PALLADIUM: A phase 4 study to evaluate a rapid drug desensitization protocol for adults with phenylketonuria experiencing hypersensitivity reactions to pegvaliase

132

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Background

- Pegvaliase (PALYNZIQ®) is a subcutaneous enzyme substitution therapy that uses bacterially derived phenylalanine ammonia lyase (PAL) to reduce blood phenylalanine levels in adults with phenylketonuria (PKU)
- In clinical trials, all participants developed antidrug antibody (ADA) responses to pegvaliase,[1,2] which can manifest clinically as immune-mediated adverse drug reactions (ADRs)/hypersensitivity reactions (HSRs) that may impact dosing and treatment discontinuations
- Rapid drug desensitization (RDD) is an established clinical procedure intended to allow safe re-administration of therapeutics that previously resulted in HSRs[3]

Eligibility

- PALLADIUM will enroll ~10 participants (≥18 years old) with PKU in the United States who are receiving pegvaliase and have experienced HSRs leading to treatment interruption, reduction of dose/dosing frequency, or inability to dose escalate
- Participants not using antihistamine premedication at the time of the qualifying reactive HSR are ineligible

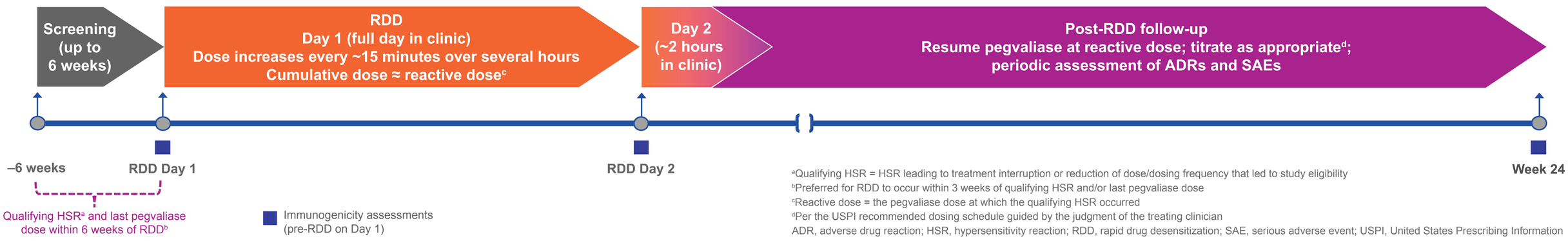
RDD Protocol

- **Day 1:** Pegvaliase will be administered in gradually increasing doses over several hours such that the cumulative dose received is approximately equal to the reactive dose
  - Doses are administered at stepwise intervals (~15 minutes apart), with dose increases no more than 2-fold and administration ≤2 mL volume per step
  - Vital signs are monitored with each step change and for 2 hours after the last step
- **Day 2:** Pegvaliase will be administered in clinic at the previously reactive dose, with 1 hour of post-dose observation
- **Post-RDD:** Participants will continue pegvaliase per the recommended dosing schedule, with modification(s) allowed as judged by the treating clinician

Assessments

- Immunogenicity assessments include polyethylene glycol (PEG), immunoglobulin (Ig)G and IgM, PAL IgG and IgM, and complement (C)3/C4
- Serious adverse events (SAEs) comprise any untoward medical occurrence temporally associated with pegvaliase administration that results in death or permanent disability/ incapacity, is life-threatening or a congenital anomaly, requires/prolongs hospitalization, or may require treatment to prevent one of these outcomes
- ADRs are any AE assessed as causally related to pegvaliase administration

Study Design



[a]Qualifying HSR = 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 = the pegvaliase dose at which the qualifying HSR occurred
[d]Per the USPI recommended dosing schedule guided by the judgment of the treating clinician
ADR, adverse drug reaction; HSR, hypersensitivity reaction; RDD, rapid drug desensitization; SAE, serious adverse event; USPI, United States Prescribing Information

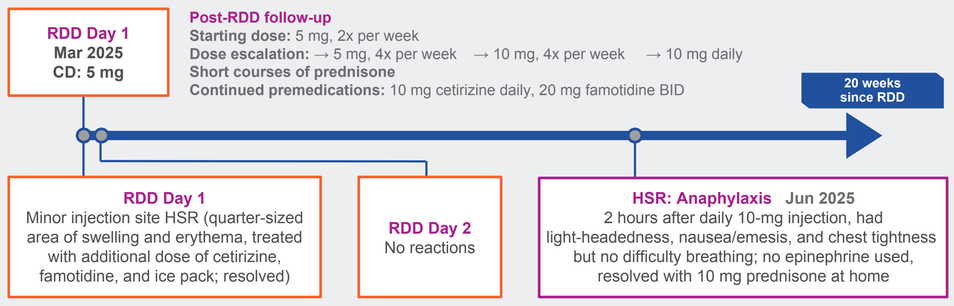
PALLADIUM is an ongoing phase 4 study (NCT06780332) evaluating whether rapid drug desensitization to pegvaliase will improve tolerability and treatment persistence in adults with phenylketonuria who have experienced hypersensitivity reactions to pegvaliase.

As of July 31, 2025, 5 participants have completed rapid drug desensitization to pegvaliase, and preliminary results suggest improved tolerability to pegvaliase. Final results, including immunogenicity assessments, will be reported once the PALLADIUM trial is completed.

Case Details

Participant 1

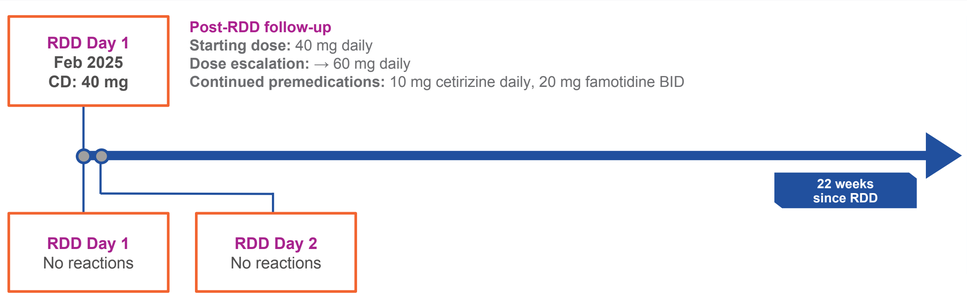
- **Relevant medical history:** Allergies: seasonal, tree pollen, amoxicillin
- **Summary of HSRs prior to RDD:** Joint stiffness (treated with ibuprofen), inguinal lymphadenopathy, recurrent redness and swelling at injection sites on the abdomen (ranging from the size of the palm to half the abdomen)
- **Duration on pegvaliase prior to qualifying HSR:** 1 year, 3 months
- **Qualifying HSR:** Recurrent injection site HSR (Grade 2) preventing upward titration
- **Reactive dose:** 5 mg, 2x per week



- Continued pegvaliase dosing with mild injection site HSRs (Grade 1/2)
- Resumed pegvaliase 10-mg dose 1 week after anaphylaxis event and resumed daily doses within 2 weeks
- Received 2 x 20-mg doses but returned to 10 mg due to low blood phenylalanine levels

Participant 2

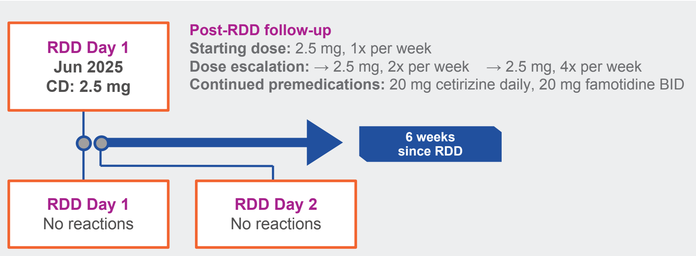
- **Relevant medical history:** N/A
- **Summary of HSRs prior to RDD:** Injection site HSR (localized injection site HSRs of induration and erythema, 5–7 cm in diameter)
- **Duration on pegvaliase prior to qualifying HSR:** 1 year, 5 months
- **Qualifying HSR:** Anaphylaxis (Grade 3; tachycardia, wheezing, facial flushing, hoarse voice), treated with IV steroids and diphenhydramine; dose interrupted
- **Reactive dose:** 40 mg daily



- Continued pegvaliase dosing post RDD, with no SAEs/ADRs noted

Participant 3

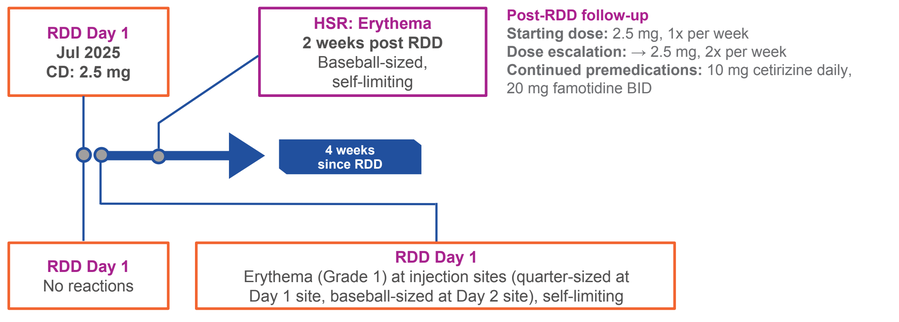
- **Relevant medical history:** Asthma, seasonal allergies, eczema
- **Summary of HSRs prior to RDD:** Consistent injection site HSRs (treated with acetaminophen), bronchospasm (treated with antihistamines and medrol dose pack), joint swelling (treated with acetaminophen)
- **Duration on pegvaliase prior to qualifying HSR:** 4 months
- **Qualifying HSR:** Injection site HSR (Grade 2) preventing upward titration
- **Reactive dose:** 2.5 mg, 1x per week



- Mild injection site HSRs (Grade 1; smaller than prior to RDD) since RDD

Participant 4

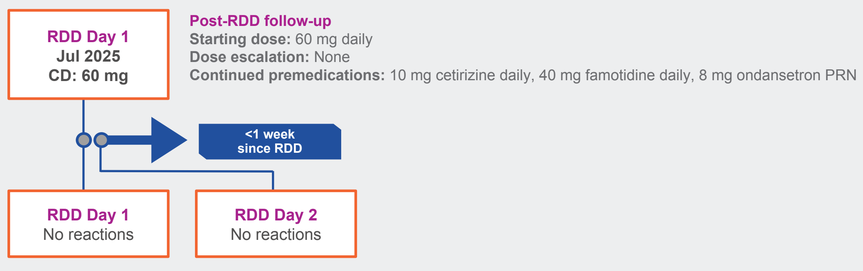
- **Relevant medical history:** Asthma
- **Summary of HSRs prior to RDD:** Injection site HSRs (treated with steroids, acetaminophen, diphenhydramine), arthralgia (treated with acetaminophen, ibuprofen), rash (treated with steroids)
- **Duration on pegvaliase prior to qualifying HSR:** 2.5 weeks
- **Qualifying HSR:** Injection site HSR (Grade 2) after injection into thigh; developed redness, swelling, itching, and sunburn-like pain from groin to knee; treated with steroids; symptoms resolved 2 days later; dose interrupted
- **Reactive dose:** 2.5 mg, 1x per week



- Continued pegvaliase dosing, with mild erythema noted at injection sites, no pain, not interfering with activities of daily living

Participant 5

- **Relevant medical history:** Acne, azithromycin allergy
- **Summary of HSRs prior to RDD:** Recurrent episodes of emesis with dose escalation to 60 mg (treated with ondansetron)
- **Duration on pegvaliase prior to qualifying HSR:** 2 years, 7 months
- **Qualifying HSR:** Emesis (Grade 2) treated with ondansetron; dose interrupted
- **Reactive dose:** 60 mg, 3x per week alternating with 40 mg, 4x per week



- No SAEs/ADRs since RDD

References

1. Gupta S et al. *EBioMedicine.* 2018;37:366–373. **2.** Hausmann O et al. *Mol Genet Metab.* 2019;128(1–2):84–91.
3. del Carmen Sancho M et al. *Chem Immunol Allergy.* 2012;97:217–233.

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Disclosures

Kyle Lamprecht: Employee and shareholder of BioMarin Pharmaceutical Inc.

Abbreviations

ADD, attention-deficit disorder; **ADR**, adverse drug reaction; **ADHD**, attention-deficit/hyperactivity disorder; **ASD**, autism spectrum disorder; **BID**, twice daily; **CD**, cumulative dose; **CI**, confidence interval; **HSR**, hypersensitivity reaction; **ICD**, International Classification of Diseases; **IV**, intravenous; **N/A**, not applicable; **OCD**, obsessive-compulsive disorder; **PAH**, phenylalanine hydroxylase; **Phe**, phenylalanine; **PKU**, phenylketonuria; **PRN**, as needed; **RDD**, rapid drug desensitization; **SAE**, serious adverse event.

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