Interim analysis of PALLADIUM: a phase 4 study to evaluate a rapid drug desensitization protocol for adults receiving pegvaliase

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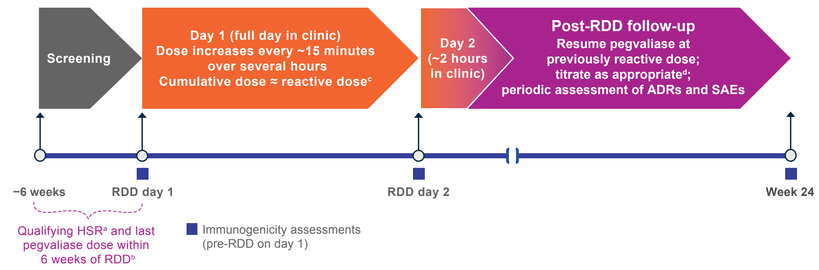
Background

- Phenylketonuria (PKU) is an autosomal recessive genetic condition caused by deficiency of phenylalanine hydroxylase, resulting in phenylalanine (Phe) accumulation in the blood and brain that leads to neurotoxic effects in the absence of lifelong management[1]
- Pegvaliase is a pegylated subcutaneous enzyme substitution therapy that reduces blood Phe levels in individuals with PKU through a genetically modified phenylalanine ammonia lyase enzyme
- Antidrug antibody responses to pegvaliase can result in hypersensitivity reactions (HSRs)[2,3]
- Rapid drug desensitization (RDD) is an established clinical procedure intended to allow safe readministration of therapeutics that previously resulted in HSRs[4]
- PALLADIUM (NCT06780332) is an ongoing phase 4 study to evaluate whether an RDD protocol will improve tolerability and treatment persistence in adults with PKU who have experienced HSRs to pegvaliase
- The objective of this analysis is to summarize interim findings, including the qualifying HSRs, safety, and tolerability, of participants who have enrolled in and completed the RDD protocol

Methods

- Eligible participants are adults (aged ≥18 years) with PKU in the US who are receiving pegvaliase and have experienced HSRs leading to treatment interruption, reduction of dose/dosing frequency, or inability to dose escalate
- Participants undergo a 2-day RDD procedure (**Figure 1**):
  - Premedication with an oral H1 antihistamine (eg, diphenhydramine), oral H2 antihistamine (eg, famotidine), and steroids (eg, prednisone) was to be administered the night prior to RDD and the morning of RDD, approximately 1 hour prior to starting the procedure
  - On day 1, pegvaliase is administered via subcutaneous injection in gradually increasing doses over several hours to a cumulative dose equal to the reactive dose at which the qualifying HSR occurred
  - On day 2, pegvaliase is administered in clinic at the previously reactive dose with 1 hour of post-dose observation
- Following RDD, participants continue pegvaliase with modification as determined by the treating clinician
- Post-RDD adverse drug reactions (ADRs), serious adverse events (SAEs), and pegvaliase dosing information are collected through 24 weeks of follow-up
- Immunogenicity is also being assessed and will be reported upon study completion

Figure 1. PALLADIUM study design



[a]Qualifying HSR was defined as an HSR leading to treatment interruption or reduction of dose/dosing frequency that led to study eligibility. [b]Preferred for RDD to occur within 3 weeks of qualifying HSR and/or last pegvaliase dose. [c]Reactive dose was defined as the pegvaliase dose at which the qualifying HSR occurred. [d]Per the United States Prescribing Information recommended dosing schedule guided by the judgment of the treating clinician

Results

Participant characteristics

- As of January 9, 2026, 7 participants had undergone RDD with pegvaliase
- Mean age was 31.9 years, and 5 participants were female (**Table 1**)
- Qualifying HSRs of enrolled participants included grade 2 events of injection site reaction (ISR) (n=3), emesis (n=1), and arthralgia (n=1), and grades 3 and 4 events of anaphylaxis (n=2)
- The reactive dose of pegvaliase ranged from 2.5 mg weekly to alternating 40 and 60 mg daily

Table 1. Baseline participant characteristics

Pre-RDD characteristic	Participants (N=7)
Age at enrollment, years	
Mean (SD)	31.9 (8.43)
Gender, n (%)	
Female	5 (71.4)
Race, n (%)	
White	6 (85.7)
Average daily prescribed dose[a], mg/day	
Median (range)	10.0 (0.4, 46.9)
Mean (SD)	13.0 (14.85)
Time since pegvaliase initiation, weeks	
Median (range)	69.4 (5.7, 134.9)
Mean (SD)	59.5 (46.02)

[a]Average daily prescribed dose is based on limited dosing information captured prior to RDD and may not be indicative of patients' entire dosing history

RDD and post-RDD follow-up

- All participants successfully completed and tolerated RDD on days 1 and 2, with the majority (4/7) having no reactions (**Table 2**)
  - 3 participants experienced grade 1 or 2 ISRs, and 1 participant experienced grade 1 arthralgia

Table 2. Summary of participants who underwent RDD

	Pre-RDD history				RDD outcome		Post-RDD outcome[b]		
ID	Summary of HSRs[a]	Time since pegvaliase initiation	Qualifying HSR and management	Reactive dose	Cumulative dose = reactive dose	RDD day 1/ day 2 reactions	Highest dose during F/U	F/U status	Summary of ADRs
1	Grade 2 ISRs, grade 2 joint stiffness, grade 2 inguinal lymphadenopathy	16 mo	Grade 2 ISR preventing upward titration	5 mg 2x/week	Yes	Grade 2 ISR (day 1)	20 mg 2x/week	Completed	• Grades 1 and 2 ISRs • Grade 3 anaphylaxis on day 86, treated with prednisone – Treatment briefly interrupted; ADR subsequently resolved
2	Grade 2 ISRs	18 mo	Grade 3 anaphylaxis treated with IV steroids, diphenhydramine; dose interruption	40 mg daily	Yes	None	60 mg daily	Completed	• None reported
3	Grade 2 ISRs, grade 2 joint swelling, grade 3 bronchospasm	5 mo	Grade 2 ISR preventing upward titration	2.5 mg 1x/week	Yes	None	20 mg daily	Completed	• Grade 1 ISRs and grade 1 arthritis, all treated with acetaminophen PRN – No dose changes; all ADRs resolved
4	Grade 2 ISRs, grade 2 arthralgia, grade 2 rash	1 mo	Grade 2 ISR treated with steroids; dose interruption	2.5 mg 1x/week	Yes	Grade 1 ISR (day 1)/ Grade 1 ISR (day 2)	20 mg daily	Ongoing	• Grade 1 ISRs – No dose changes; all ISRs resolved • Grade 1 joint pain, treated with ibuprofen – Dose temporarily reduced; ADR subsequently resolved
5	Recurrent grade 2 emesis	31 mo	Grade 2 emesis treated with ondansetron; dose interruption	60 mg 3x/week alternating with 40 mg 4x/week	Yes[c]	None	60 mg daily	Ongoing	• None reported; prescribed ondansetron for PRN use
6	Grade 2 ISRs, grade 2 arthralgia	21 mo	Grade 2 arthralgia treated with prednisone, naproxen; dose reduction	20 mg daily	Yes	Grade 1 ISR (day 1)/ Grade 1 arthralgia (day 2)	20 mg daily	Ongoing	• Grade 1 ISRs, grades 1 and 2 arthralgia (treated with naproxen; 1 grade 2 episode treated with prednisone), grade 2 foot pain, grade 2 coccyx pain (treated with naproxen) – No dose changes; all ADRs resolved
7	Grade 1 ISRs, grade 2 arthralgia	5 mo	Grade 4 anaphylaxis treated with diphenhydramine, dexamethasone; dose interruption	10 mg daily	Yes	None	20 mg 6x/week	Ongoing	• Grade 1 ISR – No dose change; resolved

Interim results for Participants 1 through 5 were presented at the International Congress of Inborn Errors of Metabolism (ICIEM) 2025 Meeting
[a]Excluding qualifying HSR. [b]As of January 9, 2026. [c]60 mg

- Follow-up time post RDD ranged from 13.6 to 27.9 weeks; 3 participants have completed the study
- Post RDD:
  - 3 of 7 participants successfully continued pegvaliase with grade 1 or 2 reactions
  - 1 participant had a short-term dose interruption of pegvaliase due to grade 3 anaphylaxis but later reached a tolerable maintenance dose
  - 1 participant had a temporary dose reduction due to grade 1 joint pain but subsequently increased to a tolerable maintenance dose
  - 2 participants reported no ADRs post RDD
- All participants continued taking premedications as instructed by the treating physician
- 6 participants were able to increase their dose beyond their reactive dose, and no participants discontinued from the study

Conclusions

- The RDD protocol was well tolerated, and participants were able to continue treatment with pegvaliase through data cut-off
- Preliminary results suggest RDD may improve the tolerability of pegvaliase in participants with PKU experiencing HSRs
  - Final results, including immunogenicity assessments, will be reported after study completion
- The RDD protocol presents a practical method for the mitigation of HSRs, allowing patients to optimize treatment with pegvaliase safely

References

1. van Spronsen FJ, et al. *Nat Rev Dis Primers.* 2021;7(1):36. **2.** Gupta S, et al. *EBioMedicine.* 2018;37:366–373. **3.** Hausmann O, et al. *Mol Genet Metab.* 2019;128(1-2):84–91. **4.** del Carmen Sancho M, et al. *Chem Immunol Allergy.* 2012;97:217–233.

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Disclosures

KL, NRMS, MBH, SJ, and CD are employees of BioMarin Pharmaceutical Inc. RB, TRL, and LA are employees of Uncommon Cures, which was paid to conduct the study on behalf of BioMarin Pharmaceutical Inc. SO has received consulting and speaker fees from, and has participated as a clinical trial investigator for, BioMarin Pharmaceutical Inc. JK has participated as a clinical trial investigator for BioMarin Pharmaceutical Inc. JR has received speaker fees from BioMarin Pharmaceutical Inc. AK and HB have no conflicts of interest to declare.

Abbreviations

ADR, adverse drug reaction; **F/U**, follow-up; **HSR**, hypersensitivity reaction; **ID**, participant identifier; **ISR**, injection site reaction; **IV**, intravenous; **mo**, month(s); **Phe**, phenylalanine; **PKU**, phenylketonuria; **PRN**, as needed; **RDD**, rapid drug desensitization; **SAE**, serious adverse event; **SD**, standard deviation.

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