Estimation of health-state utility values in phenylketonuria, via clinical-expert proxy assessment with a generic measure (SF-12®v2) of patient-reported impacts from a disease-specific measure (PKU-QOL): Interim results

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Background

Phenylketonuria (PKU) is an inherited condition caused by deficiency of the enzyme phenylalanine hydroxylase, resulting in the accumulation of phenylalanine (Phe) in the blood.[1]

Clinical guidelines recommend lifelong Phe-lowering treatment including a Phe-restricted diet and supplemental protein, to mitigate symptoms.[2]

Adherence to a Phe-restricted diet itself may impact patients' health-related quality of life (HRQoL) through psychological, physical, and social means.[3-5]

HRQoL is impacted by elevated blood-Phe control and diet restrictions. These factors are closely related (e.g., more restricted diet may improve blood-Phe control, more relaxed diet may reduce blood-Phe control), such that the HRQoL impact of each is hard to separate.

Accurate assessments of HRQoL impacts in PKU is important to inform coverage and reimbursement decisions for new treatments,[6-9] as health utility measures are used to inform economic evaluation.

Objective

To estimate the health-state utility impacts associated with blood-Phe levels and diet in individuals with PKU

Study design

The study was conducted in three steps:

1. Development of health states using trial data

Health-state descriptions were developed **based on impacts reported by patients** in clinical studies of sepiapterin

MD-003 (APHENITY) / MD-301 (AMPLIPHY) / MD-004 (Long-term extension)

- Baseline HRQoL data collected
- Follow-up HRQoL data collected (75% had ≥20 months follow-up)

Within-patient changes informed **three HRQoL-based health states**

2. Proxy HRQoL assessment

Clinical experts used a generic preference-based measure to assess the **expected impact on a patient of each health-state description**

SF-12®v2

The Short Form 12-item (version 2) (SF-12®v2)[10] – Acute Recall – Proxy Version (English language) was used to allow **proxy assessment capturing key HRQoL domains in PKU** (social and role functioning, mental health, vitality)*

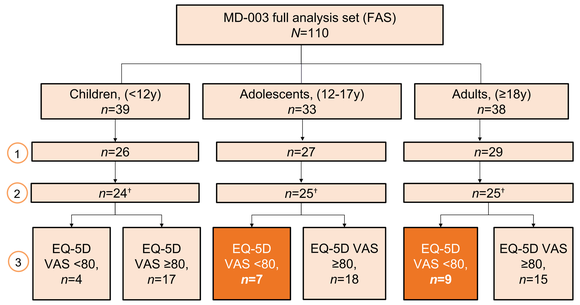
3. Scoring

Proxy assessments were scored to estimate health-state utilities, reflecting societal preferences for HRQoL†

**Validated proxy version: ("SF-12®v2 Health Survey Standard Proxy Form, United States (English)").*
†Proxy assessment: HRQoL evaluated by clinical experts based on health-state descriptions rather than patient self-report.

Methods: Development of health states

Figure 1. Study sample flow diagram



Inclusion Criteria

1. Available measure of PKU-QOL at MD-003 baseline (*n*=82)
2. Available measure of PKU-QOL in MD-004 (*n*=74)
3. Self-reported substantial HRQoL decrement* (EQ-5D VAS <80 at MD-003 baseline)

Note: Analysis was limited to adolescents and adults (n=16), as the SF-6D is not validated for younger ages
*EQ-5D is a generic HRQoL instrument and the EQ-5D VAS reflects patients' self-rated health on a 0 to 100 scale. A "substantial" HRQoL decrement was defined as EQ-5D VAS <80, based on general-population norms for ages <65 in Table 3.5 of Szende et al., 2014.[11]
†Missing EQ-5D VAS values were excluded from counts: children, *n*=3; adolescents, *n*=0; adults, *n*=1.
See **Supplementary results** for individual patient data (*n*=16).

Development of the health states was conducted using data for the N=16 patients aged ≥12 years, with mean baseline blood Phe of 615 µmol/L.

Associations of changes in blood Phe, diet, and PKU-QOL scores

The development of the health states was conducted in several steps:

Bivariate associations: Pearson correlations were assessed between changes in exposures (blood-Phe, diet) and outcomes (PKU-QOL) from baseline (MD-003) to last visit (MD-004) – *see Supplementary materials*

Multivariate associations: First-difference linear regression assessed within-patient changes; results informed health-state development

The following first-differences linear specification was used:

$$\Delta \text{ PKU-QOL item score} = \Delta \text{ blood-Phe level } (\mu mol/L / 100) + \Delta \text{ Supplemental \% of total protein} + \varepsilon$$

Note: *Δ indicates change from baseline to last visit. The last visit was used to allow for potential time delay in change in HRQoL impacts associated with change in blood Phe and/or diet restrictions.*

Health state definitions: Three health states (**Table 1**) were defined for the expert proxy assessment

Table 1. Health state definitions

Health State	Blood Phe Level	Diet (Supplemental Protein %)	Method
A: Uncontrolled Phe, restricted diet	>600 µmol/L	>50%	Based on baseline PKU-QOL scores from patients meeting this profile (*n*=4/16)
B: Controlled Phe, restricted diet	Reduced from 780 (sample mean) to 120 µmol/L	>50%	Derived from State A using regression coefficients for blood-Phe
C: Controlled Phe, liberalized diet	Reduced from 780 to 120 µmol/L	Reduced from 75% (sample mean) to 25%	Derived from State B using regression coefficients for diet restriction

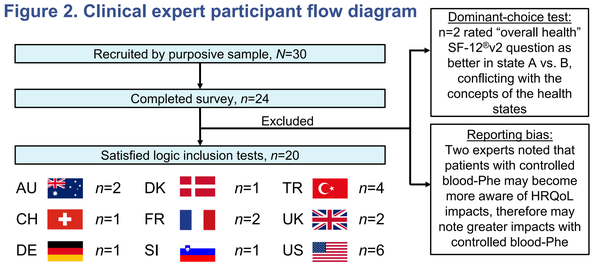
Methods: Proxy HRQoL assessment

Online survey methodology

Participants: International sample of 30 PKU experts with experience in patient care, clinical studies, and dietary/nutritional management

Assessment: Experts completed the SF-12®v2 online for each health-state description (A, B, C)

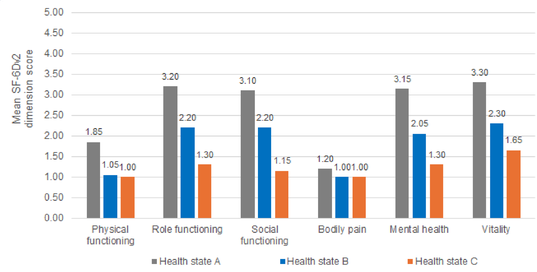
Figure 2. Clinical expert participant flow diagram



Results

- SF-12®v2 item responses were mapped to the six SF-6Dv2 dimensions – *see Supplementary materials*
- From health states A to C, the largest decreases were observed in social functioning (-1.95), role functioning (-1.90), mental health (-1.85), and vitality (-1.65) (**Figure 3**).

Figure 3. SF-6D dimension scores



Utility estimates

- Dimension scores for the SF-6Dv2 were scored using the Mulhern et al. (2020) value set for the UK.[12]
- Estimated mean utility (**Table 2**) increased from health state A (0.68) to health state B (0.90), and again from health state B to health state C (0.97).
- The difference in mean utility between health states B vs. A (0.21) was interpreted as the utility increment associated with controlled blood Phe, and between health states C vs. B (0.07) as the utility increment associated with liberalized diet.

Table 2. Mean utility estimates by health state

	N	20
Estimated utility for health state A	**Mean**	**0.68**
	SE	0.04
	SD	0.18
Estimated utility for health state B	**Mean**	**0.90**
	SE	0.01
	SD	0.05
Estimated utility for health state C	**Mean**	**0.97**
	SE	0.01
	SD	0.03

Utility increment of controlled blood Phe	0.21
Utility increment of liberalized diet	0.07

Discussion

This study estimated health-state utilities in PKU using clinical-expert proxy assessment of health-state descriptions informed by patient-reported impacts from clinical trials

Clinical experts' proxy assessments on a generic preference-based measure, informed by their experience and patient-reported impacts on a disease-specific measure, reflect that uncontrolled blood-Phe and protein-restricted diet both impact overall HRQoL in PKU.

Utility differences were mainly driven by social functioning, role functioning, mental health, and vitality.

Physical functioning and bodily pain were less influential, suggesting that generic HRQoL measures focused on physical domains may not fully capture the burden of PKU.

Blood-Phe control and diet may impact different aspects of HRQoL, as evidenced by differences in associations with the PKU-QOL identified in development of the health states, and by differences in SF-12®v2 dimension scores between health states.

Strengths include:

- The use of patient-informed health-state descriptions
- Within-patient analyses of clinical trial data
- Substantial follow-up

Limitations include:

- Small sample size
- Limited representation of patients with both uncontrolled blood-Phe and restricted diet
- Reliance on clinical-expert proxy assessment for estimating utilities, which may differ from patient self-report

Conclusions

Both uncontrolled blood Phe and diet restrictions impact the HRQoL of patients with PKU, through associations with different aspects of quality of life.

Generic HRQoL measures focused on physical domains may not fully capture the burden of PKU. Accurate assessments of HRQoL impacts are needed to model the value of new treatments for PKU.

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Abbreviations: AU, Australia; CH, Switzerland; DE, Germany; DK, Denmark; FAS, full analysis set; FR, France; HRQoL, health-related quality of life; Phe, phenylalanine; PKU, phenylketonuria; PKU-QOL, Phenylketonuria Quality of Life; SD, standard deviation; SE, standard error; SF-12®v2, Short Form 12-item Health Survey version 2; SF-6D, Short Form 6-Dimension; SI, Slovenia; TR, Türkiye; UK, United Kingdom; US, United States; VAS, visual analogue scale; y, years; µmol/L, micromoles per litre.

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