DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 19-661
NDA 21-304

Roche Pharmaceuticals
Attention: Polly Wang, Ph.D.
Drug Regulatory Affairs
3401 Hillview Avenue
Palo Alto, California 94304-1397

Dear Dr. Wang:

Reference is made to your Proposed Pediatric Study Request submitted on July 25, 2000 to IND 48,106 for valganciclovir. Reference is also made to NDA 19-661 and NDA 20-460 for ganciclovir.

To obtain needed pediatric information on ganciclovir and valganciclovir, 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:

Study #1

- *Type of study: Single*-dose, open label, dose escalation pharmacokinetic and safety study of valganciclovir in pediatric renal transplant recipients.

- *Study objectives:* 1.) To determine the once daily dose of oral valganciclovir that will achieve a ganciclovir 24-hour AUC equivalent to that achieved with standard dosage regimens of intravenous (I.V.) ganciclovir; and 2.) to determine the pharmacokinetics of ganciclovir following oral administration of valganciclovir liquid and I.V. administration of ganciclovir.

- *Indication to be studied:* Prevention of CMV disease.

- *Age group in which study will be performed*: A minimum of approximately 24 patients with at least 8 patients in each of 3 age groups: ≤ 2 years; > 2 years to puberty; and post-puberty.

- *Study endpoints:* Pharmacokinetic parameters such as: CL, V_{ss}, AUC_{0-24}, C_{max}, and $t_{1/2}$.

- *Dosage form:* Ganciclovir for I.V. infusion; age-appropriate formulation of valganciclovir.

- *Route of administration:* I.V. (ganciclovir), oral (valganciclovir)

- *Drug specific safety concerns*: Leukopenia, neutropenia, anemia, and thrombocytopenia.

- *Statistical assessments:* 1.) The pharmacokinetic analyses will be based on population approach; the parameters of interest usually include Total CL, V_{ss}, AUC_{0-24}, C_{max} and $t_{1/2}$; and 2.) descriptive analysis of safety data.

Study #2

- *Type of study:* Single dose, open label, non-comparative pharmacokinetic and safety study in pediatric liver transplant recipients.

- *Study objectives:* 1.) To determine the pharmacokinetics of ganciclovir following oral administration of valganciclovir; and 2.) to collect safety data in a population of pediatric liver transplant recipients.

- *Indication to be studied:* Prevention of CMV disease.

- *Age group in which study will be performed*: A minimum of approximately 20 liver transplant recipients from 3 months to 16 years of age with at least 4 patients in each of 3 age groups: ≤ 2 years; 2 to 6 years; and > 6 years.

- *Study endpoints:* 1.) Pharmacokinetic parameters such as: total clearance, V_{ss}, AUC_{0-12}, AUC_{0-24}, C_{max}, and $t_{1/2}$; and 2.) incidence of CMV disease.

- *Dosage form:* Ganciclovir for IV infusion; age-appropriate formulation of valganciclovir.

- *Route of administration:* I.V. (ganciclovir), oral (valganciclovir)

- *Drug specific safety concerns*: Leukopenia, neutropenia, anemia, and thrombocytopenia.

- *Statistical assessments:* 1.) Descriptive analysis of safety data; and 2.) descriptive analysis of pharmacokinetic data.

Study #3

- *Type of study:* Multi-center, open label, single dose, non-comparative safety and pharmacokinetic study in pediatric patients with solid organ transplants.

- *Study objectives:* 1.) To determine the pharmacokinetics of ganciclovir following oral administration of valganciclovir; and 2.) to collect safety data in a population of pediatric solid organ transplant recipients.

- *Indication to be studied:* Prevention of CMV disease.

- *Age group in which study will be performed*: A minimum of 60 patients with solid organ transplants at risk for CMV disease with at least 10 patients ≤ 2 years of age, and at least 15 patients in each age group of 2 years-puberty and post-puberty.

- *Study endpoints:* 1.) Pharmacokinetic parameters such as: total clearance, V_{ss}, AUC_{0-12}, AUC_{0-24}, C_{max}, and $t_{1/2}$; and 2.) incidence of CMV disease.

- *Dosage form:* Age-appropriate formulation of valganciclovir

- *Route of administration:* Oral

- *Drug specific safety concerns*: Leukopenia, neutropenia, anemia, and thrombocytopenia.

- *Statistical assessments:* 1.) Descriptive analysis of safety data; and 2.) descriptive analysis of pharmacokinetic data.

Study #4

- *Type of study*: Single-dose and multiple-dose pharmacokinetic and tolerability study of valganciclovir liquid formulation in a neonatal population with congenital CMV disease

- *Study objectives:* The determination of appropriate dosing of valganciclovir and collection of safety data in a neonatal population.

- *Indication to be studied:* Treatment of congenital CMV disease.

- *Age group:* Birth to approximately 3 months (number of patients adequate to determine dose).

- *Study endpoints:* 1.) Pharmacokinetic parameters such as CL/F, V/F, AUC, C_{max} and $t_{1/2}$; 2.) plasma CMV virologic measurements; and 3.) collection of long-term safety data following administration of valganciclovir to neonates with congenital CMV infection.

- *Dosage form:* Liquid

- *Route of administration:* Oral

- *Drug specific safety concerns:* Leukopenia, neutropenia, anemia, and thrombocytopenia.

- *Statistical assessments:* 1.) Descriptive analysis of safety data; and 2.) descriptive analysis of pharmacokinetic data.

- *Labeling that may result from these studies:* Appropriate sections of the label may incorporate dosing information for 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.

- *Timeframe for submitting reports of the study:* Reports of the above studies must be submitted to the Agency on or before January 1, 2004. Please remember that pediatric exclusivity only attaches to existing patent protection or exclusivity that has not expired 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, please call Leslie Stephens, Regulatory Project Manager, at 301-827-2335.

Sincerely,

{See appended electronic signature page}

Dianne Murphy, M.D.
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/

Mark Goldberger
6/21/01 01:48:27 PM
Mark J Goldberger signing for M. Dianne Murphy