Safety of sepiapterin and pegvaliase for the treatment of phenylketonuria (PKU): A simulated treatment comparison (STC)

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Background

PKU is an autosomal recessive inborn error of metabolism characterized by deficiency of the enzyme, phenylalanine hydroxylase.[1]

This deficiency results in the accumulation of phenylalanine (Phe) in the blood which can lead to neurological and cognitive impairment.[1]

Approved therapies for reducing blood Phe levels include sepiapterin, a once-daily, oral treatment, and pegvaliase, a subcutaneous injection administered daily.

Sepiapterin, a natural precursor of intracellular BH_4, has been shown to cross the blood-brain barrier, thereby increasing BH_4 levels. It is approved for treatment of HPA in PKU patients, for adult and pediatric patients >= 1month of age, for patients that are responsive to the treatment and in conjunction with phe restricted diet.[2,3,4,5]

Pegvaliase, an enzyme substitution therapy requiring dose titration at initiation, [6,7] is approved for adults with PKU experiencing high blood Phe levels on existing management. Immune reactions are a concern; all patients are prescribed auto-injectable epinephrine.

Safety profiles differ between these therapies; the two most common adverse events (AEs) are: sepiapterin–diarrhea (7.7%), headache (6.5%);[8] pegvaliase–arthralgia (75.9%), injection site reactions (63.6%)[9]

Immune reactions are prominent in pegvaliase-treated patients. It has a black box warning and is available only under a restricted program (Risk Evaluation and Mitigation Strategy).[7]

Comparative safety data between sepiapterin vs. pegvaliase are lacking.

Objective

This simulated treatment comparison (STC) explored the safety of sepiapterin relative to pegvaliase among individuals with PKU.

Methods

Overall approach

Data source
- A systematic literature review (SLR; conducted in December 2024)[10] identified safety data from sepiapterin and pegvaliase clinical trials

Analysis
- AEs were analyzed descriptively for those occurring in one or both treatments, and statistically for those occurring with both treatments.

Comparisons
- Based on study design characteristics, the most appropriate comparisons were APHENITY[11] vs PRISM[12] and APHENITY vs the PAL trials[13] (PAL-002, PAL-004, PAL-003,165-205 combined; **Figure 1**,**Table 1**).

References

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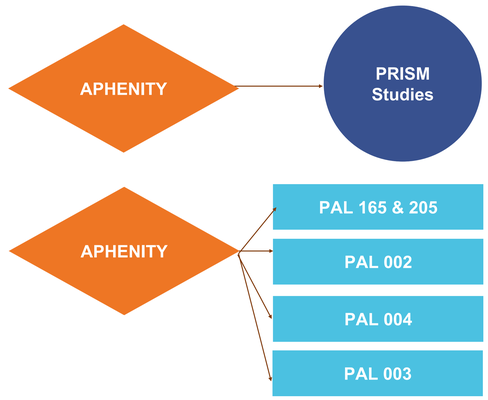
Methods (cont'd)

Figure 1: STC pairwise comparisons



Descriptive analysis

- For pegvaliase trials, event rate was calculated as total number of events divided by person-years of exposure
- For sepiapterin, event rate was calculated using individual patient data
- See **Supplementary methods** for AE definitions

Simulated treatment comparison

- AEs which occurred with both treatments were included in the STC; AEs with a high incidence rate (IR) in one drug but low event rates in the comparator were excluded.
- Risk (IR, 95% confidence interval [CI]) of AEs occurring with sepiapterin vs pegvaliase was compared (see **Supplementary methods** for additional methodology details).

Table 1: Differences between sepiapterin and pegvaliase trial designs

Treatment	Sepiapterin	Pegvaliase	
Trial	**APHENITY[10]**	**PRISM[11]**	**PAL-trials[12]**
Study design	*Two-part, phase 3 trial* *Part 1:* open-label, sepiapterin-responsiveness assessment *Part 2:* randomized, double-blind, placebo-controlled, forced-dose-escalation period	*PRISM 1:* Randomized, open-label, parallel-group, phase 3 study *PRISM 2:* four-part phase 3 clinical trial *Study 165-304:* OLE	*165-205, PAL-002, PAL-004:* Phase 2, open-label, dose-finding studies *PAL-003:* Long-term extension of phase 2, open-label dose-finding study
Sample size	*Part 1:* 157 | *Part 2:* 110	*PRISM 1:* 261 *PRISM 2:* 203 | *OLE:* 30	*165-205:* 24, *PAL-002:* 40 *PAL-004:* 16 | *PAL-003:* 68
Study duration	*Part 1:* 14-days *Part 2:* 6-weeks *OLE:* Up to 4 years	*PRISM 1:* 36 weeks *PRISM 2:* 302 weeks *OLE:* ~106 weeks	*165-205:* 24 weeks *PAL-002, PAL-004:* 16 weeks *PAL-003:* 240 weeks *Longest possible:* 264 weeks
Route of administration	Oral powder	Subcutaneous injection	Subcutaneous injection
Age requirements	No age restriction	Minimum age ≥18 years	Minimum age ≥16 years
Baseline Phe requirements	≥360 µmol/L on current therapy and from average of 3 most recent levels	>600 µmol/L at screening and from average over past 6 months	>600 µmol/L at screening and from average over past 6 months to 3 years
Baseline Phe levels	740.7 (349.6) µmol/L	1232.7 (386.4) µmol/L	1302.4 (351.5) µmol/L

Abbreviations: OLE, open-label extension; Phe, phenylalanine; wks, weeks

Results

Systematic literature review

- Nine trials were identified (17 publications): two examined sepiapterin and seven examined pegvaliase.
- Trials with appropriate comparisons based on study design characteristics were selected for analysis (**Figure 1**,**Table 1**).

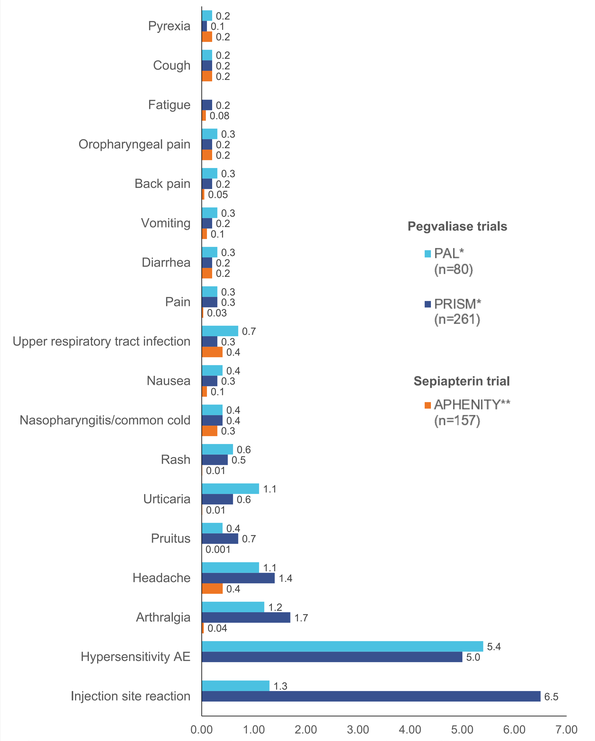
Descriptive analysis

- Injection-site reactions and hypersensitivity events were the most common AEs reported in the pegvaliase trials (**Figure 2**).
  - Neither were observed in the APHENITY trial as sepiapterin is taken as an oral powder mixed with liquids or soft foods.
- Headaches and upper respiratory tract infections were the most common AEs reported in the APHENITY sepiapterin trial (**Figure 2**).
- In general, higher total events can be observed in the pegvaliase trials compared to the sepiapterin trial.

Statistical analysis

- In the APHENITY/PRISM comparison, sepiapterin had significantly lower ($p<0.05$) overall AE risk compared to pegvaliase, and significantly lower risk of nausea and upper respiratory tract infection (**Figure 3**).
- Similar results were seen with the APHENITY/PAL comparison.
- All other comparisons had a non-significant difference (**see Supplementary results**).

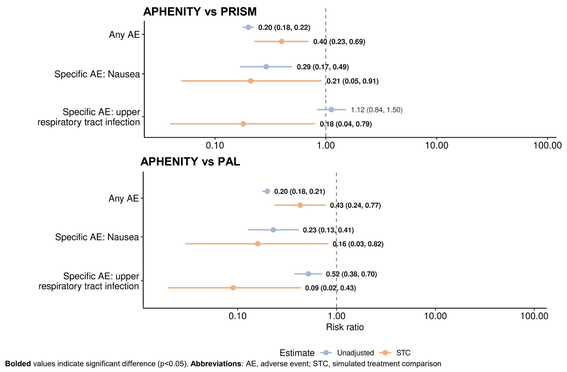
Figure 2: Descriptive analysis – AE rates in APHENITY, PRISM, and PAL trials (events/person-year)



*Event rate was calculated as total number of events divided by person-years of exposure; **Event rate was calculated using individual patient data. **Abbreviations**: AE, adverse event

Results (cont'd)

Figure 3: STC – statistically significant results in adjusted comparisons (sepiapterin with lower AE risk than pegvaliase)



Bolded values indicate significant difference ($p<0.05$). **Abbreviations**: AE, adverse event; STC, simulated treatment comparison

Discussion

- This STC compared the probability of AEs occurring with sepiapterin vs pegvaliase.
- Study design differences precluded anchored indirect treatment comparisons.
- For a number of AEs observed with relative frequency and specific to pegvaliase (e.g. injection site reactions and hypersensitivity), a comparison was not possible, given that there were no events observed for sepiapterin. These can be considered a net risk for pegvaliase vs. sepiapterin.
- Subsequent to the SLR, data from the sepiapterin AMPLIPHY trial became available.[14] Incidence of AEs for sepiapterin in AMPLIPHY was comparable to APHENITY and similarly, headaches and upper respiratory tract infections were the most common AEs (injection site reactions were not observed).

Strengths include:

- The STC approach accommodates continuous covariates, can be helpful when overlap between patient characteristics is limited, and avoids the effective-sample-size loss seen with the reweighting method.

Limitations include:

- Heterogeneity in trial characteristics: age restriction and blood Phe levels differed, resulting in very little overlap in baseline characteristics.
- PRISM included both randomized placebo-controlled and single-arm (pegvaliase-treated) induction, titration, and maintenance phases. As AEs mainly occurred during the single-arm phases of the study, it is important to take this into account when examining safety outcomes as examining safety outcomes after randomization would likely introduce bias across the analyses.[15,16]

CONCLUSIONS

- ***Findings from this analysis highlight that sepiapterin exhibited a significantly more favorable safety profile than pegvaliase.***
- Injection site reactions, hypersensitivity, and arthralgia are prominent in pegvaliase-treated patients. Immune reactions are a concern; all patients treated with pegvaliase are prescribed with auto-injectable epinephrine.
- Other safety-related factors including route of administration should be considered.
- Study findings represent the best available AE analysis given data limitations and methodological challenges in the evidence base.

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