



IND 060492
NDA 022363

WRITTEN REQUEST

Kowa Research Institute, Inc.
Attention: Ross S. Laderman, MPH
Vice President, Regulatory Affairs
430 Davis Drive, Suite 200
Morrisville, NC 27560

Dear Mr. Laderman:

Reference is made to your July 6, 2016, Proposed Pediatric Study Request for pitavastatin.

There are two proposed pediatric studies. The first study (hereafter, Study 1), titled, "A Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, 12-Week Study of Pitavastatin in High-Risk Hyperlipidemia in Childhood," proposes to investigate pitavastatin in the treatment of pediatric patients with high-risk hyperlipidemia (excluding homozygous hyperlipidemia). An open-label extension period, outlined in a separate protocol (hereafter, Study 2), titled, "A 52-Week Open-Label Extension and Safety Study of Pitavastatin in High-Risk Hyperlipidemia in Childhood," is proposed for patients completing the double-blind study as well as for additional eligible patients.

Familial hypercholesterolemia (FH) is a genetic disorder resulting in a deficient or defective LDL receptor associated with elevated cholesterol levels and premature atherosclerotic cardiovascular disease (ASCVD) with a frequency of about 1 in 300 to 500 in some populations.¹ Total cholesterol concentrations in heterozygous FH patients (HeFH) are typically in the range of 350 to 550 mg/dL. Although ASCVD does not generally manifest until middle age in patients with HeFH, in addition to diet modifications, current guidelines advocate statin treatment in HeFH patients to be considered from age 8 years and up.^{2,3,4} Neonates are not included in this written request because HeFH is not diagnosed at this age.

¹ Goldberg AC, et al. Familial Hypercholesterolemia: Screening, diagnosis and management of pediatric and adult patients. Clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J of Clinical Lipidology* 2011; 5, S1-S8.

² Goldberg AC, Toth P, et.al. Familial Hypercholesterolemia: Screening, diagnosis and management of pediatric and adult patients. Clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *Journal of Clinical Lipidology* 2011;5:S1-S8.

³ Expert Panel on Ingested Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report. *Pediatrics* 2011; 128; S213-S256.

⁴ European Atherosclerosis Society Consensus Panel. Familial hypercholesterolemia in children and adolescents: gaining decades of life by optimizing detection and treatment. *European Heart Journal* 2015; 36: 2425-2437.

To obtain needed pediatric information on pitavastatin, 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 studies described below.

- *Nonclinical study(ies):*

In order to further support the safety evaluation in children younger than 10 years of age, you should evaluate the toxicity of pitavastatin, a lipophilic statin, in juvenile animals of a pharmacologically relevant species exposed during the period of development appropriate for the intended pediatric age range. This toxicity study should evaluate the effects of pitavastatin on neurobehavioral endpoints (including learning and memory) and should include a complete histopathologic evaluation of the central and peripheral nervous systems (including effects on myelination). The results of this study will inform whether your existing clinical trial in pediatric patients with HeFH included adequate safety monitoring, especially for patients younger than 10 years.

- *Clinical studies:*

Study 1: A double-blind, randomized, placebo-controlled trial to evaluate the efficacy and safety of three dose levels of pitavastatin in pediatric patients who are 8 to 16 years (inclusive) of age with heterozygous familial hypercholesterolemia (HeFH). The trial must consist of a screening/washout period and a 12-week double-blind treatment period. Study endpoints must include safety, lipid-lowering, and PK profile of pitavastatin.

Study 2: A 52-week safety study of pitavastatin in pediatric patients who are 8 to 16 years (inclusive) of age with HeFH; blinding of treatment assignment is not required. This study will include patients who have completed Study 1, described above, but may also include eligible pediatric patients who were not enrolled in Study 1. All patients enrolled in the study will be assigned to treatment with the lowest dose of pitavastatin studied. During the study, the dose of pitavastatin may be up-titrated based on clinically appropriate, protocol-defined LDL-C thresholds.

- *Objective of Study 1:* The primary objective of this study is to compare the efficacy of pitavastatin to placebo with regard to percentage reduction in LDL-C from baseline to Week 12 in pediatric patients with HeFH.
- *Objective of Study 2:* The primary objective of this study is to assess the safety and tolerability of pitavastatin in pediatric patients with HeFH over a period of at least 52 weeks.
- *Patients to be Studied (Studies 1 & 2):*
 - Age group in which study(ies) will be performed: Patients ages ≥ 8 years to 16 years (inclusive). (Younger patients may be included in the same study if required by other global regulatory authorities.)

- Number of patients to be studied: A sufficient number of patients must be randomized to Study 1 to provide for at least 80 evaluable patients (8 to 16 years, inclusive, with HeFH and either LDL-C \geq 190 mg/dL or LDL-C \geq 160 mg/dL with additional CV risk factors) at the efficacy endpoint (Week 12). Randomization to pitavastatin or placebo (in a 3:1 ratio) must be stratified by age (\geq 10 years vs. younger) and baseline LDL-C in each dose group. All patients who complete Study 1 should be encouraged to enroll in Study 2; additional patients (8 to 16 years, inclusive, with HeFH) may be enrolled directly into Study 2 to provide for at least 80 evaluable patients \geq 8 years of age. A sufficient number of patients to characterize the safety in patients younger than 12 years of age must be enrolled.

Representation of Ethnic and Racial Minorities: The studies must take into account adequate (e.g., proportionate to disease 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.

- *Study endpoints:*

- *Pharmacokinetic Endpoints (Study 1):*

The pharmacokinetic endpoints for Study 1 must include pitavastatin and pitavastatin lactone concentrations at trough and 1-hour postdose at each dose level.

- *Efficacy Endpoints (Study 1):*

The primary efficacy endpoint for Study 1 will be the mean percent change in LDL-C from Baseline to Week 12 for each treatment group compared to placebo. Secondary endpoints must include the change in lipid and lipoprotein parameters from Baseline to Week 12 in non-HDL-C, total cholesterol, HDL-C, fasting triglycerides, and Apo B. Measures of compliance with diet and study medication must be assessed through dietary assessment and counts of unused study medication, respectively.

- *Safety Endpoints (Study 1 and Study 2):*

- Safety outcomes must include incidence and severity of adverse events, clinical laboratory measures (including assessment of liver-related chemistries such as ALT, AST, alkaline phosphatase, bilirubin, and albumin; creatine kinase; serum creatinine and urinalysis; adrenal, gonadal, and pituitary hormones), vital signs, and physical examination (including height, weight, and Tanner staging).
- All adverse events must be monitored until symptom resolution or until the condition stabilizes.
- A Data Monitoring Committee (DMC) must be included because of the possibility of rhabdomyolysis. See Guidance: Establishment and Operation of Clinical Trial Data Monitoring Committees
<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126578.pdf>

- *Known Drug Safety concerns and monitoring:*

Pitavastatin labeling includes a warning for the risk of myopathy/rhabdomyolysis and liver enzyme abnormalities. Effects on liver and muscle should be prospectively monitored by blood chemistries, as described above, at least every 4 weeks during Study 1 and at the following timepoints during Study 2: Baseline, Week 4, Week 8, Week 12, Week 16, Week 28, Week 40 and Week 52/Early Termination. The protocol must include stopping criteria relevant to these risks.

- *Extraordinary results:* In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

- *Drug information:*
 - *dosage form:* Tablet
 - *route of administration:* Oral
 - *regimen:* Once dailyUse 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.

In accordance with section 505A(e)(2), if

- you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
- the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
- you have not marketed the formulation within one year after the Agency publishes such notice,

the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

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 prepared 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 preparing an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using such a formulation, the following information must

be provided for inclusion in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step preparation 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.

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

Study 1

The primary null hypothesis is that each dose of pitavastatin is equal to placebo with respect to the primary endpoint, LDL-C change from baseline at Week 12. The alternative hypothesis is that each dose of pitavastatin and placebo are different with respect to the primary efficacy endpoint.

The primary analysis population must be all patients randomized who have received at least 1 dose of the study drug. With respect to the primary efficacy analysis, we are interested in estimating the treatment effect based on the de facto (intent-to-treat) estimand, i.e., the difference in LDL-C change in all randomized patients regardless of adherence to treatment or use of rescue. You should include provisions to limit missing data through study design and education of investigators and patients, and conduct analyses using methods to account for missing data for the primary and key secondary efficacy analyses in a fashion consistent with what the measurements would have been, had they been collected. We recommend designs that encourage continued collection of efficacy data even after study treatment discontinuation, and these post-treatment data should be included in the primary analysis.

Secondary efficacy objectives must include comparisons between each dose of pitavastatin and placebo with respect to the following parameters:

- Percent change in LDL-C from baseline over 12 weeks of treatment (Week 4, Week 8, and Week 12)
- Percent changes in HDL-C, non-HDL-C, total cholesterol, fasting triglycerides, and Apo B from baseline over 12 weeks of treatment

A total sample size of 80 patients (age ≥ 8 years) should provide both sufficient safety follow-up and at least 90% power under the assumption that treatment difference=25% and standard deviation=15%.

Sensitivity analyses should be included to study the limitations of the primary analysis. For each sensitivity analysis, you should describe what limitation(s) of the data or assumption(s) of the primary analysis are being evaluated and how the sensitivity analysis achieves this. We also expect sensitivity analyses to address the potential effect of missing data on the reliability of results regardless of the extent of the missing data. The use of LOCF is not appropriate for handling missing data because it relies on the strong,

untestable, and implausible assumption that outcomes remain constant after patients drop out and, as a single-imputation approach, it does not take into account the statistical uncertainty in the imputation process.

Study 2:

At least 80 patients (ages 8 to 16 years, inclusive, with HeFH) should be treated with pitavastatin in this 52-week, open-label safety study. Descriptive data must be provided for safety endpoints (see above). The analysis must also include a descriptive summary of the efficacy results by age group.

- *Labeling that may result from the study(ies):* You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that pitavastatin 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 study(ies). 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 study(ies).
- *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. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.

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 <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.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, 2018. 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) must 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, CDER, FDA, Document Control Room, Metro Park North VII, 7620 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.

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). These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e. complete or partial response);
2. the status of the application (i.e. withdrawn after the supplement has been filed or pending);

3. the action taken (i.e. approval, complete response); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872>

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 Martin White, M.S., Regulatory Project Manager, at (240) 402-6018.

Sincerely,

{See appended electronic signature page}

Curtis J. Rosebraugh, MD, MPH
Director
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CURTIS J ROSEBRAUGH
11/02/2016