DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

August 5, 2005

Donald Mattison, MD
Senior Advisor to the Directors of NICHD and CRMC
National Institutes of Health
6100 Executive Blvd, RM 4B05
Rockville, MD 20852

Dear Dr. Mattison,

The Food and Drug Administration (FDA) issued a Written Request to all approved application holders to study the following drug:

- Rifampin for the treatment of cerebrospinal fluid shunt infections

Per section 3 of the Best Pharmaceuticals for Children Act, the FDA is hereby referring this Written Request to the National Institutes of Health for possible conversion into a Request for Contract Proposal. Should you have any questions, please do not hesitate to contact me at 301-594-7337.

Sincerely,

Lisa Mathis, MD
Acting Director
Division of Pediatric Drug Development, HFD-960
Office of Counter-Terrorism and Pediatric Drug Development
Center for Drug Evaluation and Research

Attachments:
cc: Duane Alexander, MD
Director, NICHD

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CERTIFIED MAIL
RETURN RECEIPT REQUESTED

NDA
NDA

Dear :

To obtain needed pediatric information on the active moiety, rifampin, the Food and Drug Administration (FDA) is hereby making a formal Written Request (WR), pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from studies in pediatric patients described below. These studies investigate the use of rifampin for management of Cerebrospinal Fluid Shunt Infections in pediatric patients.

Background and rationale:

Cerebrospinal fluid (CSF) shunts are used to treat hydrocephalus by transferring CSF from the lateral ventricles to either the peritoneum, ventriculoperitoneal shunt (VP), or to the right atrium, ventriculoatrial shunt (VA). In the United States, there are approximately 18,000 CSF shunts placed in children each year for management of hydrocephalus caused by meningomyelocele, congenital communicating or obstructive hydrocephalus, intraventricular hemorrhage, tumors, or meningitis. Many CNS shunts are placed in children less than 6 months of age.

Shunt infection is a serious complication of CSF shunt placement and may result in meningitis, ventriculitis, peritonitis, bacteremia and/or endocarditis. The symptoms on presentation may include headache, stiff neck, change in consciousness, abdominal pain, and fever. However, some patients develop only indolent fever and shunt malfunction, especially with infection caused by less virulent organisms. The incidence of shunt infections reported by centers ranges from <1% to over 30%, with an average of approximately 10%. The incidence of infection when shunts are placed before 6 months of age is about 15% and for those placed after 6 months of age, the incidence is about 6%. The incidence of shunt infection is highest in the youngest patients. Because more shunts are placed before 6 months of age, more than half of all shunt infections are reported in children who have the shunt placed before 6 months of age.

The infection is usually caused by bacteria that colonize the shunt at the time of implantation; consequently, 70% of infections occur within 2 months and 90% occur within 6 months of shunt placement.

Gram-positive bacteria, particularly staphylococci, are the most common cause of shunt infections in pediatric patients. Coagulase-negative staphylococci (CONS) including *S. epidermidis* have been reported to be the etiologic agents of 20% to 80% of CSF shunt infections and *S. aureus* in 10% to 40% of infections. The percentage of CSF shunt infections due to methicillin-resistant *S. aureus* (MRSA) varies from center to center.

The American Society of Pediatric Neurosurgeons conducted a practice survey in 1999, published in 2001, on the management of CSF shunt infection and reported that approximately 60% of pediatric neurosurgeons remove the shunt and replace it with an external ventricular drain (EVD) while about 30% externalize the shunt without removing it. In present day clinical practice the percentage of pediatric neurosurgeons who remove the shunt and place an external drain is probably closer to 80% to 90%. Most surgeons replace the shunt after 2 or 3 successive daily CSF cultures have been negative for 48 to 72 hours. Some surgeons, however, treat the patient for 1 week after sterilization of CSF prior to reimplantation. The duration of antimicrobial therapy given after the shunt is replaced varies significantly.

The reported cure rate of CSF shunt infections, treated with shunt removal, placement of an external drain, and antimicrobial therapy to achieve CSF sterilization before shunt reimplantation, is approximately 88%. Intravenous vancomycin is routinely administered for all MRSA and CONS shunt infections. In some institutions, rifampin and intravenous gentamicin are included as part of the initial therapeutic regimen. If a patient fails to sterilize the CSF, some physicians may, within the practice of medicine, use other antimicrobial options. Rifampin is not currently approved by FDA for the treatment of CSF shunt infections.

Experience in the treatment of other staphylococcal infections such as prosthetic valve endocarditis suggests that the addition of rifampin may improve response compared to therapy with vancomycin alone. Published case reports describe patients with *S. aureus* meningitis and patients with gram-positive CSF shunt infections who were failing therapy and who improved following the addition of rifampin. Rifampin's better CNS penetration than vancomycin (even in the absence of inflammation) and the possibility of synergism with vancomycin are considerations in support of evaluating the effect of adding rifampin to vancomycin in the treatment of MRSA and CONS CSF shunt infections. Several studies which have looked at the *in vitro* interaction of rifampin with vancomycin have produced varying results. Most show an indifferent (or additive) effect, some show synergism, and rarely antagonism is demonstrated. Adverse events which may occur with rifampin include hepatic dysfunction, hypersensitivity reactions, hematological adverse events, rashes, and drug interactions.

Therefore, the purpose of this WR is to evaluate the effects on outcomes of adding rifampin to vancomycin to treat CNS shunt infections due to MRSA or CONS. Potential effects of adding rifampin might include a shorter time to CSF sterilization, a higher cure rate, and/or a lower relapse rate. A shorter time to sterilization might result in less time to shunt reimplantation and a shorter hospital stay. It will also be important to obtain information on dosing, pharmacokinetics (PK), pharmacodynamics (PD), and the safety of rifampin in children when used in combination with vancomycin for the treatment of staphylococcal CSF shunt infections.

Type of Study:

A randomized, active-controlled trial to evaluate the safety and efficacy of rifampin in the pediatric population when used in the treatment of CSF shunt infections due to MRSA or CONS.

- All patients will receive protocol-specified antimicrobials (vancomycin versus vancomycin plus rifampin) and will undergo shunt removal and placement of an EVD. The protocol may also include provisions for additional empiric antimicrobial therapy to treat suspected gram-negative pathogens with a third generation cephalosporin for the first 24 to 48 hours (until culture results are available).
- The study must also include a sub-study evaluating the pharmacokinetics of intravenous and oral rifampin in children with CSF shunt infections in the following age groups:
  (1) 1 month to < 6 months
  (2) 6 months to 16 years.

Study Objectives:

Primary efficacy objective:

To determine if the addition of rifampin to vancomycin is
- superior to vancomycin alone in decreasing time to CSF sterilization (sterilization defined as the first negative CSF culture confirmed by two subsequent negative CSF cultures, each taken at least approximately 24 hours apart); and
- that the relapse rate at 6 months is not inferior to vancomycin therapy alone.

Secondary objectives:
- To compare the time from onset of therapy to resolution of the clinical signs and symptoms of shunt infection between the two treatment groups.
- To compare the time from onset of therapy to shunt replacement between the two treatment groups.
- To compare the rate of failure to achieve CSF sterilization defined as failure to achieve 3 consecutively negative CSF cultures obtained at least approximately 24 hours apart between the two treatment groups.
- To compare the mortality rates and adverse event rates within the 6-month post-randomization follow-up period between the two treatment groups.
- To describe the plasma pharmacokinetics of intravenous rifampin before the shunt is replaced in pediatric patients with CSF shunt infections due to MRSA or CONS for those patients in the pharmacokinetic sub-study.
- To describe the plasma pharmacokinetics of oral rifampin before the shunt is replaced in pediatric patients with CSF shunt infections due to MRSA or CONS for those patients in the pharmacokinetic sub-study.
- To measure CSF concentrations of rifampin and other protocol-specified antimicrobials for those patients in the pharmacokinetic sub-study to determine if minimum inhibitory concentrations are being attained in the CSF.
- To determine the plasma peak and trough concentrations for other protocol-specified antimicrobials for which such measurement is clinically appropriate.

Study Design:

- The proposed study will be a randomized, multi-center, active-controlled trial, designed to demonstrate that vancomycin plus rifampin plus removal of the shunt and placement of an EVD is superior to vancomycin plus removal of the shunt and placement of an EVD in decreasing the time to CSF sterilization and that there is no difference (based upon a pre-specified non-inferiority margin) in the relapse rate during the 6 month follow-up period. Patients to be enrolled will be pediatric patients (ages 1 month to 16 years of age) with CSF shunt infections due to MRSA or CONS. All antimicrobials will be initially administered intravenously. Patients may be switched to oral rifampin therapy as specified in the protocol.

- Following enrollment in the study, a CSF sample will be obtained and cultured approximately 24 hours following the first dose of study treatment. Subsequent CSF samples will be obtained and cultured approximately every 24 hours. Bacterial isolates from all positive CSF cultures must be tested for susceptibility to the study medication, including rifampin, because rifampin-resistance may emerge during treatment.

- Three consecutive negative CSF cultures, each obtained at least approximately 24 hours apart, are required to define treatment success; therefore, patients will require a minimum of four days of study treatment to sterilize the CSF. The maximum duration of study treatment to CSF sterilization (i.e. to three consecutively negative CSF cultures) should be specified and justified in the protocol.

- Patients who achieve CSF sterilization will be regarded as treatment successes for the sterilization endpoint. Patients who fail to achieve CSF sterilization will be regarded as a treatment failure. Patients who develop resistance to the antimicrobial treatment regimen and those whose clinical condition is deteriorating at any time during the study in the opinion of the investigator will be regarded as a treatment failure. Treatment failures should receive alternative therapy as deemed appropriate by the investigator and should continue to be followed for the duration of the study. Complete clinical and postmortem information should be collected on all patients who die while on therapy or during the 6 month follow-up period. Patients who die will be regarded as treatment failures.

- The protocol will specify the criteria that need to be met before the shunt is replaced. At a minimum, one criterion should be that at least 3 consecutive negative CSF cultures, each obtained at least approximately 24 hours apart, should be documented. The protocol will state that shunt replacement should occur, if surgically feasible, within 24 to 48 hours after adequate CSF sterilization is achieved, and the time of shunt replacement must be documented in the case report form. The duration of antimicrobial therapy after the shunt is replaced will be specified in the protocol and should be of equal duration in the two arms.

Indication to be Studied:

- Use of adjunctive rifampin therapy in combination with vancomycin in the treatment of CSF shunt infections due to MRSA or CONS.

Age Groups in which Studies will be Performed:

Pediatric patients
- 1 month to <6 months
- 6 months to 16 years

Number of Patients:

The study will enroll an appropriate number of patients to be sufficiently powered (at least 80%) to detect a statistically significant treatment effect with the addition of rifampin to vancomycin. The proposed sample size must be justified and should include a discussion of expected bacteriologic cure rates, times to CSF sterilization and 6-month post-randomization relapse rates in the two treatment arms.

Pharmacokinetics Sub-studies:

In a subgroup of patients in the clinical trial, characterization of multiple-dose intravenous and oral rifampin pharmacokinetics is required during the time period prior to shunt replacement in each age group described above. The timing of the initiation of this pharmacokinetic evaluation in relation to the number of IV and oral doses of rifampin administered must be specified in the protocol. For any individual patient in this sub-study, pharmacokinetic characterization of both formulations is not required, particularly in young patients due to blood volume constraints. A minimum of 8 pediatric patients should be studied in the 1 month to <6 months age range and a minimum of 12 patients in the 6 months to 16 years age range. Patients should be approximately uniformly distributed between the sexes and across the specified age range.

Inclusion Criteria:

- Patients with any of the following:
  - gram-positive cocci only on a gram stain of the CSF in patients with VA or VP shunts (note: these patients will be empirically treated pending results of the CSF culture and confirmation of MRSA or CONS); or
  - a positive CSF culture for staphylococci only (yet to be further identified and pending confirmation of MRSA or CONS) in patients with VA or VP shunts; or
  - a positive CSF culture for MRSA or CONS only infections in patients with VA or VP shunts.

    (Note: the study protocol must include and justify reliable diagnostic methods)
- Patients in whom the infected shunt will be removed and an EVD placed at the time of randomization.

Exclusion Criteria:

- CSF shunt infection due to methicillin-sensitive *S. aureus*, (if sensitivities are known prior to enrollment), gram-negative or fungal pathogens.
- Patients in whom removal of the shunt cannot be performed.

Additional Protocol Issues:

- If the culture of the CSF sample obtained at the time of randomization does not yield MRSA or CONS, demonstrates a pathogen other than MRSA or CONS, or one resistant to the study treatment regimen, the patient will become clinically unevaluable for efficacy in the per protocol analysis, but will be followed for safety and receive appropriate therapy.
- The method of differentiating between relapse of baseline infection and re-infection should be specified and include microbiological methodology.
- The specific type of CNS shunt hardware used should be recorded for each patient.
- The dosing regimen for vancomycin will be justified and specified in the protocol.

Study Endpoints:

Co-Primary Efficacy Endpoints:

- Time to the first negative CSF culture obtained post-randomization and shunt removal and confirmed by two subsequent consecutive negative CSF cultures obtained approximately 24 hours apart.
- Relapse rate during the 6-month post-randomization follow-up period.

Secondary Endpoints:

- Time to resolution of clinical signs and symptoms.
- Time to shunt replacement.
- Rate of failure to achieve CSF sterilization defined as failure to achieve 3 consecutively negative CSF cultures obtained at least approximately 24 hours apart.
- Adverse event rates within 6 months post-randomization.
- Mortality rate within 6 months post-randomization.

Safety Endpoints:

- Safety assessments will include analysis of all clinical and laboratory adverse events, including mortality rates, within 6 months post-randomization.

Pharmacokinetic Endpoints:

- CSF concentrations of rifampin and other protocol-specified antimicrobials at protocol-specified time points.
- Plasma concentrations of rifampin at protocol-specified time points.
- Plasma peak and trough concentrations of other protocol-specified antimicrobials where clinically appropriate.

Pharmacokinetics (PK) Sub-study for Rifampin:

Plasma concentration versus time profiles of rifampin following multiple intravenous and oral dose administration will be determined for the patients enrolled in the pharmacokinetic sub-study. To the extent possible, PK parameters such as clearance (CL), volume distribution (Vd), elimination half-life ($T_{1/2}$), maximum drug concentration (Cmax) and minimum drug concentration (Cmin), time to maximum drug concentration (Tmax), and area under the

concentration-time curve (AUC), should be determined. Relevant FDA guidance documents regarding pediatric and population pharmacokinetic evaluation are available at the FDA website (http://www.fda.gov/cder/guidance/index.htm).

Drug Information:

Rifampin Dosage and Administration

The protocol will pre-specify and justify a specific dose and dosing frequency for each formulation:

- Intravenous: 10-20 mg/kg/day, up to 600 mg/day rifampin, administered in either one or two divided doses daily. The specific dose and regimen of administration will be justified and specified in the protocol.
- Oral: Rifampin (e.g., Rifadin®) 150 mg or 250 mg capsules should be administered as whole capsules, as freshly prepared suspension in a vehicle recommended in the product labeling, or given with infant formula, whichever is appropriate for the age of and acceptability to the patient. The specific dose, the dosing interval, the maximum allowable total dose, and the vehicle chosen for oral administration will be justified and specified in the protocol. The timing of administration of oral rifampin in relation to ingestion of food should also be specified in the protocol. If rifampin is not to be given with food, the time of the last feeding prior to drug administration should be recorded.

Drug Specific Safety Concerns:

Routine safety assessments, such as vital signs, weight, serum chemistry, and monitoring for adverse events must be collected at baseline and at protocol-specified intervals throughout the study. Monitoring will be appropriate for detecting adverse events, including but not limited to hepatotoxicity, renal toxicity, hemolytic anemia, thrombocytopenia, gastrointestinal effects, seizures and dermatological and hypersensitivity reactions. Patients should be maintained on protocol-specified safety monitoring even if the experimental or control regimen is discontinued, i.e., consenting subjects should remain on the safety study regardless of therapeutic course after enrollment. Compliance with protocol-specified antimicrobials must be monitored throughout the study. All efforts should be made to minimize loss to follow-up of study patients.

Statistical Information, Including Power of Study and Statistical Assessment

The study must have a pre-specified statistical analysis plan that should be finalized and submitted to the Agency for review prior to data analysis. The study must be designed to ensure adequate power (at least 80%) with a two-sided alpha level of 0.05 between the experimental and control groups on the primary endpoint of superiority in time to CSF sterilization and non-inferiority in relapse rate based on a pre-defined non-inferiority margin. Justification needs to be provided in the study protocol for selection of the non-inferiority margin in the 6-month relapse rate.

At a minimum, the primary analysis will:

- Provide descriptive analysis of all demographic and baseline data.
- Stratify by confirmed baseline infection (MRSA or CONS).
- Include all treatment failures.
- Exclude all patients enrolled and later confirmed to not have an infection due to MRSA or CONS, based on a baseline CSF culture from the efficacy analysis (all patients will be included in safety analysis).

Relapse of baseline infection within 6-months post-randomization is a clinically important endpoint. Assessment of the ultimate benefit of rifampin will include its effect on time to CSF sterilization as well as the 6-month post-randomization relapse rate and safety evaluation of the treatment regimen.

Sample Size Calculation:

Sufficient justification must be provided in the study protocol and statistical analysis plan for determining sample size for the primary endpoints. The proposed sample size must be justified by providing expected bacteriologic cure rates, expected times to CSF shunt replacement, expected 6-month relapse rates, and appropriate references. The expected number of patients failing to have a baseline infection due to MRSA or CONS must also be taken into account when determining the sample size.

Interim Analysis and Data Monitoring Review Committees:

Planned interim analyses should be discussed in the statistical analysis plan including appropriate adjustments to the alpha level. The inclusion of a Data Monitoring Committee (DMC) should be discussed along with appropriate monitoring guidelines and operating procedures. Please refer to FDA draft guidance, "Guidance for Clinical Trial Sponsors on the Establishment and Operation of Clinical Trial Data Monitoring Committees", available from the internet at http://www.fda.gov/cber/gdlns/clindatmon.htm, for specific information.

~~Labeling Changes that may Result from these~~ Studies:

~~Appropriate sections of the rifampin product labeling may~~ be revised to incorporate descriptions of the conducted studies along with clinical and microbiologic efficacy, safety and pharmacokinetic data results.

Format of Reports to be Submitted:

~~Full study reports not previously subm~~itted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. Pharmacokinetic study reports must include analytical method and assay validation, individual drug and/or metabolite concentration-time data and individual pharmacokinetic parameters.

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(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 one of the following designations should be used: Hispanic/Latino or Not Hispanic/Latino.

Time Frame for Submitting Reports of the Studies:

Reports of the above studies must be submitted to the Agency on or before March 1, 2009. 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 3, if we do not hear from you within 30 days of the date of this Written Request, we will refer this Written Request to the Director of the NIH. If you agree to the request, then you must indicate when the pediatric studies will be initiated.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED IN RESPONSE TO WRITTEN REQUEST**" 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. 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 must be submitted as a new drug application (NDA) 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 - COMPLETE RESPONSE TO WRITTEN REQUEST**" 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.

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:

- the type of response to the Written Request (complete or partial);
- the status of the supplement (withdrawn after the supplement has been filed or pending);

- the action taken (i.e. approval, approvable, not approvable); or
- the exclusivity determination (i.e. granted or denied).

FDA will post the medical and clinical pharmacology review summaries on the FDA website at http://www.fda.gov/cder/pediatric/Summaryreview.htm and publish in the *Federal Register* a notification of availability.

If you wish to discuss any amendments to this Written Request, 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.

As a reminder, you are responsible for compliance with section 113 of the Food and Drug Administration Modernization Act of 1997 and section 15 of the Best Pharmaceuticals for Children Act of 2002 by registering certain clinical trials in the Clinical Trials Data Bank (<http://clinicaltrials.gov/>) <<http://prsinfo.clinicaltrials.gov/) >>. If your drug is for the treatment of a serious or life-threatening disease or condition and you are conducting trials to test its effectiveness, then you must register the trials. For additional information on registering your clinical trials, including the required and optional data elements, refer to the Protocol Registration System (PRS) Information Site (<<http://prsinfo.clinicaltrials.gov>>) and FDA's Guidances for Industry entitled *"Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions"* (March 2002; revised draft January 2004).

If you have any questions, please call

Sincerely,

Mark J. Goldberger, M.D., M.P.H.
Director
Office of Drug Evaluation IV
Center for Drug Evaluation and Research