Adolescent immune response determines safety and efficacy of pegvaliase

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Background

- Treatment with pegvaliase among adolescents aged 12–17 years with phenylketonuria and blood Phe concentration >600 umol/L was evaluated in PEGASUS, an ongoing Phase 3, open-label, randomized control trial
- PEGASUS demonstrated that:
  - Pegvaliase delivers clinically meaningful and statistically significant reductions in blood Phe in adolescents vs diet alone
  - Pegvaliase led to a ~50% mean reduction in blood Phe at Week 72 (LS mean difference vs diet: -409 µmol/L [p<0.0001])
  - Pegvaliase supports meaningful dietary normalization – adolescents could increase intact protein intake and decrease reliance on medical food
  - Pegvaliase has a safety profile in adolescents consistent with that seen in adults

Methods

- Here we present the immunogenicity analysis, based on an interim data cut of the on-going study, for 36 adolescents that were randomized to receive pegvaliase (active arm) and followed for a minimum of 72 weeks on treatment
- In addition, examples of individual profiles highlight how the I/T/M dosing approach is well-suited to account for individual immune responses to pegvaliase

Comprehensive immunogenicity assessment

- Immunogenicity in adolescents was evaluated by routinely measuring antibodies to pegvaliase, components of pegvaliase (phenylalanine ammonia lyase [PAL] and polyethylene glycol [PEG]), and characterizing the attributes of those antibodies (ex. isotype)

Anti-PAL IgM & Anti-PEG IgM	• Efficient activator of complement cascade • Low-affinity, high-avidity
Anti-PAL IgG & Anti-PEG IgG	• Isotype most often associated with immune memory • Less efficient at complement activation
Anti-pegvaliase Ab (TAb)	• 'Total' anti-drug antibodies • Detects anti-pegvaliase IgM, IgG, or IgA antibodies
Neutralizing Ab (NAb)	• Interference with PAL enzymatic activity (assessed ex-vivo)
Anti-pegvaliase IgE	• Mediates mast cell and basophil degranulation • Generally high affinity, small amount can mediate large reaction
Complement C3	• Activated by Antigen-Ab ICs (Classical Pathway) • Can lead to Type III hypersensitivity via anaphylatoxin release • Mediates clearance of drug through complement receptors

Results

- Pegvaliase induces a sustained immune response in adolescents with early IgM and transient anti-PEG responses giving way to persistent IgG and NAb
- There is variability in each patient's immunologic experience while on pegvaliase **(Figures 1 and 2, and Table 1)**
  - Adolescents with the highest antibody titers (including NAbs) required higher pegvaliase doses to achieve similar blood Phe reductions than those with lower titers
  - Complement levels do not reliably predict the onset of efficacy (see C3 in Participant B below)
  - Hypersensitivity adverse events (HAEs) generally occurred more frequently in patients with higher antibody titers (Participant B vs Participant A in Table 1); however, both high and low titer quartiles included individuals with and without HAEs. Titers were not predictive of HAE onset, frequency or severity
  - Anti-pegvaliase IgE was not detected in adolescents who experienced anaphylaxis per NIAID/FAAN criteria. HAEs were consistent with Type III hypersensitivity[3]
  - These findings support individualized dosing and monitoring strategies, the I/T/M dosing approach, for pegvaliase in adolescent patients

Conclusions

- These analyses and profiles demonstrate that pegvaliase induces a sustained immune response in adolescents, similar to adults[1], with early IgM and transient anti-PEG responses giving way to persistent anti-PAL IgG and NAb
- HAEs are most frequent during early treatment **(Table 1)** and are linked to complement activation, but antibody titers alone do not predict hypersensitivity risk
- No immunogenicity analyte fully predicts efficacy or safety
- As with adults, adolescents benefit from personalized management through the I/T/M dosing regimen which accounted for variations in immune response timing and magnitude[1,2]

References

1. Gupta S et al. *EBioMedicine.* 2018;37:366-373. **2.** Aryal M et al. *Mol Genet Metab.* 2021;134(3):235-242. **3.** Hausmann O et al. *Mol Genet Metab.* 2019;128(1-2):84-91.

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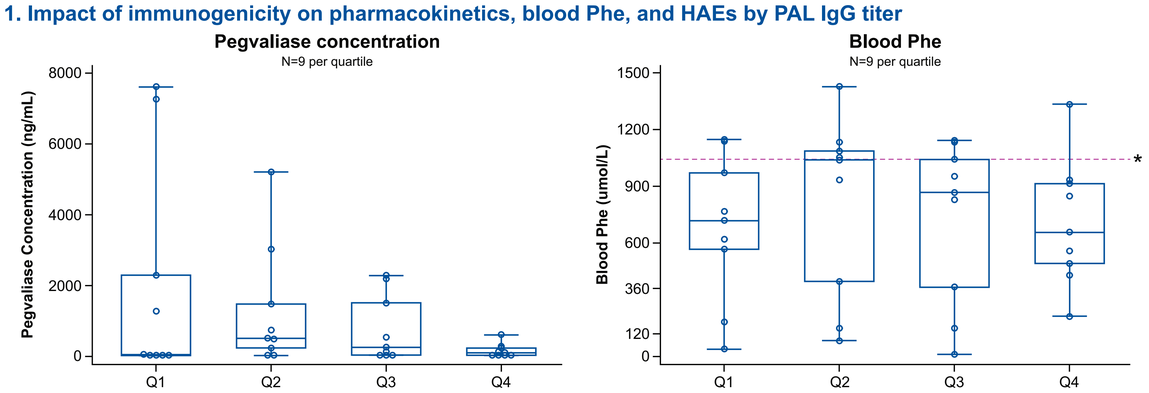
Disclosures

MBH, K. Lau, PC, RB, LL, K. Lindstrom, and SG are employees and shareholders of BioMarin Pharmaceutical Inc. KMC and SJ are employees and shareholders of BioMarin UK Ltd.

Figure 1. Impact of immunogenicity on pharmacokinetics, blood Phe, and HAEs by PAL IgG titer



	Q1	Q2	Q3	Q4
Pegvaliase concentration (mean):	2066	1306	781	165
Mean daily dose (mg):	17	39	53	47
Blood Phe (mean):	683	812	721	709
Mean daily dose (mg):	17	39	53	47
Adverse events (mean):	8	4	9	16
Mean daily dose (mg):	17	39	53	47

Q1 Lowest Titers; Q4 Highest Titers. HAE, hypersensitivity adverse event.

*Baseline Phe is 1025 umol/L (N=36)

Table 1. Hypersensitivity adverse event profiles

	Hypersensitivity[a] AEs (HAEs)			
Participant	Total HAEs	Grade 1	Grade 2	Details
A	1	0	1	Day 39: Arthralgia
B	11	8	3	Days 11-12, 22-24, 37, 75, 376: Arthralgia Day 42: Erythema
C	5	3	2	Day 10, 358: Pyrexia Days 12, 66, 336: Arthralgia
D	5	0	5	Days 54-59: Arthralgia/Joint Pain
E	6	4	2	Days 89, 463 Arthralgia, Day 102 Rash, Day 307 Erythema

[a]Hypersensitivity AEs for PEGASUS were identified using a modified Hypersensitivity Standardized MedRA Query (SMQ) which included additional preferred terms (arthralgia, arthritis, eye inflammation, eye irritation, eye pain, joint stiffness, joint swelling, polyarthritis, pyrexia and vision blurred).

Figure 2. Participant profiles