Modelling intelligence quotient (IQ) changes relative to blood Phe levels in individuals with phenylketonuria (PKU) treated with sepiapterin and sapropterin dihydrochloride

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1. Objectives

- There is a well-established association between blood phenylalanine (Phe) levels and cognitive outcomes in individuals with phenylketonuria (PKU).[1,2]
- The general goal of PKU treatment is to maintain blood Phe levels below a target level (≤360 µmol/L across all ages according to American guidelines;[3] <360 µmol/L among infants and children, <600 µmol/L among adolescents and adults according to European guidelines).[1] The justification for maintaining low blood Phe levels is to reduce the severity of symptoms.
- Treatments for PKU, including sapropterin dihydrochloride and sepiapterin (recently approved in countries that include the United States and European Union, but not currently approved in the United Kingdom), have been shown to lower blood Phe levels; thus, these are expected to mitigate the adverse cognitive impact of PKU.[4,5]

Objective: This study aims to quantitatively synthesize existing data to characterize the overall relationship between PKU treatment, blood Phe levels, and intelligence quotient (IQ).

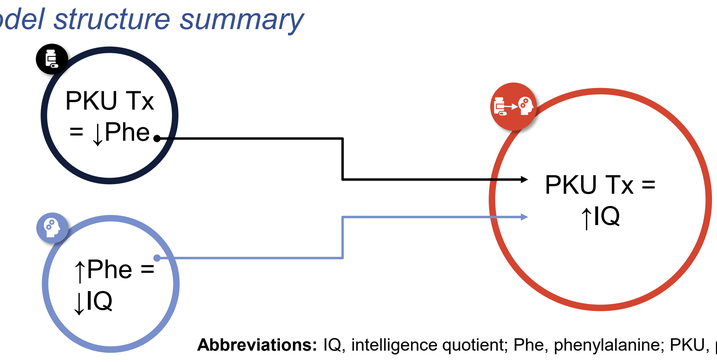
2. Methods

- A model was developed assuming baseline characteristics from the sepiapterin pivotal APHENITY trial, and estimated treatment-specific changes to blood Phe, and resulting impact on IQ (**Figure 1**).
- Model inputs for the sepiapterin versus sapropterin Phe-level comparison were adopted from an indirect treatment comparison (ITC) of controlled clinical trials (sepiapterin, n=73; sapropterin, n=186) that quantitatively estimated the relative treatment effect between the two treatments.

Outcomes were modelled, conditional on the following factors:

1. **Baseline age** — Age ≤6 years is defined as a "critical period," associated with a more pronounced relationship between Phe and IQ in published estimates, relative to individuals aged >6 years
2. **Baseline Phe**
3. **Temporal relationship being considered** — i.e. Concurrent IQ and Phe vs. historical IQ and current Phe
4. **Threshold for "low IQ"** — 70 vs. 85 points

Figure 1. *Model structure summary*



Abbreviations: IQ, intelligence quotient; Phe, phenylalanine; PKU, phenylketonuria; Tx, treatment

Methods: Data inputs

PKU treatments and Phe:

Sepiapterin and sapropterin Phe comparison data were taken from the PKU-002, PKU-003, PKU-006, PKU-016, SPARK, and APHENITY clinical trials and a resulting ITC.[6]

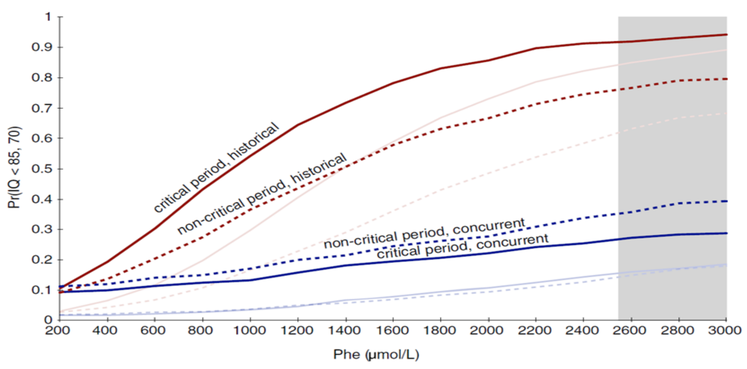
- Sepiapterin and sapropterin data were identified through a systematic literature review (SLR) and multi-level network meta-regression (ML-NMR).[6]
- Individual patient data for sepiapterin were available from the APHENITY trial.
- Mean estimates relative to placebo for change in Phe were -161.4 µmol/L for sapropterin and -382.6 µmol/L for sepiapterin, resulting in a mean difference in reduction (95% credible interval) for **sepiapterin vs. sapropterin of -221.1 (-269.4, -170.2) µmol/L**.[6]

Phe levels and IQ:

Blood Phe and IQ data inputs were extracted from two meta-analyses that quantified changes in IQ relative to blood Phe.[7,8]

- The probability of low IQ (<85 and <70) was predicted using meta-estimates of the Phe-IQ relationship.
- Both concurrent and historical findings were incorporated as inputs in the model:
  - ➢ **Concurrent** is Phe measured within six weeks prior to IQ
  - ➢ **Historical** is Phe measured more than 12 months prior to IQ.

Figure 2. *Phe levels and probability of low IQ*[7]

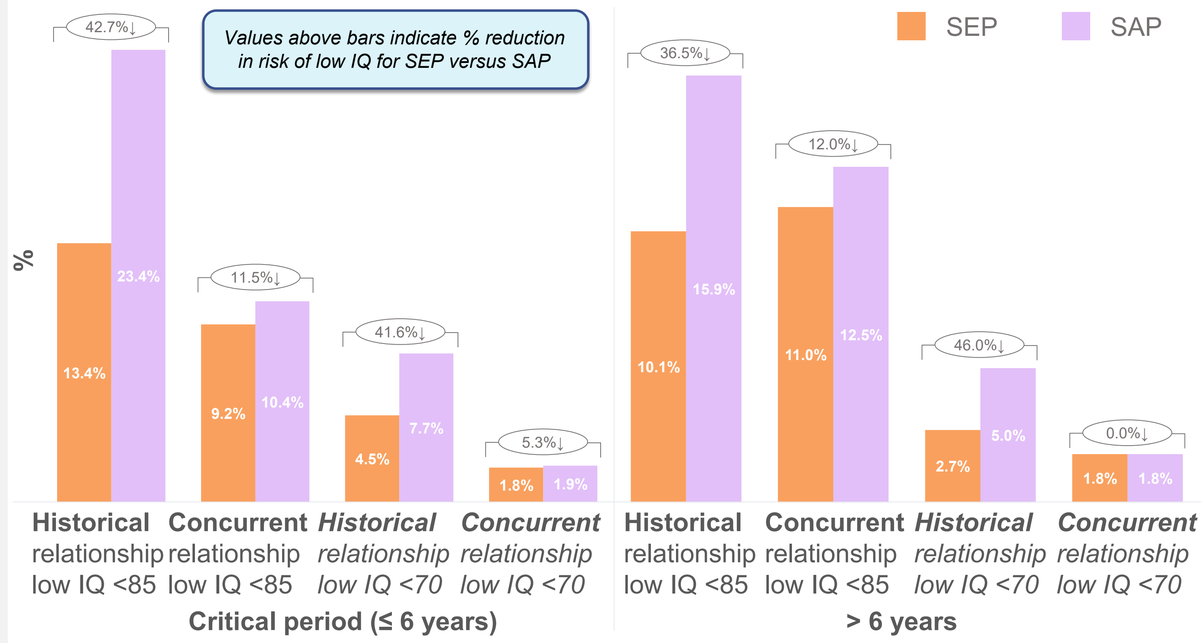


- Based on published literature, the probability of low IQ is higher when the relationship between Phe and IQ is historical (i.e. Phe measures earlier in life predicting IQ outcomes later in life), and for Phe measured during the critical period less than 6 years of age (**Figure 2**).[7,8]

3. Results: Probability of low IQ

- All results are based on the ITC:[6]
  - Initial average baseline blood Phe of 649.4 µmol/L (from APHENITY; n=110).
  - Blood Phe after treatment was estimated to be **266.4 µmol/L for sepiapterin** and **487.6 µmol/L for sapropterin.**
- The probability of low IQ for individuals ≤6 years was 13.4% for sepiapterin and 23.4% for sapropterin (10% absolute difference), **representing a 42.7% lower risk for sepiapterin versus sapropterin** (**Figure 3**).
- For patients >6 years, the risk of low IQ was 10.1% for sepiapterin and 15.9% for sapropterin (5.8% absolute difference), **a 36.5% lower risk for sepiapterin versus sapropterin.**

Figure 3. *Probability of low IQ estimated with results from Fonnesbeck et al.*[7]



Italics indicate sensitivity analysis (low IQ <70)
Abbreviations: IQ, intelligence quotient; SAP, sapropterin; SEP, sepiapterin

Results: Key findings

There was a **substantially lower risk of low IQ for patients treated with sepiapterin compared to those treated with sapropterin**, in both the critical period (≤6 years) and after the critical period (age >6 years).

The difference in probability between sepiapterin and sapropterin was greater when the model included the historical relationship compared to the concurrent relationship, **highlighting the importance of Phe management early in life**.

4. Discussion

- There is a strong relationship between blood Phe levels and cognitive outcomes in individuals with PKU, with many patients relying on pharmacological therapies to control Phe levels to improve cognitive outcomes.[1,2,6,8]
- Of note, responsiveness to sapropterin is limited, particularly among those with classical PKU.[9] As such, the current analysis pertains to the minority of patients who may benefit from sapropterin.
- The current analysis suggested that different therapies could have different impacts on cognitive outcomes. More specifically, these analyses demonstrated that sepiapterin had a greater impact on change in IQ and probability of low IQ compared to sapropterin.
- A key clinical input to the present model is the estimated difference in Phe reduction for sepiapterin vs. sapropterin. This was estimated via the ITC which was based on the respective clinical trial programs and thus reflects the patient population included in these trials.[6]
- There is evidence to suggest that variation in blood Phe levels over time can impact adult cognitive outcomes for individuals with PKU. Avoiding peaks in Phe, especially in childhood, can result in better cognitive performance throughout life.[10]
- The current analysis did not allow for exploration of variation in Phe over time, although it was hypothesized that successful management of Phe through treatment would also contribute to greater stability and less variation. Future studies should investigate how variation in Phe levels impact cognitive outcomes across different treatment strategies.

Conclusions: This model demonstrates that sepiapterin provided a greater reduction in blood Phe levels and consequently significantly lower probability of low IQ compared to sapropterin. These findings support the clinical relevance of effectively controlling blood Phe levels in PKU and highlight the value of sepiapterin in addressing the adverse cognitive outcomes that patients experience.

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