DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Center for Scientific Review; Amended Notice of Meeting

Notice is hereby given of a change in the meeting of the Center for Scientific Review Special Emphasis Panel, May 25, 2004, 8:30 a.m. to May 25, 2004, 5 p.m., Hyatt Regency Bethesda, One Bethesda Metro Center, 7400 Wisconsin Avenue, Bethesda, MD, 20814 which was published in the **Federal Register** on April 29, 69 FR 23517.

The meeting will be held at The Latham Hotel, 3000 M Street, NW., Washington, DC 2007. The date and time remain the same. The meeting is closed to the public.

Dated: May 6, 2004.

LaVerne Y. Stringfield,

Director, Office of Federal Advisory Committee Policy.

[FR Doc. 04–11096 Filed 5–14–04; 8:45 am]

BILLING CODE 4140–01–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Prospective Grant of Exclusive License: 1,8-Naphthalimide Imidazo [4,5,1-de] Acridones With Anti-Tumor Activity

AGENCY: National Institutes of Health, Public Health Service, DHHS.

ACTION: Notice.

SUMMARY: This is notice, in accordance with 35 U.S.C. 209(c)(1) and 37 CFR part 404.7(a)(1)(i), that the National Institutes of Health, Department of Health and Human Services, is contemplating the grant of an exclusive patent license to practice the inventions embodied in U.S. Patent 6,664,263 issued December 16, 2003, entitled ''1,8-Naphthalimide Imidazo [4,5,1-de] Acridones with Anti-Tumor Activity'' (DHHS Reference No. E–289–1999/0), and all related foreign patents/patent applications, to Reata Discovery, Inc., which is located in Richardson, TX. The patent rights in these inventions have been assigned to the United States of America.

The prospective exclusive license territory will be worldwide and the field of use may be limited to human pharmaceutical uses of 1,8-naphthalimide imidazo [4,5,1-de] acridones as anti-cancer agents.

DATES: Only written comments and/or applications for a license which are received by the NIH Office of Technology Transfer on or before July 16, 2004 will be considered.

ADDRESSES: Requests for copies of the patent, inquiries, comments and other materials relating to the contemplated exclusive license should be directed to: George G. Pipia, Ph.D., Technology Licensing Specialist, Office of Technology Transfer, National Institutes of Health, 6011 Executive Boulevard, Suite 325, Rockville, MD 20852–3804; Telephone: (301) 435–5560; Facsimile: (301) 402–0220; and e-mail: *pipiag@mail.nih.gov.*

SUPPLEMENTARY INFORMATION: The present invention relates to novel bifunctional molecules with anti-tumor activity. These agents are composed of an imidazoacridone moiety linked by a nitrogen containing aliphatic chain of various length and rigidity to another aromatic ring system capable of intercalation to DNA.

Previous studies on related symmetrical bis-imidazoacridones revealed that only one planar imidazoacridone moiety intercalates into DNA. The second aromatic moiety, which is crucial for biological activity, resides in a DNA groove, and is believed to interact with DNA-binding proteins. It is hypothesized that the action of bis-imidazoacridone constitutes a new paradigm of how small molecules can interfere with the gene transcription.

To enhance the biological activity, the inventors have developed asymmetrical compounds in which one imidazoacridone system, with relatively poor DNA-intercalating properties, was replaced with much stronger intercalators, such as 3-chloro-7-methoxyacridine or naphthalimide moieties. These new compounds, especially those containing a naphthalimide moiety, are extremely *cytotoxic in vitro* against variety of tumor cells (IC50 at low nanomolar range) and kill tumor cells by inducing apoptosis. *In vivo,* in nude mice xenografted with human tumors, the compounds significantly inhibited growth of such tumors as colon tumor HCT116 and Colo205 as well as pancreatic tumors.

The prospective exclusive license will be royalty bearing and will comply with the terms and conditions of 35 U.S.C. 209 and 37 CFR part 404.7. The prospective exclusive license may be granted unless within sixty (60) days from the date of this published notice, the NIH receives written evidence and argument that establish that the grant of the license would not be consistent with the requirements of 35 U.S.C. 209 and 37 CFR part 404.7.

Applications for a license in the field of use filed in response to this notice will be treated as objections to the grant of the contemplated exclusive license. Comments and objections submitted to this notice will not be made available for public inspection and, to the extent permitted by law, will not be released under the Freedom of Information Act, 5 U.S.C. 552.

Dated: May 7, 2004.

Steven M. Ferguson,

Director, Division of Technology Development and Transfer, Office of Technology Transfer, National Institutes of Health.

[FR Doc. 04–11088 Filed 5–14–04; 8:45 am]

BILLING CODE 4140–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Request for Public Comment on a Written Request Issued by the Food and Drug Administration in the Use of Azithromycin for the Treatment of *Ureaplasma urealyticum* Pneumonia in the Preterm Neonate and Prevention of Bronchopulmonary Dysplasia

ACTION: Notice.

SUMMARY: The National Institutes of Health (NIH) is requesting public comment on the following Written Request issued by the Food and Drug Administration (FDA) for off-patent drugs as defined in the Best Pharmaceuticals for Children Act (BPCA). The Written Request was referred to NIH by FDA as required by the BPCA. The Written Request was developed following formulation of an NIH-generated priority list, which prioritizes certain drugs most in need of study for use by children. The priority list was produced in consultation with the FDA, other NIH Institutes and Centers, and pediatric experts, as mandated by the BPCA. The studies that are described in the Written Request are intended to characterize the safety, efficacy, and pharmacokinetics of the drug for optimum use in pediatric patients.

DATES: Comments are requested within 90 days of publication of this notice.

ADDRESSES: Submit comments to: Anne Zajicek, M.D., Pharm. D., National Institute of Child Health and Human Development, 6100 Executive Boulevard, Suite 4B–09, Bethesda, MD 20892–7510, telephone 301–435–6865 (not a toll-free number), e-mail *BestPharmaceuticals@mail.nih.gov.*

FOR FURTHER INFORMATION CONTACT: Anne Zajicek, M.D., Pharm. D., National Institute of Child Health and Human Development, 6100 Executive Boulevard, Suite 4B–09, Bethesda, MD 20892–7510, telephone 301–435–6865 (not a toll-free number), e-mail *BestPharmaceuticals@mail.nih.gov.*

SUPPLEMENTARY INFORMATION: The NIH is providing notice of Written Requests issued by the FDA, and is requesting public comment. On January 4, 2002, President Bush signed into law the Best Pharmaceuticals for Children Act (BPCA). The BPCA mandates that NIH, in consultation with the FDA and experts in pediatric research, shall develop, prioritize, and publish an annual list of certain approved drugs for which pediatric studies are needed. In response to this list, the FDA then issues a Written Request to holders of the New Drug Application (NDA) or abbreviated New Drug Application (aNDA) to request that pediatric studies be performed in order to provide needed safety and efficacy information for pediatric labeling. If the Written Request is declined by the NDA/aNDA holder (s), the Written Request is referred to NIH, specifically the NICHD. A Request for Proposal (RFP) is then issued based on the Written Request, and proposals are reviewed by a peer-review process for contract award.

In order to assure that the most appropriate pediatric studies are delineated in the RFP, public comment of the Written Requests for the use of azithromycin in treatment of Ureaplasma urealyticum pneumonia in the preterm neonate and prevention of bronchopulmonary dysplasia is hereby requested by NIH.

Dated: May 10, 2004.

Duane Alexander,

Director, National Institute for Child Health and Human Development, National Institutes of Health.

Azithromycin Written Request

Dear Contact: To obtain pediatric information on the use of intravenous azithromycin, the FDA is hereby making a formal Written Request, pursuant to section 505A of the Federal Food, Drug and Cosmetic Act, that you submit information from studies in pediatric patients described below.

Rationale

Respiratory tract colonization with Ureaplasma urealyticum may be a factor in the development of neonatal bronchopulmonary dysplasia (BPD). Although this has not been proven, macrolide antibiotics have been used to eradicate U. urealyticum colonization from the respiratory tract in this subpopulation. Literature suggests that macrolide antibiotics may also have an anti-inflammatory effect. The objective of these studies will be to investigate the safety and effectiveness of intravenous azithromycin for the prevention of BPD in preterm neonates colonized with U. urealyticum.

Azithromycin offers several potential advantages for treatment of U. urealyticum-colonized premature neonates. In vitro data indicate that U. urealyticum is susceptible to azithromycin. The intracellular accumulation of azithromycin and its tissue penetration are potential advantages for the treatment of intracellular pathogens. Azithromycin is likely to have fewer drug interactions than the other macrolides, since it is minimally metabolized and has a low potential to inhibit hepatic CYP 450 isozymes. However, there is minimal information about azithromycin dosing, efficacy, and safety in the neonatal period. Further, some macrolide antibiotics have been associated with adverse effects, such as pyloric stenosis and cardiac arrhythmias, and it is unknown whether azithromycin carries similar risk.

Types of Studies

(1) Single Dose Pharmacokinetic (PK) Study:

- To characterize single dose intravenous (I.V.) azithromycin pharmacokinetics, safety and tolerability in mechanically ventilated preterm neonatal patients with U. urealyticum endotracheal colonization at one or more clinically relevant doses.

(2) Multiple-dose, Exposure Response Study(-ies):

- To assess the effect of two or more dose regimens of I.V. azithromycin on U. urealyticum colonization of the respiratory tract of preterm neonatal patients.
- To characterize multiple-dose PK and safety of I.V. azithromycin.
- To determine appropriate testing methods for documentation of U. urealyticum colonization and eradication.
- To explore potential for azithromycin clinical effectiveness.

(3) Efficacy and Safety Studies:

- Two studies that each assesses I.V azithromycin efficacy and safety for the prevention of BPD in mechanically ventilated preterm neonatal patients with U. urealyticum endotracheal colonization.

These studies will be performed in the above sequence and results of each study submitted to and assessed by FDA prior to proceeding with the next study(ies). Results from the single dose PK study would be used in planning the exposure-response study(ies). Similarly, results from the exposure response study(ies) will be used, to the extent possible, for planning safety and efficacy studies.

Age Group in Which Studies Will Be Performed

Studies will be performed in preterm neonatal patients <72 hours of age.

Entry Criteria

Preterm male and female patients <72 hours of age who are at least 23 weeks gestational age and 500 grams weight at time of birth will be eligible for enrollment in the studies. These patients will be endotracheally intubated, mechanically ventilated and have vascular access at the time of randomization. Patients must have documented U. urealyticum endotracheal colonization at the time of randomization.

Patients for whom a decision has been made to withdraw medical support, or in whom potentially lethal congenital defect(s) has been diagnosed by the medical team, are not eligible for study. Patients with central nervous system infections suspected to be due to U. urealyticum will be excluded. The protocol will specify additional criteria for study inclusion/exclusion, including when there has been antenatal maternal treatment with a macrolide or sulfa containing antibiotic.

Study Design

Criteria for withdrawal of individual patients from any study will be defined in the protocol.

An independent Data Monitoring Committee (DMC) will be established for all exposure-response and safety and efficacy studies. The study stopping rules used by the DMC will be specified in all protocols.

Study Types 1 and 2: Studies that assess pharmacokinetics may use sparse sampling and population PK approach to minimize blood loss to individual patients. Bioanalytical methods to determine azithromycin concentrations must be capable of evaluating microliter sample volumes. Patients will be grouped by gestational age. A rationale will be provided for the grouping of patients by gestational age.

Appropriate testing methods for documentation of U. urealyticum colonization in the safety and efficacy trials will in part be determined from the exposure-response study(ies). Study(ies) Type 2 will use both endotracheal culture and polymerase chain reaction (PCR) as methods for

establishing respiratory tract colonization and the microbiological effect of azithromycin treatment. Additionally, Study(ies) Type 2 will evaluate the relationship between azithromycin dose and/or plasma exposure and microbiological eradication, and will explore potential for azithromycin clinical effectiveness.

Study Type 3: Two studies that assess efficacy and safety will be multicenter, randomized, double blind, and placebo controlled. There are numerous potential factors related to clinical management of sick preterm infants that may impact on the development of BPD (e.g. prenatal corticosteroids, postnatal corticosteroids, surfactant, type and mode of ventilation, inspired oxygen concentration (FiO2), fluid and electrolyte management and infant nutrition, vitamin A, congenital and nosocomial infections/pneumonia). The study will track and evaluate factors that may contribute to the development of BPD.

Patients will be stratified by gestational age in efficacy and safety studies. Other factors such as maternal chorioamnionitis and disease severity may be additionally considered. The rationale for patient stratification will be provided in protocols.

Number of Patients

Study Types 1 and 2: A sufficient number of patients to characterize single-dose and multiple dose pharmacokinetics will complete these studies. The protocol for these studies will be discussed with the FDA and agreed upon prior to initiation of the studies. Preterm neonates will be reasonably distributed by gender. The gestational age of these patients will reflect gestational age range of the efficacy and safety studies.

Study Type 3: Efficacy and safety studies will enroll a sufficient number of patients to ensure at least 80% statistical power to determine a treatment effect, at a 0.05 statistical significance level (two-tailed). All parameter estimates used in the sample size calculation will be specified and justified in the protocol.

Assessment Parameters

Pharmacokinetics (Studies Type 1 and 2): The plasma clearance and volume of distribution of I.V. azithromycin will be calculated and other PK parameters such as the maximum plasma concentration (C_{max}), time of C_{max} (T_{max}), area under the plasma concentration-time curve from zero to the last quantifiable concentration (AUC_{0-t}), the elimination rate constant (Ke), terminal elimination half-life ($t_{1/2}$), and AUC extrapolated to infinity ($AUC_{0-\infty}$) will be determined to the extent possible. Adequate rationale for excluding any of the aforementioned PK parameters will be provided. The protein binding of azithromycin should be determined over the range of clinically relevant concentrations.

Pharmacodynamics (Study(ies) Type 2): Microbiologic persistence of U. urealyticum will be assessed by culture and PCR.

Efficacy (Studies Type 2 and 3): For Study(ies) Type 2, endpoints for efficacy will be explored. For powered efficacy and safety studies (Study Type 3), the protocol will specify a clinically meaningful primary endpoint to assess the treatment effect of azithromycin. Examples of such endpoints may include survival without severe BPD, survival without BPD, incidence of BPD, or incidence of severe BPD. A definition of BPD will be specified in the protocol. This protocol definition must include BPD diagnostic criteria and address how a patient's requirement for supplemental oxygen will be determined.

Secondary endpoints will include overall mortality, incidence of co-morbidities of prematurity, number of days on the ventilator, number of days receiving oxygen supplementation, use of non-study antibiotics, and adverse events. Endpoints may also include the microbiological persistence of Ureaplasma.

Safety (Studies Types 1–3): Laboratory tests for safety must be performed on microliter serum samples. In addition, safety assessments will include occurrence of any adverse events (AEs), comorbidities of prematurity {*e.g.*, necrotizing enterocolitis (NEC), sepsis, retinopathy of prematurity (ROP), intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), patent ductus arteriosus (PDA)}, incidence of superinfections (particularly fungal infections), vital signs that include heart rate (HR), blood pressure (BP), respiratory rate (RR), pulse oximetry, electrocardiogram (EKG), standard laboratory assessments of hematologic, liver and renal function, assessments of hearing, and growth (weight, length and head circumference). AEs will be followed to their resolution or stabilization. Nosocomial infection will be tracked by pathogen.

Long-term outcomes (Study Type 3): Assessments of growth, neurodevelopmental and pulmonary outcomes will be performed. These assessments may include, but are not limited to, weight, length, head circumference, physical examination with neurologic assessment, neurodevelopmental evaluation using a validated instrument, adverse events, hospitalization with emphasis on reactive airway disease and infection, medication history and use of oxygen. Provisions for these assessments may be included in the safety and efficacy protocols, or these assessments may be included in additional study protocols. At a minimum, long-term assessments will be performed through 24 months of the patient's chronological age.

Drug Information

Dosage form: Approved intravenous formulation.

Route: Intravenous.

Regimen: To be determined.

Selection of doses in the single-dose studies will be guided by literature or current medical practice. Doses chosen for the subsequent trials will be guided by the results of preceding studies.

Drug Specific Safety Concerns

1. It is unknown whether azithromycin has an adverse events profile similar to that reported for other macrolide antibiotics. These include hypertrophic pyloric stenosis, and cardiac arrhythmias.

2. It is unknown whether there will be any adverse effects in this patient population related to the occurrence of phospholipidosis with azithromycin.

3. Colonization and infection with other bacterial (including macrolide-resistant organisms) and nonbacterial organisms (*e.g.*, fungus) may occur with azithromycin treatment.

4. Macrolides have been associated with hearing loss at high doses. The potential for hearing loss with azithromycin treatment in this population will be assessed.

Statistical Information

These studies must have a pre-specified and detailed statistical analysis plan appropriate to the study design and outcome measures. It will be discussed with the FDA and agreed upon prior to initiating studies.

Demographic and safety data will be tabulated and descriptive analysis of safety data will be provided. Descriptive statistics of pharmacokinetic data must also be provided and dose-response relationships and relationships between PK parameters and patient characteristics will also be explored.

Labeling that May Result From the Study(ies)

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

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 (including assay method validation information), assessment, and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities.

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. 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 (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. 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 to 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 NAME at PHONE NUMBER.

[FR Doc. 04–11062 Filed 5–14–04; 8:45 am]

BILLING CODE 4140–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Request for Public Comment on a Written Request Issued by the Food and Drug Administration in the Use of Rifampin for the Treatment of Bacterial Endocarditis Caused by Methicillin-Resistant *Staphylococcus aureus*

ACTION: Notice.

SUMMARY: The National Institutes of Health (NIH) is requesting public comment on the following Written Request issued by the Food and Drug Administration (FDA) for off-patent drugs as defined in the Best Pharmaceuticals for Children Act (BPCA). The Written Request was referred to NIH by the FDA as required by the BPCA.

The Written Request was developed following formulation of an NIH-generated priority list, which prioritizes certain drugs most in need of study for use by children. The priority list was produced in consultation with the FDA, other NIH Institutes and Centers, and pediatric experts, as mandated by the BPCA. The studies that are described in the Written Request are intended to characterize the safety, efficacy, and pharmacokinetics of the drug for optimum use in pediatric patients.

DATES: Comments are requested within 90 days of publication of this notice.

ADDRESSES: Submit comments to: Anne Zajicek, M.D., Pharm.D., National Institute of Child Health and Human Development, 6100 Executive Boulevard, Suite 4B–09, Bethesda, MD 20892–7510, telephone 301–435–6865 (not a toll-free number), e-mail *BestPharmaceuticals@mail.nih.gov.*

FOR FURTHER INFORMATION CONTACT: Anne Zajicek, M.D., Pharm.D., National Institute of Child Health and Human Development, 6100 Executive Boulevard, Suite 4B–09, Bethesda, MD 20892–7510, telephone 301–435–6865 (not a toll-free number), e-mail *BestPharmaceuticals@mail.nih.gov.*

SUPPLEMENTARY INFORMATION: The NIH is providing notice of Written Requests issued by the FDA, and is requesting public comment. On January 4, 2002, President Bush signed into law the Best Pharmaceuticals for Children Act (BPCA). The BPCA mandates that NIH, in consultation with the FDA and experts in pediatric research, shall develop, prioritize, and publish an annual list of certain approved drugs for which pediatric studies are needed. In response to this list, the FDA then issues a Written Request to holders of the New Drug Application (NDA) or abbreviated New Drug Application (aNDA) to request that pediatric studies be performed in order to provide needed safety and efficacy information for pediatric labeling. If the Written Request is declined by the NDA/aNDA holder(s), the Written Request is referred to NIH, specifically the NICHD. A Request for Proposal (RFP) is then issued based on the Written Request, and proposals are reviewed by a peer-review process for contract award. In order to assure that the most appropriate pediatric studies are delineated in the RFP, public comment of the Written Requests for the use of Rifampin for the treatment of bacterial endocarditis caused by methicillin-resistant S. aureus in pediatric patients is hereby requested by the NIH.

Dated: May 11, 2004.

Duane Alexander,

Director, National Institute for Child Health and Human Development, National Institutes of Health.

Rifampin Written Request

Dear Contact: To obtain needed pediatric information on this active moiety, 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 studies in pediatric patients described below. These studies investigate the use of rifampin for the management of infectious bacterial endocarditis in pediatric patients.

Background and Rationale

Infective endocarditis (IE) is a serious, life-threatening infection that requires hospitalization. The frequency of IE in hospitalized pediatric patients reported in the literature varies widely. The most widely quoted estimates are 55 to 78 cases of IE per 100,000 pediatric hospital admissions (PHA) but rates as low as 22/100,000 PHA and as high as 200/100,000 have been cited in the literature. Most of these estimates are individual hospital-based retrospective reviews. In a larger survey of 26 major cardiovascular medical center hospitals, Kaplan et. al. reported an average 11 cases of IE per center per year.