Request for Proposals

Further pharmaceutical development and manufacture of rectal formulations of Ceftriaxone for neonatal sepsis

1. PURPOSE

Roughly 15% of all new-born deaths are due to sepsis, a treatable infection. Disease progression from neonatal sepsis is rapid, requiring prompt effective parenteral antibiotic therapy. This is not always possible and causes 3 million deaths annually. Alternative strategies are needed to treat sick babies quickly. A rectal antibiotic could be successful in preventing neonatal mortality by reducing lethal delays in treating critically ill newborns, and could increase early management and adherence to treatment.

Ceftriaxone is one of three injectable antibiotics recommended for treatment of sepsis. It is currently being profiled for development as initial treatment of neonatal sepsis for home or first-level facility management in high burden neonatal mortality countries where injectable treatment of critically ill neonates is difficult or not possible.

Our target is a rectal formulation of ceftriaxone that delivers therapeutic drug concentrations for 10-17 hours to babies at risk of death from neonatal sepsis.

2. DEVELOPMENT HISTORY

With financial support from Saving Lives at Birth, and contractual agreements between Hoffman la Roche and the World Health Organization (WHO), pre-formulation studies and pre-clinical work with ceftriaxone has already been carried out on ceftriaxone to determine stability and bioavailability of rectal formulations to determine the feasibility for the development for a pre-referral treatment of very sick neonates.

We accessed relevant prior data on pharmaceutical development, toxicity and bioavailability from Hoffman la Roche the inventor of ceftriaxone. Specific analytical methods were developed and validated to permit pharmaceutical formulation development and stability studies and were used for ceftriaxone analysis, i.e. ceftriaxone content in raw material, binary mixtures and ceftriaxone formulations. After screening, developing and testing more than 100 formulations, assessing the parameters for manufacture on a laboratory and pilot scale, and evaluating bioavailability of formulations which passed 6 months accelerated preliminary stability testing for tropical zones (40°C/75%RH), we have now identified several prototype formulations and carried out pre-clinical bioavailability studies using these formulations, using validated analytical methods. The formulations tested were hard-shell gelatin capsules and rectodispersible tablets. The pharmacokinetic profiles suggest that these formulations are likely to achieve peak plasma concentrations of 20 ug/ml at 1 hour and trough concentrations of 4ug/ml at 12 h post dose in man. These initial results are promising for further industrial pharmaceutical development and production of clinical batches.

In order to progress and determine which of the rectal formulations is feasible for industrial production and achieves reliable bioavailability in Phase I/II human studies, we are now seeking to work with one or more pharmaceutical companies who already have experience with the development and manufacture of beta lactam finished products and have prior experience in submitting a regulatory file to local or international regulatory authorities for a new dosage form and route of administration or for filing a new drug application (NDA).

We have been provided with limited funding by the Bill & Melinda Gates Foundation to identify and transfer technology to one or more pharmaceutical companies and work with them to optimise
manufacturing feasibility and produce one or more clinical batches for clinical bioavailability assessment. We cannot fully subsidize this development and therefore the pharmaceutical company should be willing to invest its own funds in further development of ceftriaxone for the indication above. The immediate aim is to assess feasibility of industrial production and produce a clinical trial batch for Phase I studies within 1 year.

3. CHALLENGES

The main challenges in further development of feasible formulations are poor ceftriaxone stability in formulation and very limited free flowing properties of ceftriaxone powder. Only 48 excipients out of the 87 tested were found to be compatible.

Several manufacturing processes were tested with ceftriaxone powder and immediate and long term stability of processed powder was studied. The results indicate that ceftriaxone is not highly hydroscopic and it degrades in accelerated aging conditions (40°C/75%RH) when not protected. It can be wet during processing, but ceftriaxone degrades significantly if not dried rapidly and packaged appropriately. Ceftriaxone powder can be compressed with moderate compression forces, but high frictional forces alter its stability.

The chosen pharmaceutical partner company will need to:

- Optimise the prototype formulations for laboratory and pilot-scale manufacture according to ICH guideline Q8(R2) to develop the best two candidate formulations;
- Establish ICH stability of the best two prototypes which would allow use in Climatic Zones 3 and 4; and
- Produce clinical batches of the best two candidate formulations for Phase 1 clinical bioavailability determinations

4. RFP INSTRUCTIONS

4.1 Process

Ceftriaxone is listed by the WHO as an essential medicine. Since the Rocephin® patent expired in Europe in 2000 and in North America in 2005, generic products of the injectable formulation are available in many countries. There are a variety of suppliers of the Active Pharmaceutical Ingredient (API) and the injectable product ceftriaxone, and many beta-lactam finished product manufacturers.

We invite you to submit a Letter of Intent (LOI) covering your facilities for GMP manufacture, clinical formulation development and manufacture, as well as associated analytical development and quality control services (4.2 and 4.3 below) by close of business GMT 24 February 2017. All responses should be submitted in electronic format.

Based on this information, we will invite a few applicants to submit a full proposal with costings (item 5 below). A budget template will be supplied. All short-listed bidders requested to submit a full proposal and costing may request further clarifications by addressing their questions in writing to the contact address identified, no later than 21 days after being invited to submit a full technical and financial proposal. All answers to any questions will be answered in a document shared with all bidders and we will supply a form to be used for questions.
The entire RFP and all the related discussions, meetings, information exchanges and subsequent negotiations that may occur are subject to confidentiality. We reserve the right to reject any LOI or RFP without obligation or liability or accept a proposal other than the lowest one. We reserve the right to request additional data or information, discussions or presentations to support proposals. All short-listed bidders must be available to discuss details of their proposal, and a site visit will be undertaken for all short-listed candidates.

4.2 Confirmation of Intent

Please use and sign the document attached in Annex 1 (letter) to transmit your intent to participate by close of business GMT 24 February 2017. All interested parties are required to complete and send the Intent to Participate letter.

4.3 Format and Content of LOI

This will be a 2-stage process. Responses to this RFP should be in English and should be attached to a cover letter and provide the following information, ideally in the following order attached to Annex 1/Letter of Intent:

- Contacts
  - Name and address of the service provider
  - Name, title, phone number and email address of the person authorized to commit contractually
  - Name, title, phone number and email address of the person to be contacted in regards of the content of the proposal, if different from above
  - Signature of a contractual letter by a duly authorized representative of the company

- Company profile
  - History, locations and management
  - Key figures: headcounts and revenue of the past 3 years.
  - General services provided and capabilities in terms of formulation development, process development, analytical development and validation as well as production manufacture, quality control, regulatory affairs etc. This should include details of equipment - eg fluidized bed granulation capability, tabletting and/or hard gelatine capsule filling capabilities.
  - Evidence of satisfactory GMP inspections by local and international authorities (e.g FDA, EU)
  - Description of laboratory and pilot-scale technical capabilities for development and testing of beta lactam products produced by tabletting, hard-shell encapsulation and then packaging.
  - Customer’s references.
  - Any other relevant information enabling us to assess the opportunity of contracting with your company.

5. WHAT WE WILL LOOK FOR IN A FULL PROPOSAL

We will share, under Confidentiality Agreements, further technical information on results of pre-formulations studies with a short-list of bidders invited to submit a full proposal, and seek from them:

- A technical proposal
  Detailed proposal explaining how your company’s approach will enable our team to meet project timelines and ensure quality results.

- A financial proposal
  A detailed budget and timeline linked to the technical proposal. A budget template will be provided.
We will identify partners on the basis of commitment (willingness to invest), feasibility, technical competence, prior history in working in a private-public partnership, experience with beta lactam finished products manufactured to GMP, ability to develop and test new formulations (or partnering with a company that can do so) and cost. Our limited funding will be used to audit the facilities and partially subsidize and provide technical support to the initial development.

Our aim is to use the competitive process to identify one or more interested and proficient pharmaceutical partners, to transfer and validate information on prior pre-formulation work and analytical methods and to work with the partner for formulating and producing the formulation on a laboratory scale to GMP, and eventually producing clinical batches.

The University of Oxford Ceftriaxone Development Expert Committee (experienced in formulation development, chemistry/ manufacturing/ controls aspects of regulatory submissions and the ability to inspect potential partners) will make their recommendations on the best potential partners on the basis of written submissions.

Before choosing the final partner(s), we will visit sites. We will transfer the complete know-how for the formulation, production process and analytical methods under a Memorandum of Understanding (MOU) to the final partners. The MOU will include price controls for the public sector in high burden countries.

6. BENEFITS OF PARTNERING WITH UNIVERSITY OF OXFORD / MAHIDOL- OXFORD TROPICAL MEDICINE RESEARCH UNIT

Our objective is a non-profit development of a formulation of ceftriaxone which is bioavailable, and might have the potential to save lives. From the pharma industry perspective, partnering with us might be perceived as a strategic option to enter the field of global health and fulfil corporate social responsibility objectives. A successful development can positively impact on the image of the company.

We propose to supplement funds to R&D development work in this initiative through complementary funding - Saving Lives at Birth, BMGF and Wellcome Trust - as a mechanism of reducing early stage development risks.