

Development of an algorithm to assess the risk–benefit ratio of the use of pegvaliase during pregnancy

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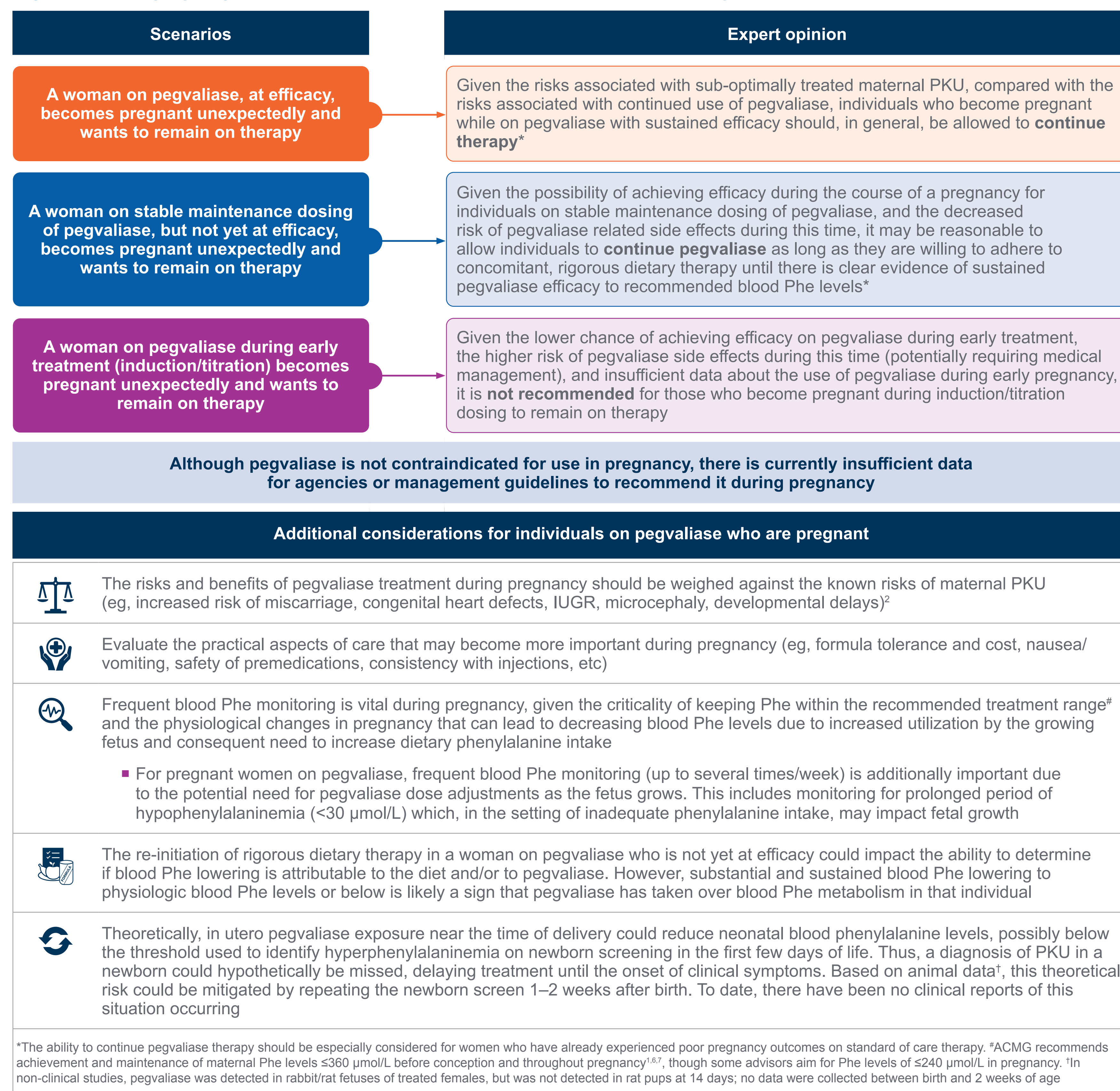
Background

- Phenylketonuria (PKU) is an autosomal recessive genetic condition caused by deficiency of phenylalanine hydroxylase, resulting in phenylalanine (Phe) accumulation in the blood and brain that leads to neurotoxic effects in the absence of lifelong management¹
- Maternal elevated Phe levels are teratogenic to a developing fetus²
- The American College of Medical Genetics and Genomics (ACMG), European, and American College of Obstetricians and Gynecologists (ACOG) guidelines recommend maintaining maternal blood Phe ≤ 360 $\mu\text{mol/L}$ before and during pregnancy to prevent negative gestational outcomes^{1,3,4}
- Traditional PKU treatment centered on medical nutrition therapy is challenging and may be insufficient to maintain blood Phe control⁴
- Achieving target blood Phe levels is possible with advanced therapeutic agents such as pegvaliase, an enzyme substitution therapy that significantly reduces Phe levels in individuals with PKU⁵
- Use of pegvaliase during pregnancy has not been studied in clinical trials and published data are currently limited to case reports^{6,7}
 - The PALomino registry is enrolling women with exposure to pegvaliase during pregnancy (NCT05579548; US, CAN, GER, IT)
- The objective was to develop the first structured, expert-led algorithm of pegvaliase use during pregnancy to support clinicians during risk–benefit evaluation discussions

Results

- While not all advisors had used pegvaliase in the management of PKU during pregnancy, the majority stated that they would consider continuing pegvaliase if the individual expressed interest in remaining on treatment
- In the scenario where an individual with PKU on pegvaliase becomes pregnant, advisors agreed that the stage in the treatment journey is the most important factor (Figure 1)
- Breastfeeding is a practical aspect of postpartum care that requires a risk–benefit evaluation not covered in the pregnancy algorithms. Limited evidence suggests active pegvaliase does not pass into breast milk⁸

Figure 1. Managing pegvaliase use in individuals with PKU who become pregnant while on treatment



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Acknowledgements

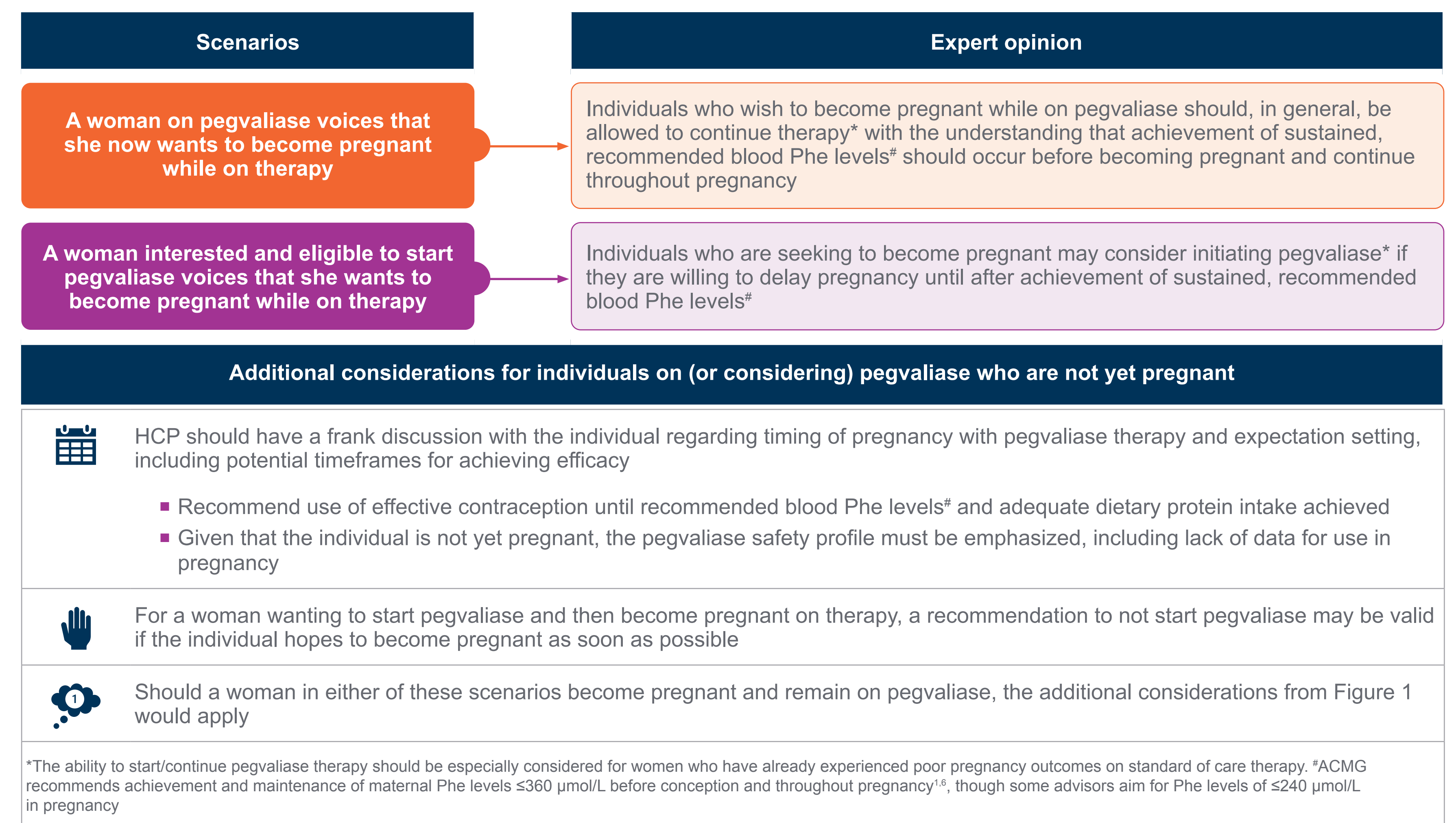
Medical writing assistance was provided by Ismar Healthcare

Algorithm development

- A multi-stage expert consensus process was conducted with a panel of 13 international PKU experts (physicians, a nurse practitioner, and 2 dietitians across the US, Europe, and Japan) to inform development of an algorithm to guide clinicians through assessing the risk–benefit ratio of using pegvaliase to manage blood Phe during pregnancy
- The topic was discussed during an in-person (June 2024) and virtual follow-up meeting (December 2024). Pre-meeting surveys were used to level-set advisor experience and systematically assess how patient- and treatment-related factors influence decisions to continue pegvaliase during pregnancy
- Available evidence, including advisors sharing their own clinical experience, review of published case reports and case series^{7–10}, and available guideline recommendations¹¹ were reviewed for context
- Survey findings from both meetings were synthesized into draft clinical scenarios and decision trees, which were reviewed, debated, and refined during the second meeting, with areas of agreement and uncertainty documented
- Iterative post-meeting refinement resulted in qualitative agreement on the two pregnancy algorithms presented herein

- In the scenario where an individual with PKU is not yet pregnant, but is considering pregnancy, advisors discussed considerations for individuals already on pegvaliase as well as for those who might be considering starting pegvaliase (Figure 2)
- Advisors emphasized the need for a transparent discussion with the individual regarding timing of pregnancy and pegvaliase safety considerations was highlighted, including setting clear expectations about the length of time needed to achieve therapeutic efficacy

Figure 2. Guidance for pregnancy planning in individuals on pegvaliase or considering initiating treatment



Summary

- There is currently insufficient evidence for regulatory agencies or clinical guidelines to provide formal recommendations for the use of pegvaliase during pregnancy, despite the absence of formal contraindications
- The scenario-based algorithm was developed using expert opinions to address this gap and is intended to support shared decision-making between HCPs and individuals with PKU
- Case-by-case discussions should account for patient preferences, consider the stage of treatment, and balance the known risks of maternal PKU and the potential benefits and uncertainties associated with pegvaliase use during pregnancy
- To further inform and refine clinical decision-making, HCPs are encouraged to share real-world experiences with pegvaliase use during pregnancy, with the goal of progressively strengthening the evidence base and optimizing maternal and fetal outcomes

Disclosures

COH, AH, SH, ACM, VR, SS, JAT, FvS, and ML have received consulting payments and travel support from BioMarin Pharmaceutical Inc. EV, JCR, TH and TI have received consulting payments, speaker fees, and travel support from BioMarin Pharmaceutical Inc. AHunt and KL are employees and shareholders of BioMarin Pharmaceutical Inc.

Abbreviations

ACMG, American College of Medical Genetics and Genomics; ACOG, American College of Obstetricians and Gynecologists; HCP, healthcare professional; IUGR, intrauterine growth restriction; Phe, phenylalanine; PKU, phenylketonuria

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