Supplementary materials

Cost-Utility Analysis (CUA) of Sepiapterin for Treatment of Phenylketonuria (PKU): Development of a De-novo Conceptual Model

Rongrong Zhang,[1] Anupam Chakrapani,[2] Takashi Hamazaki,[3] Melissa Dawn Lah,[4] Ania C. Muntau,[5] Danielle J. Ruebel,[4] Suresh Vijay,[6] Roberto T. Zori,[7] Francois Feillet,[8] Thomas O'Connell,[9] Jonathan J. Woolley,[9] Yixi Teng,[9] Margorie Crowell[9] and Ioannis Tomazos[10]

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Clinical-expert survey

Key points

- The e-Delphi panel achieved consensus on the mechanisms that may account for the association of PKU with chronic comorbidities. However, experts noted the mechanisms differ across comorbidities.
- Accordingly, aligning with guidance for modeling effects of surrogate endpoints,[16] a survey was conducted to assess the biological plausibility of different mechanisms for change in risk of each comorbidity.
- Clinical expert participants (n=30 from 15 countries) rated their agreement with statements on the plausibility that, for each of 10 comorbidities:
  - Prevalence of each of the comorbidity is higher in individuals with PKU vs the general population
  - Increased natural protein in diet (e.g., consumption of less medical food) may reduce comorbidity risk
  - Control of elevated blood Phe levels (i.e., reduction to within the target range) may reduce comorbidity risk

Supplementary table 1: Clinical expert survey results

Responses for N=30			It is clinically / biologically plausible that:			
	Comorbidity	Response	Overall prevalence of [comorbidity] is higher in patients with PKU compared to the general population	Control of elevated blood Phe levels (i.e., reduction to within the target range) may reduce risk of [comorbidity]	Increased natural protein in diet (and direct / indirect impacts - e.g., consumption of less medical food) may reduce risk of [comorbidity]	**Diet > Phe**
1	**Anaemia**	Any agreement:	60%	30%	83%	1
		Agreement among those agreeing with higher prevalence:		50%	94%	1
		Don't Know	0%	0%	0%	
2	**Asthma**	Any agreement:	20%	14%	18%	1
		Agreement among those agreeing with higher prevalence:		67%	67%	0
		Don't Know	0%	3%	7%	
3	**Chronic ischaemic heart disease**	Any agreement:	45%	46%	54%	1
		Agreement among those agreeing with higher prevalence:		69%	100%	1
		Don't Know	3%	7%	7%	
4	**Depression**	Any agreement:	93%	87%	70%	0
		Agreement among those agreeing with higher prevalence:		93%	75%	0
		Don't Know	0%	0%	0%	
5	**Osteoporosis**	Any agreement:	83%	50%	83%	1
		Agreement among those agreeing with higher prevalence:		60%	96%	1
		Don't Know	0%	0%	0%	
6	**Overweight (BMI ≥25 kg/m2)**	Any agreement:	83%	57%	77%	1
		Agreement among those agreeing with higher prevalence:		64%	88%	1
		Don't Know	0%	0%	0%	
7	**Renal insufficiency with hypertension**	Any agreement:	53%	44%	64%	1
		Agreement among those agreeing with higher prevalence:		56%	69%	1
		Don't Know	0%	10%	7%	
8	**Renal insufficiency without hypertension**	Any agreement:	50%	36%	52%	1
		Agreement among those agreeing with higher prevalence:		57%	79%	1
		Don't Know	7%	17%	17%	
9	**Type 2 diabetes**	Any agreement:	67%	41%	70%	1
		Agreement among those agreeing with higher prevalence:		50%	90%	1
		Don't Know	0%	3%	0%	
10	**Other / unspecified diabetes**	Any agreement:	27%	26%	30%	1
		Agreement among those agreeing with higher prevalence:		71%	86%	1
		Don't Know	13%	10%	10%	

ABBREVIATIONS: ADHD, attention deficit hyperactivity disorder; BMI, body mass index; CUA, cost utility analysis; CIHD, chronic ischaemic heart disease; HR: hazard ratio; HRQoL, health related quality of life; HTA, health technology assessment; Phe, phenylalanine; PKU, phenylketonuria; PRD, protein restricted diet; T2DM, type 2 diabetes mellitus.

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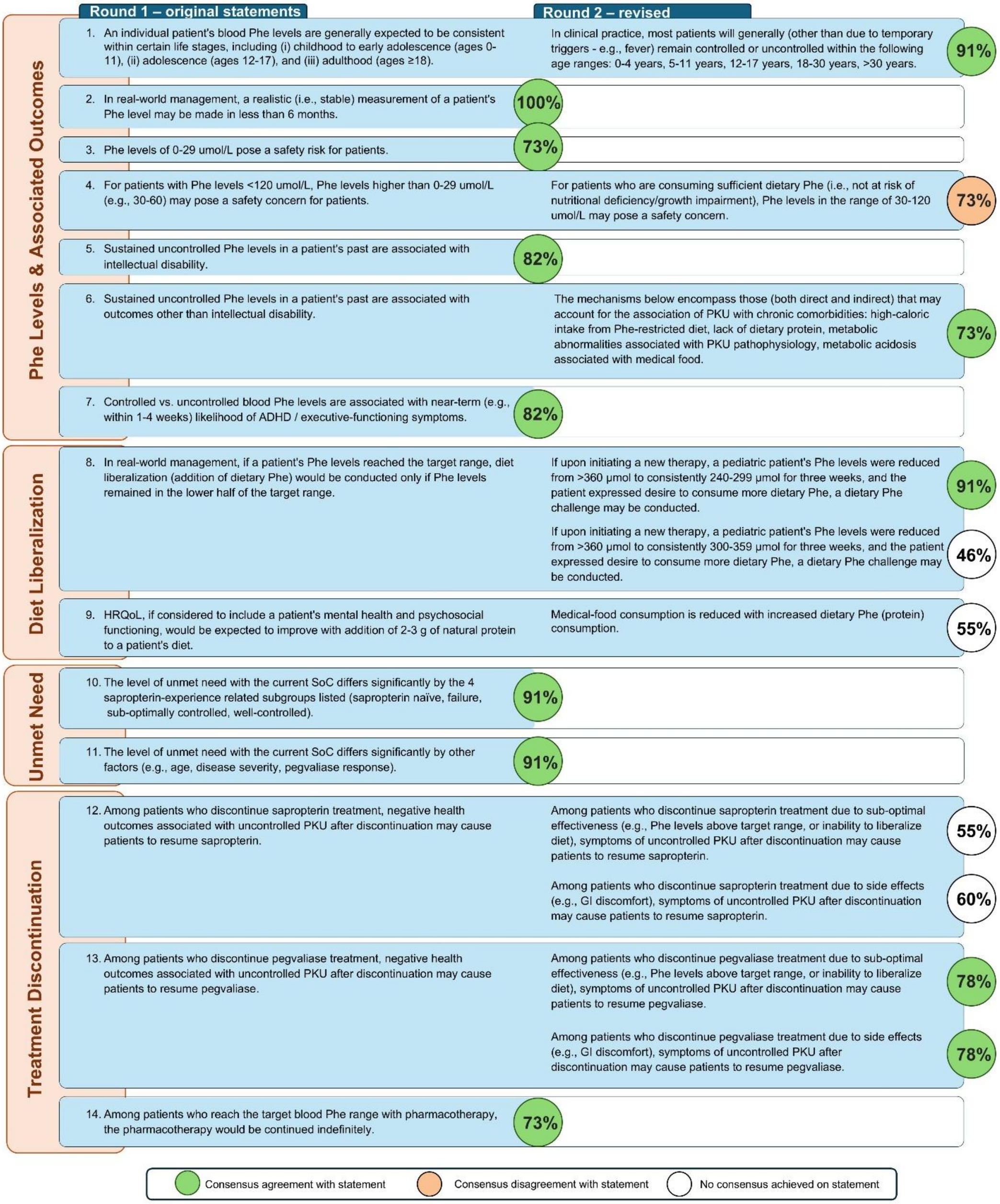
Modified e-Delphi panel

Supplementary figure 1: Delphi panel results



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Disclosures

Rongrong Zhang and Ioannis Tomazos were/are employees of PTC Therapeutics Inc. Thomas O'Connell, Yixi Teng, Marjorie Crowell, and Jonathan J. Woolley are employees of Medicus Economics which was contracted by PTC Therapeutics Inc. for the conduct of this study. Ania C. Muntau participated in strategic advisory boards and received honoraria as a consultant and as a speaker for Actelion, Applied Pharma Research, Arla Food, BioMarin, Censa, Merck Serono, Nestlé Health Science (SHS), PTC Therapeutics, Retrophin (now Travere Therapeutics), Jnana Therapeutics (now Otsuka), Pluvia, and Synlogic Therapeutics and received research grants from: Dr Schär, Merck Serono, Nutricia, SHS, and Vitaflo. Takashi Hamazaki has participated in advisory boards and received clinical trial support from PTC Therapeutics Inc., and has also received funding and research support from BioMarin Pharmaceuticals Inc., Sanofi, and JCR Pharma. Melissa Lah participated as a clinical trial investigator for BioMarin, Homology Medicines, Moderna, and PTC Therapeutics; received consulting payments from BioMarin, PTC Therapeutics, and Travere Therapeutics; and travel support from BioMarin and PTC Therapeutics. Danielle J. Ruebel has served as an advisory board participant, consultant, and/or paid speaker for PTC Therapeutics and Biomarin Pharmaceutical. Francois Feillet declares serving on Scientific boards (Biomarin, Genzyme, Vitaflo, Danone, Alexion, Recordati, Jnana Therapeutics), a grant from Recordati (to INSERM), participation to the DSMB of Aphenity study (PTC Therapeutics). Roberto T. Zori reports support as principal investigator on studies for BioMarin Pharmaceutical, PTC Therapeutics, Inc and Jnana Therapeutics. Anupam Chakrapani and Suresh Vijay have no conflicts to declare.

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