



NDA 21-445

**WRITTEN REQUEST
AMENDMENT #1**

MSP Singapore Co., LLC
Schering Corporation, U.S. Agent
Attention: Deborah Urquhart, Ph.D.
Regulatory Fellow, Global Regulatory Affairs
2000 Galloping Hill Road
Kenilworth, NJ 07033

Dear Dr. Urquhart:

Please refer to your correspondence dated July 23, 2004, requesting changes to FDA's April 15, 2004, Written Request for pediatric studies for ezetimibe. We also refer to our April 19, 2004, letter.

We have reviewed your proposed changes and are amending the Written Request. We have removed the requirement for the measurement of bone age and insulin-like growth factor and the timeframe for submitting reports of the study has been lengthened. The full text of the Written Request, as amended, follows. The changes are indicated by underline and strikeout. This Written Request supersedes the Written Request dated April 15, 2004.

Type of study: A three-period, efficacy and safety study of ezetimibe combined with an approved statin for the treatment of heterozygous familial hypercholesterolemia (HeFH) in adolescents with HeFH who have failed dietary intervention per guidelines of the American Academy of Pediatrics (Reference 1):

- Period One: Six-week, randomized, double-blind, parallel dose group study. Dose groups are to include approved (for heterozygous familial hypercholesterolemia) pediatric doses of the selected statin given as monotherapy or with ezetimibe. For example, if the selected statin has doses of 10 mg, 20 mg, and 40 mg approved for use in adolescents, there are to be six dose groups in the study: statin 10 mg plus placebo, statin 20 mg plus placebo, statin 40 mg plus placebo, statin 10 mg plus ezetimibe 10 mg, statin 20 mg plus ezetimibe 10 mg, and statin 40 mg plus ezetimibe 10 mg. The study is to include at least 180 randomized subjects, and at least 30 subjects randomized per Step One treatment group. After completion of Step One, patients will then enter:
- Period Two: Twenty-seven-week, double-blind, parallel group study of the maximum approved (for heterozygous familial hypercholesterolemia) pediatric dose of the selected statin, given with ezetimibe 10 mg or matching placebo. Patients will then enter:
- Period Three: Twenty-week, open-label, extension study of ezetimibe 10 mg given in combination with the selected statin, with titration of the statin dose to low-density lipoprotein cholesterol (LDL-C) goal (by National Cholesterol Education Program guidelines).

Indication to be studied:

Treatment (adjunctive to diet) of heterozygous familial hypercholesterolemia.

Age group in which study will be performed:

Boys and postmenarchal girls, ages ≥ 10 years and ≤ 17 years, Tanner stage \geq II. A reasonable balance of gender (e.g., no fewer than 30% of one gender) should be attained at randomization.

Study endpoints:

- Primary:
Percent change from baseline in LDL-C at six weeks; pooled ezetimibe/statin versus statin monotherapy.
- Secondary:
Percent change from baseline in LDL-C at six weeks; ezetimibe/statin versus statin monotherapy at each given statin dose level.

Percent change from baseline in LDL-C, total cholesterol (total-C), and apolipoprotein B (Apo B) at 33 weeks: ezetimibe/statin versus statin monotherapy.

Proportion of subjects who reach LDL-C goal at week 33.

Change in stadiometric linear growth, Tanner stage, ~~bone age~~, menstrual cycle monitoring (in girls), ~~insulin-like growth factor I (IGF-1) levels~~, steroid hormone levels, and other pertinent safety laboratory values at 33 and 53 weeks.

Drug information:

- ***Dosage form:*** tablet
- ***Route of administration:*** oral
- ***Regimen:*** 10-mg ezetimibe tablet once daily, given with a statin approved for treatment of heterozygous familial hypercholesterolemia in adolescents.

Drug-specific safety concerns:

- Liver function test abnormalities
- Linear growth
- Sexual maturation
- Steroid hormone biosynthesis
- Angioedema
- Pancreatitis
- Statin-related concerns, e.g., myopathy, rhabdomyolysis, and drug interactions

Statistical information, including power of study and statistical assessments:

The primary efficacy variable will be percent change from baseline in LDL-C at 6 weeks (Period 1). The primary analysis will use an ANOVA model with fixed effects for a statin dose (e.g., 10, 20, 40 mg), treatment (ezetimibe, placebo), statin dose x treatment interaction, and appropriate covariates.

The primary comparison of ezetimibe versus placebo, pooled across doses of statin, will be assessed using this model. The primary comparison will be performed using a two-tailed test, at the 5% significance level, of the null hypothesis that the mean percent changes in LDL-C in the ezetimibe and placebo treatment groups (pooled across statin doses) are equal. The test of interaction will be performed to assess whether data from each treatment group can be pooled across statin doses.

If the primary treatment comparison is statistically significant, LDL-C at week 33 (Period 2) will be compared between ezetimibe/statin versus placebo/statin using an ANOVA with fixed effects for treatment and appropriate covariates.

Secondary efficacy parameters at Weeks 6 and 33 include HDL-C, total-C, ApoB, and TG and will be analyzed using appropriate statistical models.

The primary analysis population is the ITT population consisting of all randomized patients with at least one baseline and one on-treatment LDL-C value.

Labeling that may result from the study:

Appropriate sections of the label may be changed to incorporate the findings of the study.

Format of reports to be submitted:

Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study must 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 one of the following designations must be used: Hispanic/Latino or Not Hispanic/Latino.

Timeframe for submitting reports of the study:

Reports of the above studies must be submitted to the Agency on or before ~~April 28, 2004,~~ November 22, 2008. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Response to Written Request:

As per the Best Pharmaceuticals for Children Act, section 4(A), within 180 days of receipt of this Written Request, you must notify the Agency as to your intention to act on the Written Request. If you agree to the request, then you must indicate when the pediatric studies will be initiated.

Submit protocols for the above studies 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. Notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Please clearly mark your submission, **“PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES”** in large font, bolded type at the beginning of the cover letter of the submission.

Submit reports of the studies as a **supplement to an approved NDA** with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, 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. In addition, send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

In accordance with section 9 of the Best Pharmaceuticals for Children Act, *Dissemination of Pediatric Information*, if a pediatric supplement is submitted in response to a Written Request and filed by FDA, FDA will make public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted. This disclosure, which will occur within 180 days of supplement submission, will apply to all supplements submitted in response to a Written Request and filed by FDA, regardless of the following circumstances:

1. the type of response to the Written Request (complete or partial);
2. the status of the supplement (withdrawn after the supplement has been filed or pending);
3. the action taken (i.e., approval, approvable, not approvable); or
4. the exclusivity determination (i.e., granted or denied).

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request “**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**” in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

Additionally, item #4 in our April 19, 2004, letter regarding the protocol is deleted. The remaining items are as follows:

1. Your current entry criteria include a mode of entry for “LDL-C > 159 mg/dL with at least one biologic parent with genotype-confirmed heterozygous familial hypercholesterolemia.” The biologic parent with the specified genotype should also have an LDL > 159 mg/dL.
2. Include a maximum untreated study subject LDL of 600 mg/dL at entry.
3. Perform stadiometry and assessment of sexual maturation phase at 53 weeks as well as at your other planned time points.
4. Use the American Academy of Pediatrics’ guidelines for the trial of dietary intervention and for the definition of dietary treatment failure (Committee on Nutrition, American Academy of Pediatrics. Cholesterol in Childhood. Pediatrics 1998 Jan. 101(1):141-7).
5. Specify criteria for study discontinuation for abnormal liver function tests and creatine phosphokinase levels.
6. Include menstrual cycle monitoring for girls.
7. Require that girls use an acceptable mode of contraception.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

If you have any questions, call Valerie Jimenez, Regulatory Project Manager, at (301) 827-9090.

Sincerely,

{See appended electronic signature page}

Robert J. Meyer, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Reference:

1. Committee on Nutrition, American Academy of Pediatrics. Cholesterol in Childhood. Pediatrics 1998 Jan. 101(1):141-7.

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/s/

Robert Meyer

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