DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WRITTEN REQUEST

IND 69,708

BioMarin Pharmaceutical, Inc.
Attention: Ben Dewees, Senior Manager, Regulatory Affairs
105 Digital Drive
Novato, CA 94949

Dear Mr. Dewees:

Reference is made to your February 22, 2007, Proposed Pediatric Study Request for Kuvan™ (sapropterin dihydrochloride).

To obtain needed pediatric information on Kuvan, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the following studies:

Type of studies:

A study to evaluate the pharmacokinetics, safety, and effectiveness of Kuvan (sapropterin dihydrochloride) administration to pediatric patients with tetrahydrobiopterin- (BH4-) responsive phenylketonuria (PKU), ages 0 months (birth) through four years of age, inclusive. Effectiveness will be extrapolated from studies in the older pediatric patients, since the pathophysiology of PKU is the same in all ages.

You may either perform this as two separate studies, or as a combined study in two parts as indicated below.

Single Study in Two Parts or Two Separate Studies

Part 1: Pharmacokinetic (PK), pharmacodynamic (PD), and safety study of Kuvan administration to pediatric patients with PKU, ages 0 months (birth) through four years of age. All patients must be diet controlled on a PKU diet at entry and throughout the study. Patients will receive Kuvan 20 mg/kg/day for at least one week. Response to treatment in Part 1 will be defined as a $\geq$20% decrease from Baseline blood Phe levels (from entry into Part 1 of the study) at End of Part 1 (e.g., Day 7 of treatment). A population PK approach with optimal samplings may be used. An open-label, uncontrolled study design is acceptable.

Part 2: PK, PD, and safety study of Kuvan administration to pediatric patients with PKU, ages 0 months (birth) through four years of age, who respond to treatment with Kuvan in Part 1 of the study. Response will be defined as a $\geq$20% decrease from Baseline blood Phe levels (from entry into Part 1 of the study) at End of Part 1 (e.g., Day 7 of treatment). Effectiveness will be assessed in Part 2 by change in blood Phe levels from Baseline (no-treatment) during treatment in the study. Patients will be administered Kuvan for six months (including one week of treatment in Part 1). A population PK

approach with optimal samplings may be used. An open-label, uncontrolled study design is acceptable.

A minimum of 60 BH4-responsive patients with PKU (responders) will complete at least six months of treatment with Kuvan in Part 2 of the study. BH4-responsive patients will be defined as patients who demonstrate a ≥20% decrease in blood Phe from Baseline at End of Part 1 (while on a PKU-controlled diet). The number of patients enrolled into Part 1 of the study should be estimated based on the projected number of responders in Part 1 (defined as patients who demonstrate a ≥20% decrease in blood Phe from Baseline at End of Part 1), and on the projected numbers of drop-outs over the course of the entire study (Parts 1 and 2).

These studies must take into account adequate (e.g., proportionate to study population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

Indication to be studied:

Treatment to reduce blood phenylalanine (Phe) levels in patients with hyperphenylalaninemia (HPA) due to BH4-responsive PKU.

Age group in which study(ies) will be performed:

Patients with PKU, ages 0 months (birth) through four years old, are to be entered in the study. At least half of the patients enrolled must be less than one year of age at the time of entry into the study.

Number of subjects:

A minimum of 60 BH4-responsive patients with PKU (responders) will complete at least six months of treatment with Kuvan in Part 2 of the study. BH4-responsive patients will be defined as patients who demonstrate a ≥20% decrease in blood Phe from Baseline at End of Part 1 (while on a PKU-controlled diet). The number of patients enrolled into Part 1 of the study should be estimated based on the projected number of responders in Part 1, and on the projected numbers of drop-outs over the course of the entire study (Parts 1 and 2).

Study endpoints:

The objectives and endpoints for the study are:

1. To evaluate the safety and tolerability of Kuvan administration for up to six months of treatment to pediatric patients with BH4-responsive PKU, ages 0 months to 4 years. Safety assessments must include, at minimum, physical examinations (to include, at a minimum, height, weight, and head circumference), medical history, and safety laboratory collections (including, at minimum, chemistry panel, complete blood count, and urinalysis) at Baseline and at intervals during treatment, and the collection of Adverse Events during treatment.

   Growth and neurocognitive development must be assessed periodically as age-appropriate. Standardized and replicated measurements of head circumference (less than 3 years of age), weight and length/height must be obtained. Neurodevelopment must be assessed using well-

validated and age-appropriate measures, including the Bayley III and an additional validated scale in patients two years of age and older.

2. To evaluate the pharmacokinetics of Kuvan administration for up to six months of treatment to pediatric patients with BH4-responsive PKU, ages 0 months to 4 years. Appropriate PK parameters should be assessed (e.g., AUC, apparent clearance, Tmax, $T_{½}$, apparent volume of distribution, Cmax, and other parameters as appropriate).

3. To evaluate the effectiveness of Kuvan administration for up to six months of treatment to pediatric patients with BH4-responsive PKU, ages 0 months to 4 years. Effectiveness will be assessed by the pharmacodynamic measure of change in blood Phe levels from Baseline during treatment in these patients. In Part 1, the efficacy outcome variable is the number of patients who respond to treatment with Kuvan administration, as evidenced by a $\geq$20% decrease in blood Phe level from Baseline (pre-treatment) after one week of treatment. In Part 2, the efficacy outcome variable is the change in blood Phe level from Baseline (no treatment) after six months of treatment in the subgroup of patients who respond to treatment with Kuvan in Part 1 of the study.

Inclusion criteria:

Patients must meet all of the following criteria to be enrolled in this study:

- Patients will have a laboratory-confirmed diagnosis of PKU documented in the medical record.

- Documentation in the medical record of two blood Phe laboratory test results obtained at least three days apart while the patient was otherwise healthy, and within three months prior to enrollment.

- Patients must be PKU-diet controlled at entry and throughout the study.

Exclusion criteria:

Patients will be excluded if the meet any one of the following criteria:

- Patient has undergone liver transplantation.

- Patient has been diagnosed with tetrahydrobiopterin (endogenous BH4) deficiency.

Study Stop Criteria:

The study will be stopped, a safety review will be conducted by the medical monitor, and FDA will be notified, if two patients experience grade 3, or one patient experiences grade 4 or greater adverse events according to Common Terminology Criteria for Adverse Events v3.0 (CTCAE; http://ctep.cancer.gov/forms/CTCAEv3.pdf).

Patient Withdrawal Criteria:

Patients will be withdrawn for therapeutic failure, defined as failure of blood Phe to decrease by a minimum of 20% upon completion of at least one week of dosing (completion of Part 1).

Drug information

- *dosage form:*

  Fully dissolvable tablets, fully dissolvable powder, or liquid may be administered. Whole tablet formulations are not appropriate for the ages being studied.

- *route of administration:*

  Oral

- *regimen*

  Kuvan will be administered at a starting dose of 20 mg/kg/day once daily. In patients who respond to Kuvan, the dose may be adjusted within the range of 5 to 20 mg/kg/day according to response to therapy.

  Use an age-appropriate formulation in the study(ies) described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

  If 1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives marketing approval), 2) the Agency publishes the exclusivity determination notice required under section 505A(e)(1) of the Act, and 3) you have not marketed the formulation within one year after the Agency publishes such notice, the Agency will publish a second notice reflecting the fact that the approved pediatric formulation has not been marketed, in accordance with section 505A(e)(2).

  If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

Drug specific safety concerns:

Your safety monitoring plan will include a baseline medical history, vital signs, physical examination, including measurements of growth (i.e., height and weight, and head circumference for patients less than two years of age), developmental assessments (e.g., Bailey III, WISC), electrocardiograms, and clinical laboratory tests (chemistry, hematology, and urinalysis).

Patients will remain at the study site for six hours after receipt of the first dose, and will have vital signs measured every fifteen minutes for the first hour, and hourly up through the sixth hour. Electrocardiograms will be performed at the sixth hour (estimated time of maximum concentration). Medical history, vital signs, physical examinations, and clinical laboratory tests will be performed weekly for the first month of dosing, then monthly until the completion of the study. Developmental assessments will be performed at Screening/Baseline and after six months of treatment with Kuvan (or at study discontinuation/withdrawal).

Provide a complete list of chemistry, hematology, and urine analyses you plan to test. Blood chemistry analysis should include, at minimum, liver enzyme tests, such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, and gamma-glutamyl transferase (GGT). Hematology testing should include, at minimum, a complete blood count (CBC), including hemoglobin, hematocrit, platelet count, and white blood cell count (WBC) with differential.

Safety will be assessed by evaluating the number and type of adverse events occurring during the study, and by changes from baseline in vital signs, physical examinations, clinical laboratory testing, electrocardiograms, and developmental assessment results.

Statistical information, including power of study(ies) and statistical assessments:

In the PK study, the PK parameters of tetrahydrobiopterin may be summarized using descriptive statistics.

Safety and effectiveness: Provide a statistical test of the null hypothesis that the mean change from baseline in blood Phe levels at the end of Part 2 equals zero. Use descriptive statistics for other measures.

Labeling that may result from the studies:

You must submit proposed pediatric labeling to incorporate the findings of the studies. Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that Kuvan is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the studies. Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the studies.

Format and types of reports to be submitted:

You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. These postmarketing adverse event reports should be submitted as narrative and tabular reports.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the FDA website at http://www.fda.gov/CDER/REGULATORY/ersr/Studydata.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www.fda.gov/Cder/guidance/7087rev.htm.

Timeframe for submitting reports of the study(ies):

Reports of the above studies must be submitted to the Agency on or before May 31, 2009. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

Response to Written Request:

Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

Furthermore, if you agree to conduct the study(ies), but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit protocols for the above study(ies) to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC**

EXCLUSIVITY STUDY" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the study(ies) should be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 301-827-5911.

1. In accordance with section 505A(k)(1) of the Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/cder/pediatric/index.htm

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found at www.ClinicalTrials.gov.

If you have any questions, call Cristi Stark, Regulatory Project Manager, at 301-796-1007.

Sincerely,

{See appended electronic signature page}

Dan Shames, M.D.
Deputy Director
Office of Drug Evaluation III, HFD-180
Center for Drug Evaluation and Research

Linked Applications	Sponsor Name	Drug Name
IND 69708	BIOMARIN PHARMACEUTICALS INC	PHENOPTIN(SAPROPTERIN HCL/6R-BH4/TABLETS

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/s/

BRIAN K STRONGIN
01/08/2008
Please sign

DANIEL A SHAMES
01/14/2008