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

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Supplementary methods

Simulated treatment comparison (STC)

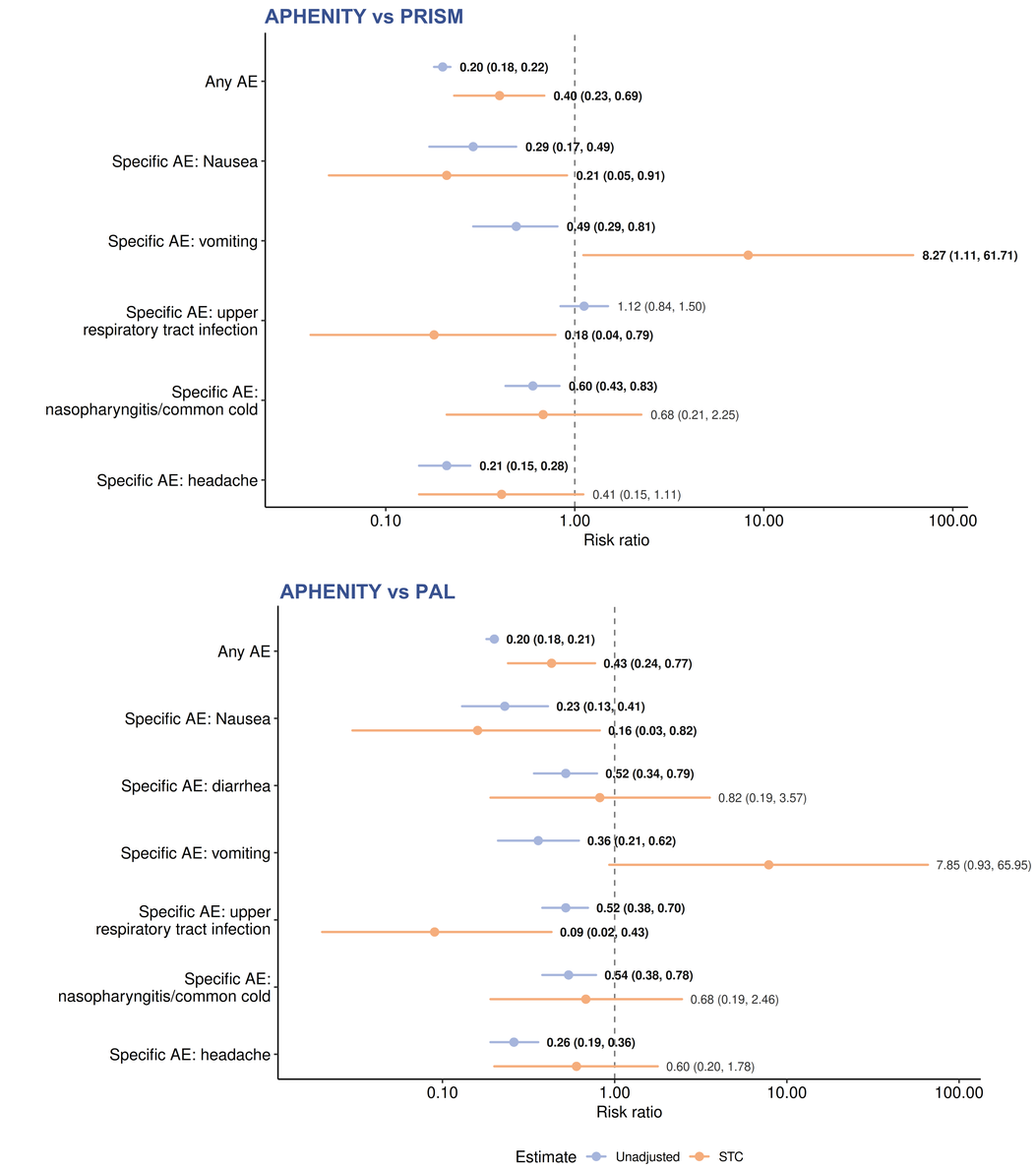
- STC involves an outcome-regression approach using individual patient data (IPD) from the index trial (APHENITY) and published aggregate baseline characteristics from the comparator trials (PRISM & PAL trials).
- Pairwise STCs fitted patient-level trial data using predictive equations, adjusting for baseline characteristics that were identified as potential prognostic factors or treatment effect modifiers. The equations were used to predict treatment outcomes in the context of the comparator population
- Because this is unanchored, a prespecified set of variables were adjusted for, chosen as both prognostic and potential effect-modifying factors—age, sex, BMI, and baseline Phe—by incorporating them directly into the regression model.
  - ➢This approach accommodates continuous covariates, can be helpful when overlap is limited, and avoids the effective-sample-size loss seen with reweighting method.
- For each outcome, incidence rate ratios (IRRs) and 95% confidence intervals (CIs) were estimated. Counts were modeled with a negative binomial generalized linear model (log link) to accommodate overdispersion, and a log person-time offset was included to account for different follow-up durations.
- The adjusted effect for sepiapterin in the comparator population was obtained by setting covariates to the published means from the comparator trial. Model-based standard errors were used for CIs.

Adverse event (AE) definitions

Study	Treatment emergent or on-treatment AEs
APHENITY	AE data were collected from screening through participants' final study visit. Events were coded with the MeDRA, version 26.0. Event rate was calculated using individual patient data.
PRISM	Event rate was calculated as total number of events divided by person-years of exposure. For each treatment phase and time interval, only AEs with onset within that phase or interval were included. Safety was monitored by assessment of vital signs, physical examination, electrocardiograms, AEs (coded by preferred terms using MedDRA version 18.0). Safety assessments were conducted at baseline, weekly during the induction period, and at least monthly during the titration and maintenance periods until Week 25 of PRISM-2 Part 4, when assessments were conducted bimonthly.
PAL trials	Event rate was calculated as total number of events divided by person-years of exposure. Safety was assessed every 4 weeks and immune response every 12 weeks. Safety was assessed by vital signs, physical examination, AEs, and clinical laboratory tests. The incidence, exposure-adjusted event rate, and severity grade (per National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE], version 4.03: mild, moderate, severe, life-threatening, or death) of AEs were reported. All AEs were coded according to MedDRA; version 18.0 preferred terms. In addition to the Sponsor of the study, an independent Data Monitoring Committee monitored the safety of participants, acting in an advisory capacity to the Sponsor.

Supplementary results

STC results of APHENITY vs PRISM and APHENITY vs PAL trials



AE, adverse event; STC, simulated treatment comparison
Bolded values indicate significant difference (p<0.05)

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