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Safety of extended treatment with sapropterin dihydrochloride in patients with phenylketonuria: Results of a phase 3b study

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ABSTRACT

Background: Phenylketonuria (PKU) results from impaired breakdown of phenylalanine (Phe) due to deficient phenylalanine hydroxylase (PAH) activity. Sapropterin dihydrochloride (sapropterin, Kuvan®) is the only US- and EU-approved pharmaceutical version of naturally occurring 6R-BH_4, the cofactor required for PAH activity. Sapropterin enhances residual PAH activity in sapropterin-responsive PKU patients and, in conjunction with dietary management, helps reduce blood Phe concentrations for optimal control. Approval was based on the positive safety and efficacy results of four international clinical studies, the longest of which was 22 weeks in duration.

Objective: To evaluate the safety of long-term treatment with sapropterin in PKU subjects who participated in previous Phase 3 sapropterin trials.

Methods: PKU-008 was designed as a Phase 3b, multicenter, multinational, open-label, 3-year extension trial to evaluate the long-term safety of sapropterin in patients with PKU who were classified as sapropterin responders and participated in prior Phase 3 sapropterin studies: 111 subjects aged 4–50 years completed prior studies and were subsequently enrolled in study PKU-008. Routine safety monitoring was performed at 3-month intervals and included adverse event reporting, blood Phe monitoring, clinical laboratory evaluations, physical examinations and vital sign measurements.

Results: Average exposure during PKU-008 was 658.7 ± 221.3 days (range, 56–953; median, 595). The average total duration of participation in multiple studies (PKU-001, PKU-003, PKU-004, and PKU-008; or PKU-006 and PKU-008) was 799.0 ± 237.5 days (range, 135-1151). The mean sapropterin dose was 16.2 ± 4.7 mg/kg/day. Most adverse events were considered unrelated to treatment, were mild or moderate in severity, and were consistent with prior studies of sapropterin. No age-specific differences were observed in adverse event reporting. Three subjects discontinued treatment due to adverse events that were considered possibly or probably related to study treatment (one each of difficulty concentrating, decreased platelet count, and intermittent diarrhea). No deaths were reported. Of seven reported serious adverse events, one was considered possibly related to study treatment (gastroesophageal reflux). There were no laboratory or physical examination abnormalities requiring medical interventions. For most subjects, blood Phe concentrations were consistently within target range, confirming the durability of response in subjects undergoing extended treatment with sapropterin.

Conclusion: Sapropterin treatment was found to be safe and well tolerated at doses of 5 to 20 mg/kg/day for an average exposure of 659 days. This study supports the safety and tolerability of sapropterin as long-term treatment for patients with PKU.

Abbreviations: 6R-BH_4, 6R-tetrahydrobiopterin; AE, adverse event; PKU, phenylketonuria; PAH, phenylalanine hydroxylase; Phe, phenylalanine; SAE, serious adverse event; ULN, upper limit of normal.

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1. Introduction

Phenylketonuria (PKU) is a rare, autosomal recessive, metabolic disorder caused by mutations in the gene encoding phenylalanine hydroxylase (PAH) [1]. Impaired hydroxylation of phenylalanine (Phe), an essential amino acid solely obtainable through dietary sources, results in the toxic accumulation of Phe [1]; elevated blood Phe is the biochemical hallmark of PKU. Left untreated, PKU manifests in severe neurocognitive, neuropsychiatric, and neuromotor impairment [1,2]. Prior to publication of the 2000 NIH guidelines, PKU management strategies focused on strict control of blood Phe concentrations mainly during childhood [3]. Evidence-based review of the literature regarding suboptimal outcomes and relationship to elevated blood Phe concentrations for PKU patients in all age groups caused consensus groups to recommend that patients with PKU should maintain adequate control of blood Phe concentrations throughout their lives [3].

For the first approximately 40 years after initiation of routine screening of newborns for PKU, the only widespread treatment option available to control toxic Phe concentrations and prevent severe intellectual dysfunction in these patients was strict dietary restriction of Phe intake. Unfortunately, adherence with a Phe-restricted diet has historically been suboptimal [reviewed by Ref. 4]. In 1999, Kure et al. [5] demonstrated that orally administered 6R-tetrahydrobiopterin (6R-BH_4), an endogenous enzyme cofactor that is essential for PAH enzyme activity, effectively lowers blood Phe concentrations in a subset of PKU patients (further supported by subsequent studies [5–11]). In 2007 and 2008, respectively, the US and EU approved sapropterin dihydrochloride (sapropterin, Kuvan®), a pharmaceutical version of naturally occurring 6R-BH_4, as a new treatment option for reducing blood Phe concentrations in sapropterin-responsive PKU patients (≥4 years old in EU). Sapropterin, which can be used as a once-daily oral therapy in conjunction with dietary management, is the only drug that is approved for the treatment of PKU. Approval was based on positive safety and efficacy results of four international clinical studies [12–15]. The first three studies (PKU-001, PKU-003, and PKU-004) were conducted sequentially with the study population of the next being selected from the previous. Subjects in these studies were PKU patients ≥8 years old with poorly controlled hyperphenylalaninemia. PKU-001 was an open-label Phase 2 screening study that classified 96 of 485 patients as responders to sapropterin therapy (10 mg/kg/day), defined as a ≥30% reduction from baseline in blood Phe concentrations at the end of the 8-day study [12]. PKU-003 was a 6-week, Phase 3, randomized, placebo-controlled, efficacy study that enrolled 89 of the 96 responders from study PKU-001. PKU-003 demonstrated a statistically significant and consistent reduction in weekly blood Phe concentrations over 6 weeks with sapropterin treatment (10 mg/kg/day) versus placebo ($p<0.001$) [13]. PKU-004, an open-label extension study to PKU-003, was a 22-week safety and efficacy Phase 3 study that enrolled 80 of the 87 subjects who completed PKU-003. PKU-004 showed that 5, 10, and 20 mg/kg/day doses were well-tolerated and led to sustained plasma Phe reductions over a 22-week period [14], and that once-daily dosing at ≥10 mg/kg can sustain stable blood Phe concentrations. In addition, this study demonstrated a dose–response relationship between sapropterin and blood Phe reduction. [14]. PKU-006, a two-part Phase 3 efficacy trial for sapropterin dosed at 20 mg/kg/day, was conducted on 90 PKU children aged 4–12 years with blood Phe concentrations under control with a Phe-restricted diet. Forty-six of the 50 sapropterin responders (defined as ≥30% decrease in blood Phe and blood Phe concentration ≤300 μmol/L) who were identified in the 8-day, open-label, Part 1 of PKU-006 enrolled in the 10-week, randomized, placebo-controlled, Part 2 of the study to assess tolerance to increased Phe intake. Children taking sapropterin had a significant reduction in blood Phe ($p<0.001$; Part 1) and a significant increase in Phe intake ($p<0.001$; Part 2) [15]. Both PKU-004 and PKU-006 trials demonstrated acceptable safety profiles, with no severe or serious treatment-related adverse events reported [14,15].

2. Materials and methods

This Phase 3b, multicenter, multinational, open-label study was a 3-year extension trial to evaluate the long-term safety of sapropterin in patients with PKU who participated in studies PKU-004 (after previously completing PKU-001 and PKU-003) or PKU-006. Subjects were enrolled at 15 sites in the United States and Canada and 13 European sites in the United Kingdom, France, Germany, Ireland, Italy, Poland, and Spain. Conduct of the protocol was approved at individual centers by local institutional review boards or ethics committees. Study PKU-008 began in July 2006. The study was conducted in accordance with the US Code of Federal Regulations for clinical research studies, the International Conference on Harmonization Guidelines for Good Clinical Practice, and the Declaration of Helsinki. The study was registered on ClinicalTrials.gov under the study registration number NCT00332189.

2.1. Subjects

Inclusion to PKU-008 was limited to sapropterin responders who completed either PKU-004 [14] or PKU-006 or subjects in PKU-006 who terminated early due to elevated Phe concentrations after experimental increases in Phe intake [15]. Exclusion criteria included a screening alanine aminotransferase value >2× upper limit of normal (ULN; Grade 1 or higher per WHO Toxicity Criteria); concurrent use of levodopa or folate inhibitors; and pregnant females or subjects of childbearing potential not currently using or unwilling to continue with birth control.

Informed written consent was obtained from all subjects before inclusion in the study. For children <18 years old, written informed consent was obtained from a parent or guardian, and children provided their assent, if required as per local regulations.

2.2. Study design

Fig. B.1 shows the series of PKU studies that led to enrollment in PKU-008. Some subjects were off of sapropterin therapy between completion of PKU-004 or PKU-006 and enrollment in PKU-008. After study PKU-008 was open for enrollment at their clinic site, subjects who were actively participating in studies PKU-004 or PKU-006 could enroll and participate in PKU-008 without interruption in therapy.

Subjects enrolled in PKU-008 were to receive once-daily oral administration of sapropterin and be evaluated for safety for up to three years (36 months) or until one of the following occurred: the subject withdrew consent and discontinued the study; the subject discontinued the study at the discretion of the investigator and in accordance with the investigator's clinical judgment; the drug became available via the appropriate marketing approval; or the study was terminated.

2.3. Dosing and mode of administration

Subjects were prescribed between 5 and 20 mg/kg/day oral sapropterin taken once daily and provided as tablets containing 100 mg of sapropterin each; daily doses were rounded up or down to the nearest 100 mg. All subjects who enrolled from PKU-004 began PKU-008 at the dose they were taking at the end of PKU-004. Because PKU-006 Part 2 was a blinded study and drug assignments were not revealed before subjects were enrolled in PKU-008, all subjects who enrolled from PKU-006 began PKU-008 at 20 mg/kg/day sapropterin despite PKU-006 treatment assignment (sapropterin or placebo). Investigators could adjust subjects' dose levels up or down in increments of approximately 5 mg/kg/day within a range of 5 to 20 mg/kg/day to control blood Phe concentrations in accordance with local clinical site recommendations.

Subjects dissolved sapropterin tablets in 4 to 8 oz (120 to 240 mL) of water or apple juice for at least the first 3 months. After a Phase 1