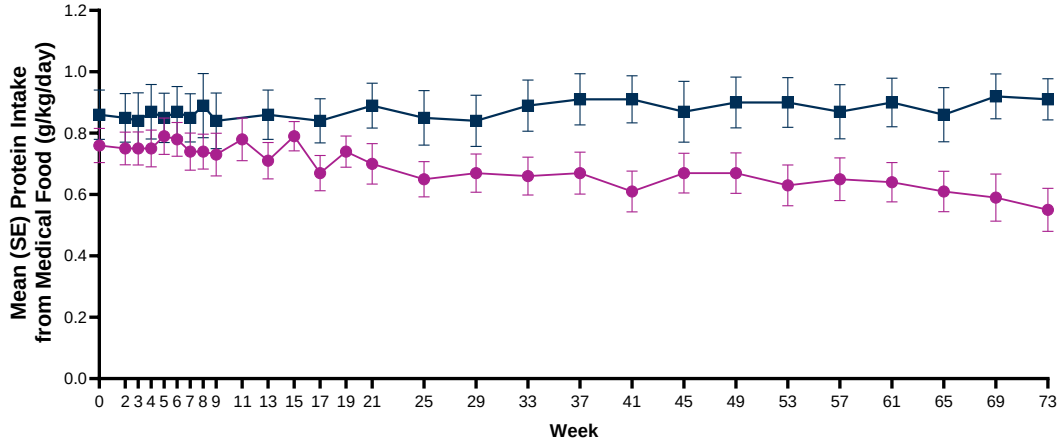
Protein intake from intact food increased and intake from medical food decreased among pegvaliase-treated participants

Intact Food



Mean	Pegvaliase	Diet Only
Baseline	0.30 g/kg/day	0.24 g/kg/day
Average of weeks 69 and 73[a]	0.52 g/kg/day	0.23 g/kg/day
Change from baseline[a]	+0.21 g/kg/day	–0.02 g/kg/day
Percent change from baseline[a]	**+107%**	**–10%**

Medical Food



Mean	Pegvaliase	Diet Only
Baseline	0.76 g/kg/day	0.86 g/kg/day
Average of weeks 69 and 73[a]	0.57 g/kg/day	0.92 g/kg/day
Change from baseline[a]	–0.20 g/kg/day	0.03 g/kg/day
Percent change from baseline[a]	**–29%**	**+22%**

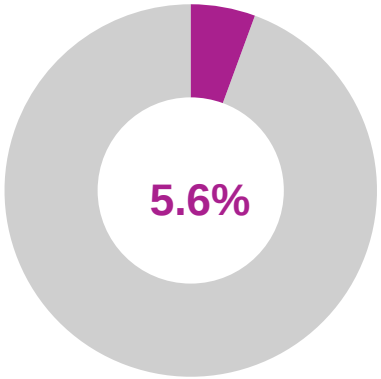
Based on observed data. Missing data not imputed
SE, standard error

[a]Calculated for participants with data at weeks 69 and 73 (pegvaliase, n=31; diet only, n=17)

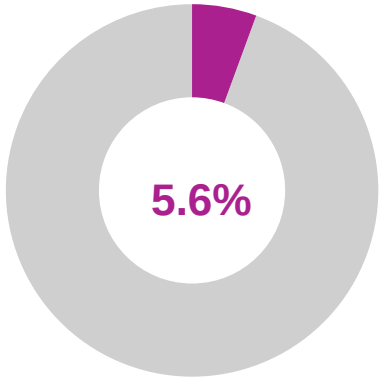
Part 1 Safety Summary – Pegvaliase Arm

All participants in the pegvaliase group (n=36) experienced ≥1 AE

SAEs (anaphylactic reaction)

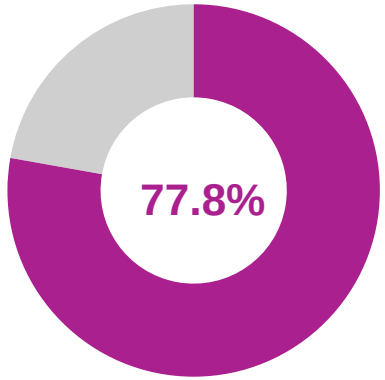


AEs leading to study drug discontinuation[a]

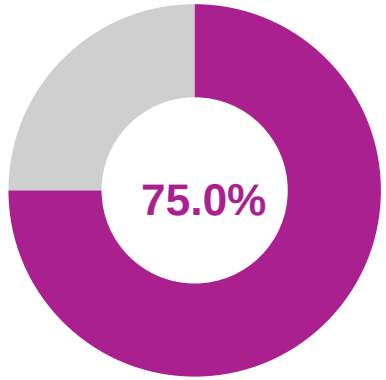


Common AEs

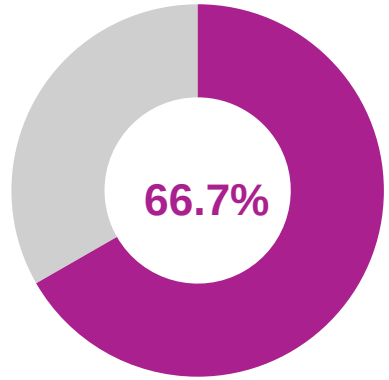
Injection site erythema



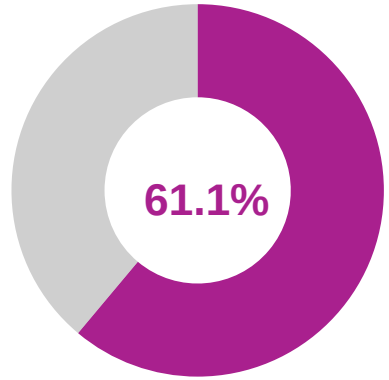
Arthralgia



Headache



Injection site pain



[a]1 of 2 participants with AEs leading to study drug discontinuation also discontinued the study
AE, adverse event; SAE, serious adverse event

AEs Occurring During the Primary Treatment Phase

Participants with AE, n (%)	**Pegvaliase** (N=36)	**Diet Only** (N=19)
Any AE	**36 (100%)**	**17 (89.5%)**
AEs assessed by investigator as related to study drug	36 (100%)	0
AEs leading to dose reduction	9 (25.0%)	0
AEs leading to dose interruption	19 (52.8%)	0
AEs leading to study drug discontinuation	2 (5.6%)	0
AEs leading to study discontinuation	1 (2.8%)	0
Any SAE	**2 (5.6%)**	**1 (5.3%)**
Most common (≥30% in pegvaliase arm) AEs by Preferred Term		
Injection site erythema	28 (77.8%)	0
Arthralgia	27 (75.0%)	1 (5.3%)
Headache	24 (66.7%)	8 (42.1%)
Injection site pain	22 (61.1%)	0
Injection site pruritus	19 (52.8%)	0
Injection site swelling	17 (47.2%)	0
Upper respiratory tract infection	15 (41.7%)	7 (36.8%)
Pyrexia	15 (41.7%)	1 (5.3%)
Injection site induration	12 (33.3%)	0
Dizziness	11 (30.6%)	2 (10.5%)
Nausea	11 (30.6%)	3 (15.8%)

AE, adverse event; SAE, serious adverse event

Conclusions

Pegvaliase treatment for 72 weeks in adolescents with PKU

Significant reduction in mean blood Phe

~100% ↑ in protein from intact food
~30% ↓ in protein from medical food
Total protein intake unchanged

Safety profile consistent with that seen in adults[1]

Results from the Primary Treatment Phase of PEGASUS support the safety and efficacy of pegvaliase for the control of blood Phe in adolescents with PKU

The ongoing Extension Phase will characterize long-term pegvaliase treatment in this population

Phe, phenylalanine; PKU, phenylketonuria

1. Thomas J et al. *Mol Genet Metab.* 2018;124(1):27–38.

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Back-up

Pegvaliase Exposure in the Primary Treatment Phase

- Overall mean (SD) daily dose was 21.4 (9.60) mg
- Overall mean (SD) duration of treatment was 460.8 (150.73) days
- During the Primary Treatment Phase, 34 participants titrated up to ≥20 to <40 mg/day, 26 participants titrated up to ≥40 to <60 mg/day, and 14 participants titrated up to ≥60 mg/day

SD, standard deviation

Adherence to Pegvaliase in the Primary Treatment Phase

The rate of study drug use was calculated as the total amount of study drug used (as reported by participants in workbooks) divided by the total amount of study drug dispensed

	Pegvaliase (N=36)
Dosage usage	
Mean (SD), %	97.0 (15.02)
Median (min, max), %	98.6 (23, 122)
≥80% usage, n (%)	34 (94.4%)

max, maximum; min, minimum; SD, standard deviation