DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

IND 58,627

GlaxoSmithKline
Attention: Anne Stokely, M.S.P.H.
Director, Antiviral/Anti-infective Regulatory Affairs
Five Moore Drive
Research Triangle Park
North Carolina 27709

Dear Ms. Stokely:

Reference is made to your Proposed Pediatric Study Request submitted on July 16, 2001 to IND 58,627 for GW433908 for treatment of HIV disease.

To obtain needed pediatric information on GW433908, 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), that you submit information from the following studies:

- Type of study:

  Multiple-dose pharmacokinetic and safety study of GW433908 alone and GW433908 in combination with low-dose ritonavir in HIV-infected pediatric patients and HIV-exposed neonates (born to HIV-infected mothers).

- Indication to be studied:

  Treatment of HIV infection

- Age group in which studies will be performed:

  Birth to less than 17 years

- Study endpoints:

  Pharmacokinetics
  Pharmacokinetic parameters such as: Cmax, Cmin, Cavg, Tmax, t ½, AUC, and clearance

  Safety and tolerability
  Safety data should be collected on approximately 100 patients with at least 25 being HIV-exposed neonates.

  HIV-infected pediatric patients should be followed for safety for a minimum of six months at the recommended dose. HIV-exposed neonates (born to HIV-infected mothers) should have safety assessments for a minimum of six months after start of therapy. In addition, please also submit

your plans for long-term safety monitoring in HIV-exposed neonates and HIV-infected pediatric patients who have received GW433908.

Activity
Assessment of changes in plasma HIV RNA levels and in CD4 cell counts (in HIV-infected pediatric patients).

- Drug information:

-Dosage form: capsules and age-appropriate formulation
-Route of administration: oral
-Regimen: to be determined by development program

- Drug specific safety concerns:

GW433908
Potential amprenavir drug interactions (as described in the APV labels)
Rash, including Stevens-Johnson syndrome
Gastrointestinal symptoms
Elevated liver transaminase levels
Elevated trigylcerides
Metabolic disorders such as hyperglycemia, hyperlipidemia, abnormal fat redistribution.

Ritonavir
Asthenia
Nausea
Anorexia
Abdominal pain
Diarrhea
Vomiting
Taste perversion
Circumoral and peripheral paresthesias
Elevated liver transaminase levels
Metabolic disorders such as hyperglycemia, hyperlipidemia, abnormal fat redistribution
Potential drug interactions (as described in the Ritonavir labels)

- Data analysis:

1. *Descriptive analyses of multiple-dose pharmacokinetic, safety and activity data in HIV-infected pediatric patients generated by studies requested in this letter.*

2. *Descriptive analyses of multiple-dose pharmacokinetic and safety data in HIV-exposed neonates (born to HIV-infected mothers).*

3. *Assessment of how tolerability of the liquid formulation affects total dose consumed (e.g., how much of each administered dose is completely swallowed). For each child, include general information for the entire study and specific information for pharmacokinetic sampling days.*

4. *Information related to the proper re-suspension of the formulation by caregivers.*

5. *Characterization of genotypic and phenotypic resistance in pediatric patients.*

6. *A minimum number of pediatric patients (as stated below) should complete the pharmacokinetic study(ies) conducted to characterize pharmacokinetics for dose selections. Final selection of the sample size for each age group should take into account all potential sources of variability. As study data are evaluated, the sample size should be increased as necessary for characterization of pharmacokinetics across the intended age range.*

   Birth to < six weeks: 12 patients
   Six weeks to < six months: 12 patients
   Six months to < two years: 12 patients
   Two years to < six years: 12 patients
   Six years to < 12 years: eight patients
   12 years to < 17 years: six patients

- Labeling that may result from the studies:

  Information regarding dosing, safety and activity in HIV-infected pediatric patients and dosing and safety in HIV-exposed neonates

- 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. Please include other information as appropriate.

- Timeframe for submitting reports of the studies:

  Reports of the above studies must be submitted to the Agency on or before August 2004. Please remember that pediatric exclusivity extends only existing patent protection or exclusivity that has not expired or been previously extended at the time you submit your reports of studies in response to this Written Request.

Please 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. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. 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.

Reports of the studies should be submitted as **a new drug application or as a supplement to an approved NDA** with the proposed labeling changes you believe would be 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, 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.

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.

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 in the pediatric population.

If you have any questions, call Destry M. Sillivan, Regulatory Project Manager, at 301-827-2335.

Sincerely,

{See appended electronic signature page}

Jeffrey Murray, M.D., for
Mark Goldberger, M.D.
Acting Director
Office of Drug Evaluation IV
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/

Jeffrey Murray

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