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Efficacy and safety of sapropterin before and during pregnancy: Final analysis of the Kuvan® Adult Maternal Paediatric European Registry (KAMPER) and Phenylketonuria Developmental Outcomes and Safety (PKUDOS) PKU-MOMs sub-registries

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Introduction

- Phenylketonuria (PKU) is an inherited disorder caused by deficiency of phenylalanine hydroxylase that converts phenylalanine (Phe) into tyrosine, thus resulting in elevated blood Phe levels[1]
- In pregnant women with PKU, high Phe levels can severely affect intrauterine fetal growth and development, increasing the risk of congenital abnormalities;[2,3] it is hence recommended that blood Phe levels be maintained between 120–360 µmol/L during the entire pregnancy[4-6]
- Sapropterin dihydrochloride (Kuvan®, BioMarin Pharmaceutical Inc., Novato, CA) is approved in Europe for the treatment of hyperphenylalaninaemia (HPA) in tetrahydrobiopterin (BH_4)-responsive patients with PKU or BH_4 deficiency, to reduce blood Phe levels and improve Phe tolerance[7]
- Use of sapropterin is recommended with caution during pregnancy due to limited knowledge about its safety in pregnant women and their infants

Objective

- Results based on the final analyses of the following long-term (up to 15 years) maternal sub-registries collecting data on the use of sapropterin in pregnant women are reported
  - Kuvan® Adult Maternal Paediatric European Registry (KAMPER; NCT01016392) maternal sub-registry[8] (hereafter referred to as $KAMPER_{Sub\text{-}R}$), part of the KAMPER registry: This sub-registry provided data (up to 15 years) on the use of sapropterin in pregnant women with HPA due to PKU or BH_4 deficiency; this sub-registry included BH_4-responsive women
  - PKU-MOMs sub-registry, part of the Phenylketonuria Developmental Outcomes and Safety Registry (PKUDOS; NCT00778206)[9]: This sub-registry collected data on sapropterin use in all pregnant women registered in the PKUDOS registry who were receiving sapropterin or were due to receive it within 90 days of participation in the registry, irrespective of their BH_4 responsiveness

Methods

- Efficacy and safety data on sapropterin use prior to and/or during pregnancy in women with PKU were collected from $KAMPER_{Sub\text{-}R}$ and PKU-MOMs
- Data are reported on pregnancy outcomes, blood Phe levels, sapropterin dose, infant anthropometry, adverse events (AEs), and serious adverse events (SAEs)
- Normalized values of various parameters (e.g. height and weight) were computed using World Health Organization (WHO) growth charts; categorical variables (e.g. gender) were summarized as n (%) for each category, and continuous variables (e.g. age) were summarized using descriptive statistics such as mean and standard deviation (SD)

Results

Participants

- Results from 79 pregnancies in 57 women are reported. In $KAMPER_{Sub\text{-}R}$, there were 26 pregnancies in 16 women, with mean (SD) maternal age at delivery being 29.9 (4.8) years. In PKU-MOMs, there were 53 pregnancies in 41 women, with mean (SD) maternal age at delivery being 29.0 (5.0) years (**Table 1**)

Sapropterin dose and blood Phe levels and Phe intake

- In both sub-registries, sapropterin dose remained fairly constant before and during pregnancy (**Figure 1**), although the average dose was higher in PKU-MOMs (18.1±3.8 versus 11.0±5.9 mg/kg/day)
- Blood Phe levels were maintained in the recommended target range (120–360 µmol/L) during the entire pregnancy in the majority of women (**Figures 1 and 2**), with lower Phe levels during the second trimester
- Dietary intake of Phe in $KAMPER_{Sub\text{-}R}$ and PKU-MOMs increased after initiation of sapropterin treatment (results not shown here)

Figure 1. Sapropterin dose (line graph) and blood Phe levels (bar graph) before, during and after pregnancy in $KAMPER_{Sub\text{-}R}$ and PKU-MOMs*

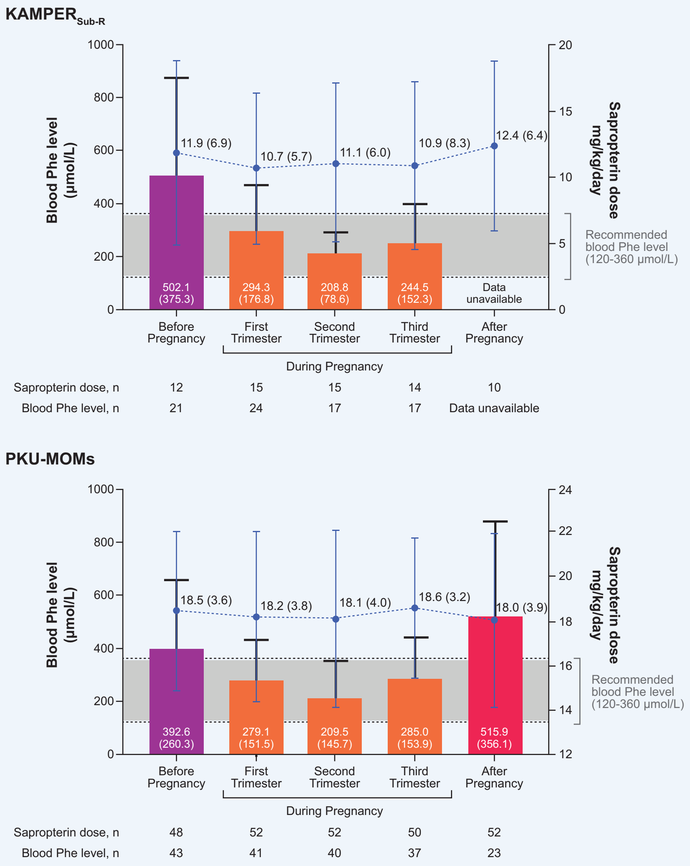
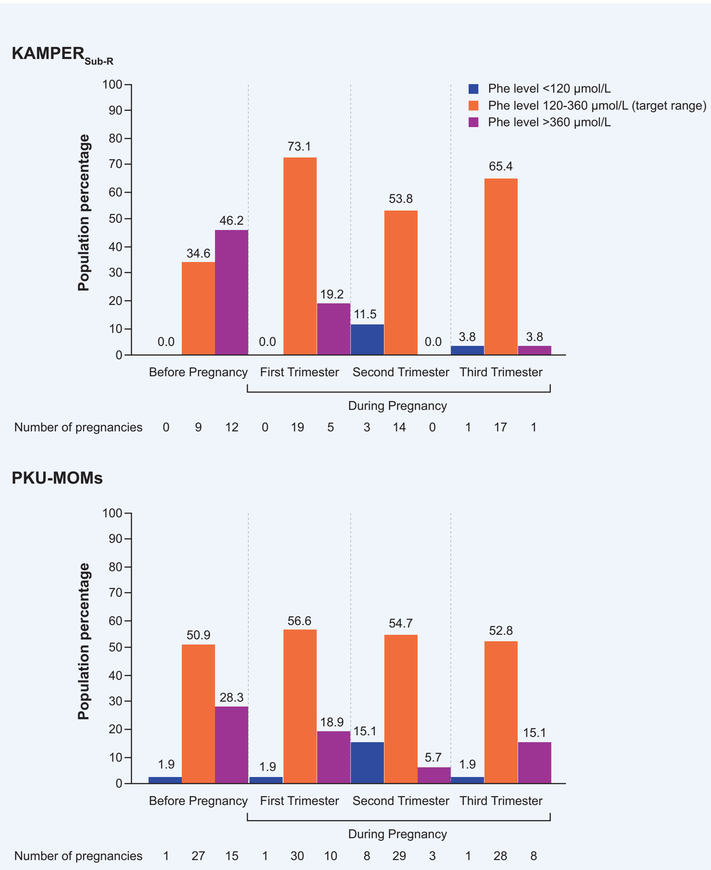


Figure 2. Distribution of blood Phe levels in women with PKU before pregnancy and by trimester during pregnancy in $KAMPER_{Sub\text{-}R}$ and PKU-MOMs*



*The sum of various categories within a period does not add up to 100% due to the missing data for some pregnancies during each period.

Pregnancy and infant birth outcomes

- Pregnancy and infant birth outcomes in $KAMPER_{Sub\text{-}R}$ and PKU-MOMs are reported in **Tables 1 and 2**
- In KAMPER, 18/19 pregnancies resulted in normal live births (1 missing)
- In PKU-MOMs, 39/47 pregnancies resulted in normal live births (4 missing); 4/47 were reported as abnormal by the investigator
  - One case each of microcephaly, cleft palate, tongue tie and premature birth was reported. Two of these (microcephaly, cleft palate) were associated with Phe levels >360 µmol/L during pregnancy
    - While one case of microcephaly was reported by the investigator, formal criteria for microcephaly based on head circumference z-score was not met
- In general, infant growth based on indices noted in **Table 2** were aligned to the WHO growth charts, indicating normal infant growth

Table 1. Pregnancy outcomes in women in $KAMPER_{Sub\text{-}R}$ and PKU-MOMs

Characteristic		$KAMPER_{Sub\text{-}R}$	PKU-MOMs
Number of pregnant women	N	16	41
Number of pregnancies	n	26	53
Maternal age at delivery, years	n Mean (SD)	25 29.9 (4.8)	50 29.2 (4.7)
Weeks of pregnancy when reported, weeks	n Mean (SD)	23 10.6 (7.7)	52 5.9 (1.7)
Average sapropterin dose during pregnancy, mg/kg/day	n Mean (SD)	15 11.0 (5.9)	53 18.1 (3.8)
Duration of sapropterin use during pregnancy, days	n Mean (SD)	15 247.5 (52.1)	53 270.2 (61.6)
Pregnancy terminated, n (%)	n Yes (spontaneous) No	20 0 20 (76.9)	53 3 (5.7) 50 (94.3)
Participant breastfeeding at 1 month, n (%)	n Yes No	20 10 (38.5) 10 (38.5)	47 17 (36.2) 30 (63.8)

Based on available data; Note one SAE of spontaneous abortion reported in $KAMPER_{Sub\text{-}R}$. Due to the nature of the study (registry with no active follow-up), data for some parameters may not have been available when tabulating pregnancy outcomes

Table 2. Infant birth outcomes in women in $KAMPER_{Sub\text{-}R}$ and PKU-MOMs

Characteristic		$KAMPER_{Sub\text{-}R}$ (n=19)	PKU-MOMs (n=47)
Gender, n (%)	n Male Female	19 15 (78.9) 4 (21.1)	47 19 (40.4) 28 (59.6)
Gestational age˙, weeks	n Mean (SD)	19 39.8 (2.1)	47 39.3 (1.4)
Weight, g	n Mean (SD)	18 3584.4 (230.1)	41 3395.7 (441.0)
Weight Z-score	n Mean (SD)	18 0.6 (0.5)	41 0.3 (0.9)
Length, cm	n Mean (SD)	18 51.5 (1.4)	35 50.5 (2.6)
Length Z-score	n Mean (SD)	18 0.9 (0.8)	35 0.5 (1.4)
Head circumference, cm†	n Mean (SD)	16 34.8 (1.1)	17 33.4 (1.7)
Head circumference Z-score†	n Mean (SD)	16 0.3 (0.9)	17 -0.7 (1.4)
Apgar at 1 min, n (%)	7 8 9 10	0 3 (15.8) 8 (42.1) 5 (26.3)	1 (2.1) 12 (25.5) 4 (8.5) 0
Apgar at 5 min, n (%)	7 8 9 10	0 1 (5.3) 0 14 (73.7)	1 (2.1) 0 17 (36.2) 0
Condition at birth‡, n (%)	n Normal Abnormal	18 18 (94.7) 0	43 39 (83.0) 4 (8.5)

Based on available data; due to the nature of the study (registry with no active timely follow-up), data for some parameters may not have been available when estimating infant outcomes.

˙Gestational age was derived from the date of the last reported menstrual period to the date of infant birth. If menstrual period information is unavailable, the estimated number of pregnant weeks are used.

†Head circumference measurements and their corresponding Z-scores were excluded from analysis when the Z-score value was either ≥7 or ≤-7. This is due to the physiologic improbability that the anthropometric measurement is correct.

‡As reported by the investigator.

Safety

$KAMPER_{Sub\text{-}R}$

- In $KAMPER_{Sub\text{-}R}$, 11 AEs were reported in 9 pregnant women (**Table 3**)
  - Most of these were mild or moderate in nature (n=10), with one case of uterine contraction being considered to be severe
  - One woman discontinued the sub-registry during pregnancy due to the occurrence of an AE
- There were 3 SAEs in 3 women – uterine hypotonus, cytomegalovirus infection, and spontaneous abortion; all were assessed as unrelated to sapropterin
- One infant experienced 2 mild AEs of jaundice and ocular icterus in $KAMPER_{Sub\text{-}R}$; both were assessed as unrelated to sapropterin

PKU-MOMs

- In PKU-MOMs, 169 AEs were reported in 37 women (**Table 3**)
  - Most were mild to moderate in nature (n=148), with 5 being reported as severe (1 event each of spontaneous abortion (also noted as an SAE), premature labour, failed labour induction, fetal distress syndrome and gestational hypertension)
  - One woman discontinued the sub-registry due to occurrence of an AE
- In total, 17 SAEs were reported in 13 women in PKU-MOMs – 3 cases of spontaneous abortion, 3 cases of increased amino acid, 2 cases of premature labour, and one case each of breech presentation, cervix dystocia, failed labour induction, fetal distress syndrome, gestational hypertension, HELLP syndrome, pre-eclampsia, abnormal uterine contractions and psychotic disorder
  - Two SAEs were assessed to be possibly related to sapropterin treatment, one case each of spontaneous abortion and premature labour
- 40 AEs in 18 infants were seen in PKU-MOMs; of these, one event of hypophagia was assessed as possibly related to sapropterin treatment and was resolved subsequently

Table 3. Safety in $KAMPER_{Sub\text{-}R}$ and PKU-MOMs

$KAMPER_{Sub\text{-}R}$ (N=16)	n (%)	Number of events
Participants with at least 1 adverse event	9 (56.3)	11
Participants with at least 1 serious adverse event	3 (18.8)	3
Adverse events as per system organ class		
Pregnancy, puerperium and perinatal conditions	3 (18.8)	3
Infections and infestations	2 (12.5)	2
Cardiac disorders	1 (6.3)	1
Endocrine disorders	1 (6.3)	1
Gastrointestinal disorders	1 (6.3)	1
Musculoskeletal and connective tissue disorders	1 (6.3)	1

PKU-MOMs (N=41)	n (%)	Number of events
Participants with at least 1 adverse event	37 (69.8)	169
Participants with at least 1 serious adverse event	13 (24.5)	17
Adverse events as per system organ class		
Gastrointestinal disorders	20 (37.7)	35
Infections and infestations	15 (28.3)	21
Pregnancy, puerperium and perinatal conditions	15 (28.3)	21
Musculoskeletal and connective tissue disorders	13 (24.5)	14
Nervous system disorders	12 (22.6)	15
Psychiatric disorders	11 (20.8)	15

Limitations

- Limitations related to the observational nature of the study include the lack of a control group comprising sapropterin-naïve subjects, limited follow-up assessment data, and differences in methodology
- As participation in the registries was voluntary, selection bias cannot be ruled out, and so no statements can be made regarding rates of AEs or infant outcomes relative to the general population

Conclusions

- To our knowledge, this report represents the largest population of pregnant women with PKU exposed to sapropterin
- Results demonstrate that in women with PKU, exposure to sapropterin during pregnancy was well-tolerated, and associated with maintenance of blood Phe levels within the target range and generally with normal birth outcomes
- This critical real-world data will greatly facilitate physicians and patients to make informed treatment decisions about the use of sapropterin in pregnant women with PKU and in women of childbearing age with PKU

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Disclosures

FF is a member of different Scientific Advisory Boards and has received honoraria from BioMarin, Merck-Serono, Genzyme, Shire, Vitaflo, Sobi, Recordati, and Alexion.

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