CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218230Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 111885

MEETING MINUTES

GlaxoSmithKline Intellectual Property Development Limited, England
Attention: Xuying Wang, PhD
Associate Director, Global Regulatory Affairs
1250 Collegeville Road
Mailstop UP 4400
Collegeville, PA 19426-0989

Dear Dr. Wang:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for gepotidacin (GSK2140944).

We also refer to the teleconference between representatives of your firm and the FDA on April 21, 2023. The purpose of the meeting was to discuss your planned submission of a marketing application for gepotidacin.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call J. Christopher Davi, MS, Senior Regulatory Project Manager at (301) 796-0702.

Sincerely,

{See appended electronic signature page}

Peter Kim, MD, MS
Director
Division of Anti-Infectives
Office of Infectious Diseases
Center for Drug Evaluation and Research

Enclosures: Meeting Minutes
Division's Preliminary Responses dated April 18, 2023

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: April 21, 2023

Application Number: IND 111885
Product Name: Gepotidacin (GSK2140944)
Indication: Uncomplicated Urinary Tract Infections (uUTI)
Sponsor Name: GlaxoSmithKline Intellectual Property Development Limited, England

Regulatory Pathway: 505(b)(1)

Meeting Chair: Peter Kim, MD, MS, Director
Meeting Recorder: J. Christopher Davi, MS, Senior RPM

CDER Participants: Division of Anti-Infectives and Office of Infectious Diseases (OID) where specified:
John Farley, MD, MPH, Director, OID
Adam Sherwat, MD, Deputy Director, OID
Peter Kim, MD, MS, Division Director
Dmitri Iarikov, MD, PhD, Deputy Director
Ramya Gopinath, MD, Associate Director for Therapeutic Review
Angela Kopack, MD, Clinical Reviewer
Daniel Rubin, PhD, Secondary Biostatistics Reviewer
Xianbin Li, PhD, Biostatistics Reviewer
Dakshina Chilukuri, PhD, Clinical Pharmacology Team Leader
Cristina Miglis, PharmD, MS, Clinical Pharmacology Reviewer
Terry Miller, PhD, Pharmacology/Toxicology Team Leader
Amy Ellis, PhD, Pharmacology/Toxicology Reviewer
Dorota Matecka, PhD, Pharmaceutical Assessment Lead
Avery Goodwin, PhD, Clinical Microbiology Team Leader
Kerian Grande, PhD, Clinical Microbiology Reviewer
Maureen Dillon-Parker, Director, Project Management Staff
Gregory DiBernardo, Chief, Project Management Staff
J. Christopher Davi, MS, Senior Regulatory Project Manager

SPONSOR ATTENDEES: GlaxoSmithKline Intellectual Property Development Limited, England:
Ramineh Zoka Vice President, Medicine Development Leader, GSK
Salim Janmohamed, MD, Senior Director, Clinical Development, GSK
Marcy Powell MD, Senior Director, Global Clinical Safety and Pharmacovigilance, GSK
Nicole Scangarella-Oman, Scientific Director, Diagnostics & Clinical Microbiology, GSK
Caroline Perry Senior Director, Clinical Development, GSK
Amanda Sheets Director, Clinical Development, GSK
Helen Millns, Statistics Director, Clinical Statistics, GSK
Annie Foster, Senior Director, Global Regulatory Affairs, GSK
Xuying Wang, Associate Director, Global Regulatory Affairs, GSK
Cameron Bess, Project Officer CBRN Antimicrobials, BARDA
Sue Cammarata, Senior Clinical Subject Matter Expert, BARDA
Corrina Pavetto, Program Analyst Regulatory and Quality Affairs, BARDA

1.0 BACKGROUND

GlaxoSmithKline Intellectual Property Development Limited, England ("Sponsor") requested a type B, Pre-NDA meeting on February 24, 2023, to discuss their plans to submit a marketing application for gepotidacin for the treatment of uncomplicated Urinary Tract Infections (uUTI). The Division of Anti-Infectives (Division) granted the meeting on March 2, 2023, and the Sponsor provided briefing materials for the meeting on March 27, 2023. On April 18, 2023, the Division provided preliminary responses to the questions included in the Sponsor's briefing materials. Discussion points related to the questions are provided herein.

2.0 DISCUSSION

- With regard to Question 5, the Sponsor informed the Division that they (Sponsor) planned to submit the narratives for all participants who experienced SAEs, death, pregnancy, or adverse events leading to treatment discontinuation, or AEs leading to study withdrawal in the NDA. The Sponsor additionally proposed to submit narratives for all participants who experienced an SAE (including those leading to study withdrawal or discontinuation), death and pregnancy for all other completed studies. For participants who discontinued drug or withdrew from the study for all other completed studies for non-serious AEs, the Sponsor proposed not to submit narratives, as they are not available. However, the Sponsor did indicate that a description of drug discontinuations and withdrawals will be summarized in each CSR. The Division acknowledged this and indicated that the Sponsor's plan was acceptable.

- The Sponsor informed the Division that they would be providing randomized subject lists (ITT population) with subject IDs for the two phase 3 studies no later than April 24, 2023. The Sponsor requested that the Division respond with 10% random samples within 5 days of receipt. The Sponsor proposed to submit the 10% random samples of the phase 3 CRFs no later than 30 days after the submission of the original application. The Division acknowledged this and indicated that the plan was acceptable.

- With regard to Question 7 (Financial Disclosure), the Sponsor stated (b) (4) Thus, the Sponsor did not feel it was appropriate to include financial disclosure information pertaining to these studies. (b) (4) The Division acknowledged this and indicated that the Sponsor's approach was acceptable.

- The Sponsor inquired as to whether the in vitro/in vivo study templates were for clinical pharmacology studies only. The Division indicated both in vitro and in vivo data would be needed. For in vitro data, the Division indicated that if all required information from the template has been summarized in module 2.6.4/5, it would be acceptable to submit the tabulated summaries in module 2.6.5 (in lieu of the template) in both a pdf and a MS Word document file. For in vivo clinical pharmacology data, the Sponsor indicated that they would submit this information in the provided template within 30 days of the NDA submission. The Division acknowledged this, indicating it was acceptable.

- With regard to the bioanalytical method performance template, the Sponsor proposed to provide this for gepotidacin only. The Division indicated that this would not be acceptable, noting that the bioanalytical methods for other analytes including those done for DDI studies need to be summarized and provided in the marketing application. For bioanalytical methods on gepotidacin that are in the appendices of module 2.7.1 (if all required information from the template has been included) the Division will accept the data in module 2.7.1 (word and PDF) in place of the template. The Sponsor stated that bioanalytical methods for some of the analytes in the DDI studies may be proprietary to the CRO conducting the analyses and that it may take time to obtain the information. The Sponsor asked if it would be acceptable to provide this information for the other drugs within 30 days of the NDA submission. The Division agreed with this approach.

  Post meeting note: FDA stated that the bioanalytical method information and associated tables should be submitted in Section 5.3.1.4.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our March 2, 2023, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VII. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at FDA.gov.[1]

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. The Division and Sponsor agreed that the following components could be submitted within 30 days of the NDA submission:

    - The 10% random samples of the CRFs from the Phase 3 studies
    - The template for in vivo pharmacology data
    - Bioanalytical methods for other drugs (i.e., DDI Studies)

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

[1] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm

- A preliminary discussion was held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan. The Division informed the Sponsor that it is not currently anticipated that a REMS will be required for their submission.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission.

Prominently identify each submission containing your late component(s) with the following wording in bold capital letters at the top of the first page of the submission:

NDA/BLA NUMBER: LATE COMPONENT – CLINICAL
NDA/BLA NUMBER: LATE COMPONENT – CLINICAL PHARMACOLOGY

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.[2] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[3]

[2] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[4] and Pregnancy and Lactation Labeling Final Rule[5] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable).

Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[6] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[7]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[8]

ATTACHMENTS AND HANDOUTS

- Division's preliminary responses dated April 18, 2023

[6] https://www.fda.gov/media/84223/download
[7] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and
[8] https://www.fda.gov/media/85061/download

IND 111885

MEETING PRELIMINARY COMMENTS

GlaxoSmithKline Intellectual Property Development Limited, England
Attention: Xuying Wang, PhD
Associate Director, Global Regulatory Affairs
1250 Collegeville Road
Mailstop UP4400
Collegeville, PA 19426-0989

Dear Dr. Wang:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Gepotidacin (GSK2140944).

We also refer to your February 24, 2023, correspondence requesting a Pre-NDA teleconference to discuss your planned submission of a marketing application for Gepotidacin (b) (4) for the treatment of uncomplicated urinary tract infections.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hard copy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with FDA policy, you should not make audio or visual recordings of the discussion at this meeting. Consistent with 21 CFR 10.65(e), the official record of this meeting will be the FDA-generated minutes.

If you have any questions, call J. Christopher Davi, MS, Senior Regulatory Project Manager at (301) 796-0702.

Sincerely,

{See appended electronic signature page}

Gregory DiBernardo
Chief, Regulatory Project Management Staff
Anti-Infectives
Division of Regulatory Operations for Infectious Diseases
Office of Regulatory Operations
Center for Drug Evaluation and Research

ENCLOSURE: Preliminary Meeting Comments

U.S. FOOD & DRUG ADMINISTRATION

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: April 21, 2023, from 11:00 AM to 12:00 PM, EDT

Application Number: IND 111885
Product Name: Gepotidacin (GSK2140944) (b) (4)
Indication: Uncomplicated Urinary Tract Infections (uUTI)

Sponsor: GlaxoSmithKline Intellectual Property Development Limited, England

Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

Introduction: This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for April 21, 2023, at 11:00 AM, between GlaxoSmithKline Intellectual Property Development Limited, England (Sponsor) and the Division of Anti-Infectives. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

GlaxoSmithKline Intellectual Property Development Limited, England (Sponsor) requested a type B Pre-NDA meeting on February 24, 2023, with the Division of Anti-Infectives (Division) to discuss plans for a new drug application (NDA) regulatory submission for gepotidacin (b) (4) for the treatment of uUTI. The Division granted an April 21, 2023, meeting (teleconference) on March 2, 2023. The Sponsor provided the briefing materials and final questions for the meeting on March 21, 2023. Preliminary responses to the questions provided in the briefing document are included herein *(italics).*

2.0 QUESTIONS AND RESPONSES

QUESTION 1: As already agreed with the Agency (in the 23 June 2022 Type C Written Responses, Reference ID 5003671) and documented in the study protocols and statistical analysis plans, the primary inferential analysis is defined as the analysis conducted on the IA set of patients. GSK has conducted this inferential analysis on the data cut used for the IA (as used by the IDMC to make their decision) and GSK has repeated this analysis (which uses only the subset of patients included in the interim) on the final locked dataset. There were no differences between the results from these analyses. Given there were no changes between the results from these analyses, does the Agency agree that the following data sets and outputs for each Phase 3 study are adequate and appropriate to support a substantive review of the dossier in support of the intended indication?

- Primary inferential analysis table produced on the data cut used for the IA.
- TLFs on the IA set of patients produced using the final EoS locked data set, including replication of the inferential analysis (agreed with the Agency in the 23 June 2022 Type C Written Responses, Reference ID 5003671)
- All other TLFs for complete trial data (IA subjects + over-run subjects) produced using the final EoS locked dataset (agreed with the Agency in the 23 June 2022 Type C Written Responses, Reference ID 5003671)
- CDISC datasets from the final EoS locked database. These datasets have a flag to indicate whether a patient was included in the IA subset of patients.

Division Response: *We agree.*

QUESTION 2: Gepotidacin tablet for oral use for uUTI has been designated as a qualified infectious disease product. Does the Division agree that the NDA for uUTI meets the criteria for priority review?

Division Response: *A product that receives QIDP designation for the submitted product/dosage form and indication will be eligible for priority review. You will be notified of the priority review status of your application by day 60 of the filing period.*

QUESTION 3: Provided priority review is granted for the NDA (refer to Question 2), GSK proposes providing a 90-day post NDA submission safety update. Does the Division agree with the proposal and the content that GSK plans to submit as the NDA safety update post-submission?

Division Response: *Please see our response to Question 2. If a priority review is granted, we agree with the timing of your safety update.*

QUESTION 4: Does the FDA agree with GSK's plan to include integrated analysis datasets and associated tables, figures, and listings for study population and efficacy analyses based on both CLSI and EUCAST criteria? Although EUCAST-based outputs will be included, the results of these analyses will not be discussed in the NDA.

Division Response: *We agree.*

QUESTION 5: Does the FDA agree with GSK's proposal to provide CRFs for all subjects who died during the study or who discontinued from the study due to an AE, in accordance with 21 CFR 314.50(f)(2)?

Division Response: *We agree. As specified in your briefing document, we also agree with your plans to provide CRFs and narratives for all participants in studies 204989 and 212390 who experienced any of the following: SAE, death, pregnancy, AE leading to treatment discontinuation, or AE leading to study withdrawal. In addition, we request you provide narratives for all participants who died, discontinued drug or discontinued study from all completed studies listed in Table 11.*

In addition to the proposed submission of the CRFs, 10% random samples of all CRFs would be needed. Please submit the subject lists with subject IDs for the two Phase 3 studies so that 10% random samples can be generated before the NDA submission.

QUESTION 6: Does the FDA agree with GSK's revised plan for the provision of Bioresearch Monitoring (BIMO) submission deliverables?

Division Response: *We agree.*

QUESTION 7: GSK plans to submit Financial Disclosures only for Phase 3 studies, 204989 (EAGLE-2) and 212390 (EAGLE-3). Does the FDA agree?

Division Response: *No, we do not agree. Because you plan to utilize safety data from three ongoing trials (214144, BTZ116577, 208541) in the initial NDA package and a 90-day safety update, financial disclosures for these trials should be submitted in addition to financial disclosures from 204989 and 212390.*

QUESTION 8: Does the Agency agree that the content of Modules 1, 2, 3, 4 and 5 of the dossier as outlined in the proposed draft table of contents constitute a complete application? Does the Agency agree that the proposed content will support a substantive review of the dossier in support of the intended indication?

Division Response: *We agree.*

QUESTION 9: GSK considers gepotidacin to be a NCE that is eligible for NCE exclusivity provisions, i.e., 5-year market exclusivity. Does the Agency agree with this classification and qualification for NCE exclusivity?

Division Response: *Please be advised that the Agency does not make exclusivity determinations pursuant to sections 505(c)(3)(E) and (j)(5)(F) of the Federal Food, Drug, and Cosmetic Act, and 21 CFR 314.108, until after approval of an NDA. As described at 314.50(j), an applicant should include in its NDA a description of the exclusivity to which the applicant believes it is entitled. FDA will consider the applicant's assertions regarding exclusivity in the review of the application. Please also note that the New Molecular Entity (NME) determination for an application is distinct from and independent of the New Chemical Entity (NCE) determination and any related exclusivity determinations.*

Question 10: Does the Division anticipate or deem it necessary to refer the gepotidacin NDA to an Advisory Committee? If an advisory committee meeting is anticipated, can the Division share the timing of such a meeting if the NDA submission is made in June/July 2023 and assuming a priority review is granted for the NDA (refer to Question 2 for priority review)?

Division Response: *Determination of the need for an advisory committee will be made and communicated to you after NDA filing. We are unable to comment on the timing of a meeting, if needed, in advance.*

Additional Clinical Pharmacology Comments:

To facilitate efficient review, please submit the following summary documents with your NDA: 1) the provided method validation template for each respective clinical pharmacology study and 2) the attached in vitro ADME and in vivo PK study table template as a MS Word document file (.doc or .docx).

We note in the Applicant's briefing document that gepotidacin in moderate renal impairment (RI) subjects had ~34% urine AUC reduction; for severe RI or ESRD subjects (not on dialysis), a decrease of 77% urine AUC was observed when compared to healthy controls. If you intend to propose dosing adjustments for the special population in the setting of RI (including ESRD subjects on or not on dialysis) in the NDA package, provide justifications, literature support where applicable, and/or relevant analyses based on these observations.

For population pharmacokinetic analysis and exposure-response analyses:

- *For general format and content, please check the requirements at FDA Guidance for Industry – Population Pharmacokinetics (https://www.fda.gov/media/128793/download) and FDA Guidance for Industry – Exposure-Response Relationships (https://www.fda.gov/media/71277/download).*

- *All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any data point and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets. The flag of exclusion should be clearly explained in the define.pdf file.*
- *NONMEM model control streams and output listings for population PK or PKPD reports should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model (as found in Appendices). These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_lst.txt).*
- *General expectations of model and data files format conformation can be found here: https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/model-data-format*

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our March 2, 2023, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VII. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

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In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at FDA.gov.[1]

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PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

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PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[4] and Pregnancy and Lactation Labeling Final Rule[5] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.

[2] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.

- Regulations and related guidance documents.

- A sample tool illustrating the format for Highlights and Contents, and

- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address.

Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[6] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[7]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

Please be advised that the Agency does not make exclusivity determinations pursuant to sections 505(c)(3)(E) and (j)(5)(F) of the Federal Food, Drug, and Cosmetic Act, and 21 CFR 314.108, until after approval of an NDA. As described at 314.50(j), an applicant should include in its NDA a description of the exclusivity to which the applicant believes it is entitled. FDA will consider the applicant's assertions regarding exclusivity in the review of the application. Please also note that the New Molecular Entity (NME)

[6] https://www.fda.gov/media/84223/download
[7] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

determination for an application is distinct from and independent of the New Chemical Entity (NCE) determination and any related exclusivity determinations.

FDA has made a preliminary determination that the application for this product would be reviewed as a new molecular entity (NME) and therefore subject to the Program, under PDUFA VII. Please note that this is a preliminary determination, based on information available to FDA at this time, and will be re-evaluated at the time your application is submitted. This determination is based on our understanding of the active moiety (21 CFR 314.108(a)) and whether another marketing application containing the same active moiety is approved or marketed. Please also note that the NME determination for an application is distinct from and independent of the new chemical entity (NCE) determination and any related exclusivity determinations, which are made after approval of an NDA.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[8]

-End.

[8] https://www.fda.gov/media/85061/download

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/s/

GREGORY F DIBERNARDO
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PETER W KIM
05/15/2023 01:12:44 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 111885

MEETING MINUTES

GlaxoSmithKline Intellectual Property Ltd., England
Attention: Edward M. Yuhas, PhD
Senior Director, Global Regulatory Affairs
1250 Collegeville Road
Collegeville, PA 19426-0989

Dear Dr. Yuhas:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for gepotidacin (GSK 2140944) (b) (4)

We also refer to the meeting between representatives of your firm and the FDA on April 12, 2018. The purpose of the End-of Phase 2 meeting was to discuss your drug development program for gepotidacin as you progress into Phase 3.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call J. Christopher Davi, MS, Senior Regulatory Project Manager, at (301) 796-0702.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, MD, MPH
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes
Division's Preliminary Responses dated April 9, 2018
Sponsor's responses dated April 10, 2018

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	End-of-Phase 2
Meeting Date and Time:	April 12, 2018, 11:00 am – 12:00 pm ET
Meeting Location:	CDER White Oak Campus, Bldg 22, Room 1313
Application Number:	IND 111885
Product Name:	GSK 2140944 (gepotidacin)
Indication:	Uncomplicated urinary tract infections (uUTI) (b) (4)
Sponsor/Applicant Name:	GlaxoSmithKline Intellectual Property Ltd., England
Meeting Recorder:	J. Christopher Davi, MS, Senior Regulatory Project Manager Division of Anti-Infective Products (DAIP)

CDER Participants – Division of Anti-Infective Products (DAIP)*

***Unless otherwise specified**

Edward M. Cox, MD, MPH, Director, Office of Anti-Microbial Products (OAP)
John Farley, MD, MPH, Deputy Director, OAP
Sumathi Nambiar, MD, MPH, Director
Dmitri Iarikov, MD, PhD, Acting Deputy Director
Peter Kim, MD, MS, Acting Clinical Team Leader
Hiwot Hiruy, MD, PhD, Clinical Reviewer
Zhixia (Grace) Yan, PhD, Clinical Pharmacology Team Leader
Christina Miglis, PharmD, Clinical Pharmacology Reviewer
Avery Goodwin, PhD, Acting Clinical Microbiology Team Leader
Kerian Grande, PhD, Clinical Microbiology Reviewer
Karen Higgins, ScD, Biostatistics Team Leader
Daniel Rubin, PhD, Biostatistics Reviewer
Terry Miller, PhD, Non-Clinical Pharmacology Team Leader
Amy Ellis, PhD, Non-Clinical Pharmacology Reviewer
Maureen Dillon-Parker, Chief, Project Management Staff
J. Christopher Davi, MS, Senior Regulatory Project Manager

SPONSOR ATTENDEES - GlaxoSmithKline Intellectual Property Ltd **(GSK):**
Etienne Dumont, MD, Physician Project Leader
Cindy Fishman, DVM, PhD, DACVP, Director, Pathology
David Gardiner, MD, MD, FACP, Medical Development Leader, Infectious Diseases Discovery
Mohammad Hossain, PhD, Director, Clinical Pharmacology Modeling and Simulation
Ian Hunt, BSc, Vice President, Global Regulatory Affairs
Caroline Perry, PhD, Director, Clinical Development, Infectious Diseases
Aparna Raychaudhuri, PhD, Director, Clinical Statistics, R&D Clinical Platforms
Nicole E. Scangarella-Oman, MS, Senior Scientific Investigator
Courtney Tiffany, BSc, Clinical Development, R&D, Project Clinical Platforms
Edward M. Yuhas, PhD, Senior Director, Infectious Diseases, Global Regulatory Affairs

Biomedical Advanced Research and Development Authority (BARDA):
Claiborne Hughes, MSc, Antibacterials Project Officer
Louise Latriano, PhD, PhD, Toxicology and Pharmacokinetics
Melissa Willens, MS, Regulatory Quality Affairs Specialist
Chris Houchens, PhD, Antibacterials Branch Chief

BACKGROUND

GlaxoSmithKline (Sponsor) requested a Type B, End-of-Phase 2 meeting, on January 9, 2018, to discuss the Phase 3 clinical trials for gepotidacin. The Sponsor provided a briefing document on February 21, 2018, and the Division of Anti-Infective Products (DAIP) provided preliminary responses to the questions in the briefing document on April 9, 2018 (appended). The Sponsor responded to the preliminary responses on April 10, 2018 (appended). Discussion points generated from these responses are recorded herein. Additionally, post-meeting notes have been provided to address follow-up inquiries submitted by the Sponsor on April 24, 2018.

DISCUSSION

(b) (4)

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8.4.2. GSK has designed the proposed pivotal uUTI trial study pursuant to the advice previously received from FDA. Does FDA agree that the protocol for the Phase 3 uUTI study is acceptable?

More specifically,

a) The study is a randomized double blind, non-inferiority study with a 10% NI margin with a primary endpoint of therapeutic response. Does FDA agree this is acceptable?

Division Response: *We recommend that the primary analysis be restricted to the subset of the micro-ITT analysis population with pathogens susceptible to nitrofurantoin. In addition, we recommend that the TOC visit be scheduled in a post-randomization window, rather than a post-treatment window.*

b) GSK plans to use a questionnaire (administered by the principal investigator) that uses 4 signs and symptoms with a 0-3 grading score [which includes the assessment of dysuria, frequency, urgency, and lower abdominal (suprapubic pain)]. Does FDA agree with the investigator assessment of clinical response which comprises the clinical component of the therapeutic response endpoint?

Division Response: *We agree with the use of this questionnaire in the study because it will characterize the severity of the symptoms at enrollment. The use of a questionnaire in your study should be straightforward and should not be burdensome, and can help advance scientific information in the area of symptom improvement and resolution for uUTI. However, the responder primary efficacy endpoint should consist of both: (1) a negative urine culture, and (2) complete resolution of symptoms, that is, the clinical response component should be defined as a score of zero on your symptom scale (no symptoms) and not as a score of less than or equal to 1 (improvement without necessarily complete resolution).*

If you wish to define clinical response based on a total scoring system and its changes from baseline as part of the responder primary efficacy endpoint (e.g., improvement of symptoms but not complete resolution), the questionnaire will need to undergo a qualitative and quantitative research development program and the Patient Reported Outcome should be qualified for its context of use as

part of the responder primary efficacy outcome assessment. For additional information, see the guidance document on Patient Reported Outcomes, found at:

https://www.fda.gov/downloads/drugs/guidances/ucm193282.pdf.

c) Does FDA agree with defining urine culture growth of $\geq 10^5$CFU/mL of a single qualifying uropathogen at baseline for inclusion of randomized subjects in the micro-ITT population and microbiological success being defined as a reduction of uropathogens to $<10^3$ CFU/mL at the test of cure visit?

Division Response: *We agree with the proposed definitions.*

d) Base on FDA's advice (August 15, 2016) (Section 13.2), use of subjects ≥ 12 years of age were acceptable for use in clinical trials. GSK proposes to allow adolescents ≥age 12 to enroll in the study if eligible. Can FDA reconfirm that this acceptable?

Division Response: *Enrollment of adolescents ≥12 years is acceptable for the proposed uUTI study.*

e) For subjects who have first & recurrent episodes, GSK proposes to stratify these patients for balance and we will conduct sub group analyses by age & episode recurrence. Is this acceptable?

Division Response: *We agree with the proposed stratification and subgroup analyses.*

f) GSK proposes to conduct only sparse PK in the Phase 3 study, as a separate Phase 2 experimental medicine study will be conducted to collect serial PK in a similar target population (ie, patients with acute cystitis based on clinical symptoms & dipstick analysis). Is this acceptable?

Division Response: *Yes, it is acceptable.*

(b) (4)

8.4.4. GSK proposes that at the time of filing, it is anticipated that:

- approximately 500 – 600 subjects will have received oral gepotidacin ≥ 1500 mg BID for 5 days (target dose regimen for uUTI indication)

(b) (4)

Does FDA agree that the number of subjects exposed to these dose regimens meets FDA requirements?

Division Response: *The proposed safety database for the uUTI indication appears reasonable.* (b) (4) *fairly large patient population, so it would be ideal to have a larger safety database.*

8.4.5. GSK plans to present ISS (Integrated Summary of Safety) by integrating safety data in the following groupings:

(b) (4)

b) Uncomplicated Urinary Tract Infection Studies - 204989, 206899;
Dose groups – All Gepotidacin combined, Gepotidacin 1500 mg BID for 5 days, Nitrofurantoin 100 mg BID

Safety data from all other studies with GSK 2140944 will be presented from individual studies as outlined in the Study Data Standardization Plan (Appendix 13.6). Does the Agency agree with proposed analysis plan for the integrated summary of safety?

Division Response: *We note that comparisons between gepotidacin groups and comparator groups in the ISS may not be fully randomized comparisons, because different studies used different controls and randomization ratios.*

Your proposal is acceptable for the ISS, provided safety findings for the individual Phase 3 trials are also comprehensively summarized in the respective Clinical Study Reports.

8.4.6. GSK intends to submit the summary-level clinical site data (b) (4) Study 204989). A summary-level dataset and DEFINE.pdf will be provided in the format described in the draft guidance "Specifications for Preparing and Submitting Summary Level Clinical Site Data for CDER's Inspection Planning" dated December 2012. The dataset will contain the principal investigator name and information. The MAXIMUM FINANCIAL DISCLOSURE AMOUNT and FINANCIAL DISCLOSURE INFORMATION will be presented by principal investigator, but will reflect the financial disclosure information for all sub-investigators listed on the 1572. Does the Agency agree with the plans for the submission of the summary-level clinical site data?

Division Response: *We acknowledge and generally agree with your response. The Office of Scientific Investigations (OSI) has the following updated reference for your request.*

We request that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf.

We can discuss the preliminary responses above in more detail at our April 12, 2018 meeting. If you have questions in the interim, I can be reached at (301) 796-0702.

J. Christopher Davi, MS, Sr. RPM, DAIP

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/s/

SUMATHI NAMBIAR
05/10/2018