CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207356Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 108674

MEETING MINUTES

Insmed Incorporated
Attention: Sandra Cottrell, MA, PhD
Vice President, Global Regulatory Affairs
10 Finderne Ave Building 10
Bridgewater, New Jersey 08807-3365 USA

Dear Dr. Cottrell:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Arikayce (amikacin liposome inhalation suspension).

We also refer to the teleconference between representatives of your firm and the FDA on November 29, 2017. The purpose of the meeting was to discuss the Chemistry, Manufacturing and Control (CMC) proposals in preparation for the NDA submission.

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, please contact me at (240) 402-1001.

Sincerely,

{See appended electronic signature page}

Dorota Matecka, PhD
Chemistry, Manufacturing, and Control Lead
Division of New Drug Product I
Office of New Drug Products
Center for Drug Evaluation and Research Branch

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	Wednesday, November 29, 2017, 10:00- 11:00 AM (EST)
Meeting Location:	Teleconference
Application Number:	IND 108674
Product Name:	Arikayce (amikacin liposome inhalation suspension)
Indication:	Treatment of nontuberculous mycobacteria (NTM) lung infection caused by *Mycobacterium avium* complex (MAC) as part of a combination antibiotic regimen for adult patients.
Sponsor/Applicant Name:	Insmed Incorporated
Meeting Chair:	Dorota Matecka
Meeting Recorder:	Anh-Thy Ly

FDA ATTENDEES

1. Dorota Matecka, Ph.D., CMC Lead, Office of New Drug Product (ONDP), Office of Pharmaceutical Quality (OPQ)
2. Erika Englund, Ph.D., Drug Product Reviewer, ONDP, OPQ
3. Deepika Arora Lakhani, Ph.D., CDRH Reviewer, Division of Respiratory and Pulmonary Devices Branch
4. Banu Zolnik, Ph.D., Biopharmaceutics Reviewer, ONDP/OPQ
5. Elsbeth G Chikhale, Ph.D., Biopharmaceutics Team Leader, ONDP/OPQ
6. Peter Guerrieri, Ph.D., C MC Lead, Office of Process and Facilities (OPF), OPQ
7. Dmitri Iarikov, M.D., Deputy Director (Acting), Division of Anti-Infective Products (DAIP), Office of New Drugs (OND)
8. Hiwot Hiruy, M.D., Clinical Reviewer, DAIP, OND
9. Gregory DiBernardo, Regulatory Project Manager, DAIP, OND
10. LCDR Luz E Rivera, Psy.D., Team Lead (Acting), Office of Program and Regulatory Operations (OPRO), OPQ
11. Anh-Thy Ly Pharm.D, Regulatory Business Process Manager, OPRO, OPQ

SPONSOR ATTENDEES

Insmed

1. Sandra Cottrell, Vice President Regulatory Affairs

2. Jeffrey Ding, Senior Director, CMC Regulatory Affairs
3. Diane Fiorenza, Executive Director, Regulatory Affairs
4. Peggy McCann, Director, CMC Regulatory Affairs
5. Brian Miller, Assoc. Dir, Manufacturing Science & Technology, Manufacturing
6. Don Nociolo, Vice President of Technical Operations
7. Mark Quigley, Vice President of Quality
8. Toni Shaler, Senior Director, Analytical Services, Quality Control & Stability
9. Drayton Wise, General Manager, ALIS Program
10. Paul Streck

PARI Pharma GmbH/PRE US

11. Matthias Brosig, Program Manager, eFlow
12. Mike Judge, VP Operations and Regulatory Affairs

1.0 BACKGROUND

On October 13, 2017 Insmed Incorporated submitted a Type B Pre-NDA meeting request to discuss the Chemistry, Manufacturing and Control proposals for the pending NDA submission for ARIKAYCE® (amikacin liposome inhalation suspension). The FDA Office of Pharmaceutical Quality granted a teleconference meeting on November 29, 2017.

Arikayce is amikacin sulfate liposome inhalation suspension indicated for the treatment of nontuberculous mycobacteria (NTM) lung infection caused by *Mycobacterium avium* complex (MAC) as part of a combination antibiotic regimen for adult patients.

ARIKAYCE (amikacin liposome inhalation suspension) is provided as a sterile aqueous liposomal suspension for oral inhalation via nebulization. The unit dose of 590 mg is administered once daily. The product is a co-packaged drug-device combination. The drug is provided in a unit dose configuration consisting of a single-use, Type I clear (b) (4) glass vial with a (b) (4) finish using a closure system consisting of a (b) (4) stopper and a (b) (4). The device component of the combination product is based on an eFlow Nebulizer System provided by PARI Respiratory Equipment, Midlothian, VA, a subsidiary of PARI Pharma GmbH, Germany, and is provided as the LAMINA™ nebulizer handset along with the eFlow® rapid control unit.

The purpose of this meeting was to reach agreement with the Agency on proposals for the pending NDA submission for ARIKAYCE® (amikacin liposome inhalation suspension). Specifically, Insmed wanted to confirm that CMC submission plans and documentation approaches will be adequate and appropriate to support a successful, efficient review process.

The Agency sent Preliminary Comments to Insmed Incorporated on November 22, 2017. Insmed Incorporated addressed the FDA comments with slide presentation during the teleconference meeting.

2. DISCUSSION

Question 1: *Due t* (b) (4) *as described above, is an acceptable and sufficient approach for ARIKAYCE?*

FDA Response to Question 1:

We do not have adequate information to evaluate your proposal. USP <5> recommends that fine particulates (less than 10 µm) should be determined throughout the stability storage period. The possible sources of the particles in your proposed drug product are unclear. (b) (4) If foreign particulate matter in the submicron range cannot be measured in the final drug product, provide the particulate matter control strategy. The proposed acceptance criteria for the particulate matter test will be a review issue.

Discussion:

The Agency recommended that the Sponsor submit the justification for the test method and particulate matter acceptance criteria to the NDA. In addition, the Agency stated that the Sponsor should also provide information in the NDA regarding the number of particulates measured from the (b) (6) described on slide 4 and clarify if the (b) (4) as described on Slide 4, or produced a (b) (4) as described on Slide 6.

Question 2: *Does the Agency agree to this approach for providing in the NDA a representative executed batch record from both Althea and TBI?*

FDA Response to Question 2:

The proposal to submit representative executed batch records for both proposed commercial drug product manufacturing sites is reasonable. However, please note that in accordance with 21 CFR 314.50(d)(ii)(c), the NDA should also contain the proposed or actual master production record, including a description of the equipment, to be used for the manufacture of a commercial lot of the drug product or a comparably detailed description of the production process for a representative batch of the drug product. If the commercial manufacturing process at the two sites is different, the differences should be clearly identified. A comparative table is recommended to describe the differences.

A comprehensive evaluation of the product's critical quality attributes and potential risk for impact of critical manufacturing steps and controls is expected in the NDA submission, based on

the complexity of liposomal product formulations. This should include assessment of any differences in equipment and process parameters (including scale-up) between sites for impact on said attributes. To support commercial manufacture at each site, please provide release and stability for batches made at each site.

Discussion:

The Sponsor acknowledged and understood the Agency's response. No further discussion was needed.

Additional Comments:

- It is not clear how many subjects will receive drug product manufactured at the Althea or TBI sites. Submit a table containing detailed information showing the study number, the number of subjects, drug product batch number, and manufacturing site etc. used in each clinical study. Please note that based on your response, the adequacy of the number of subjects in each clinical study that receive drug products manufactured at different sites will be evaluated by the Clinical Division.

- We acknowledge that you submitted an in vitro drug release method description in the IND amendment SN0055 dated March 20, 2015. However, we would like to remind you that an in vitro drug release method development report should include a detailed description and justification for the selection of the in vitro drug release method parameters, which was conveyed to you in the Preliminary Meeting Comments dated June 30, 2014. We recommend that you submit a detailed in vitro drug release method development report as an IND amendment. Request in the cover letter feedback from the Division of Biopharmaceutics.

- Once the in vitro drug release method is found acceptable, submit comparative complete in vitro drug release data (individual, mean, SD, profiles, for example at 15 min, 30 min, 1 hr., 2 hr. etc.) for drug products manufactured at Althea and TBI.

Discussion:

The Sponsor provided a summary table in their slide presentation to further clarify the use of product from Althea and TBI during the clinical development and stated that such information with additional details (as outlined in Slide 9) would be submitted in the NDA. The Sponsor also stated that they will submit a detailed in vitro release method development report as an IND amendment in December, 2017. The Sponsor has requested that the Agency review the report and provide comments within 30 days after receiving the report. The Agency agreed to review the detailed in vitro release method development report in a timely manner. The Agency stated that the cover latter of the IND amendment should clearly indicate that feedback from the Division of Biopharmaceutics is requested. The Agency also requested that a courtesy electronic copy be sent to the attention of Anh-Thy Ly (RBPM) via email.

Question 3: *Does the Agency agree to the comparability approach to support shelf-life for both long-term storage for up to* (b) (6) *months when stored at 2 – 8°C and for up to* (b) *weeks at 25°C upon distribution to a patient by a limited specialty pharmacy network? Does the Agency agree to allow addition stability data on four TBI batches to be submitted during the 30 days post initial NDA submission, as described under PDUFA VI?*

FDA Response to Question 3:

We do not have adequate information in the meeting package to evaluate your proposal regarding the proposed shelf life. We note that only the (b) (4) degradation results were analyzed via linear regression, but is not inclusive of the other quality attributes. The shelf life should be established based on the results from all tests conducted in the stability studies. In addition, it is not clear why a shelf life of (b) (6) months in long-term storage is proposed, when the stability protocol includes testing for up to (b) (4) months under long-term storage conditions. Please clarify the proposed shelf life for your drug product.

(b) (4) TBI is a separate manufacturing site where the product is manufactured on a different scale. The stability data from both sites should be analyzed separately.

We also note that there is inadequate information to evaluate your proposal on the additional stability data for the TBI batches. Provide a table with batch number, batch size, manufacturing site and batch use for all batches that will be submitted to support the drug product stability. Clarify the amount of data, including the number of batches, storage time and conditions for the stability batches that you propose to submit in the initial NDA submission, and the NDA amendment.

Additional Comments:

Please note that the proposed drug product specification, including tests and acceptance criteria, should be the same for the drug product manufactured at different scales and at different sites. However, the proposed stability protocols for the (b) (4) and (b) (4) batches (Table 9), include tests which are different than tests in the stability protocol for the (b) (4) scale batches (Table 7).

The stability protocol for the room temperature testing is missing many of the tests from the long-term testing. For example, there is no test for amikacin degradation products in the room temperature testing (Table 10). This is not acceptable. The room temperature testing post long-term storage should include the same stability tests as the long-term testing.

The protocol for room temperature stability testing is described as post (b) (4) months at the (b) (4) scale, but post (b) (4) months at (b) (4) and (b) (4) kg scale. Clarify if the stability protocol for the drug product commercial batches will include room temperature testing after (b) (4) months.

Discussion:

The Sponsor proposed to submit additional stability data for the 4 drug product batches manufactured at Therapure Biopharma within 30 days of NDA submission. The Agency agreed with the proposal and stated that the data should demonstrate that the two manufacturing sites can be bridged. The Sponsor committed to include in the original NDA submission a complete data comparison for both manufacturing sites including a comparison of stability, batch and formulation data.

The Sponsor sought approval of the stability testing protocol to be submitted in the NDA. The Agency did not agree with (b) (6) (b) (6)) and indicated that full testing should be done at 25°C to support the requested shelf life. The Agency clarified that the post-approval protocol will be evaluated as part of the NDA review.

Post- Meeting Comment:

Full testing at 25°C following (b) (4) months of storage at 2-8 °C should be submitted to the NDA to support the requested shelf life. However, including the 25 °C testing following long term testing might not be required in the post-approval stability protocol. This will be a review issue.

Late Submission Agreement:

The Agency agreed to accept the additional stability data for the drug product batches manufactured at Therapure Biopharma, as indicated in the slide presentation (i.e., 18-month long term stability data for one batch and 6-month of both long term and accelerated stability data for three other batches manufactured at Therapure Biopharma) within 30 days of the initial NDA submission.

***Question 4*:** *Does the Agency agree to the proposed presentation of information for this device specific section?*

FDA Response to Question 4:

You have provided an index of the information you intend to submit in the NDA. The outline appears to contain the typical information that must be submitted to support the device; however, it is not feasible to comment on acceptability of the presentation of information from an index. To specifically note, it appears that you have changed the marketed device configuration from what was used in the clinical studies. Such changes must be adequately and carefully bridged by extensive in vitro bench data and sometimes clinical studies/HF studies etc. You can seek additional FDA feedback, specifically for the device, if you deem necessary.

Discussion:

The Sponsor stated that they are currently conducting a human factor study and will submit the finding reports in the NDA. The Agency commented that the commercial device should the same as the one used in the clinical studies and advised that any device changes should be reported in the NDA.

3.0 SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

Insmed Incorporated Power Point Slides

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANH-THY LY
12/20/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 108674

MEETING MINUTES

Insmed Incorporated
Attention: Sandra Cottrell, M.A., Ph.D.
Vice President, Global Regulatory Affairs
10 Finderne Avenue, Building 10
Bridgewater, NJ 08807-3665

Dear Dr. Cottrell:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ARIKAYCE.

We also refer to the meeting between representatives of your firm and the FDA on November 15, 2017. The purpose of the meeting was to discuss the planned NDA submission for ARIKAYCE.

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 Mr. Gregory DiBernardo, Regulatory Project Manager at (301) 796-4063.

Sincerely,

{See appended electronic signature page}

Sumathi Nambiar, M.D., M.P.H.
Director
Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	November 15, 2017, at 9:00 AM-10:00 PM
Meeting Location:	White Oak Campus, Room 1419
Application Number:	IND 108674
Product Name:	ARIKAYCE [(amikacin liposome inhalation suspension (ALIS)]
Indication:	Treatment of Nontuberculous Mycobacterial (NTM) lung infection caused by *Mycobacterium avium* complex
Sponsor Name:	Insmed Incorporated, Inc.
Meeting Chair:	Sumathi Nambiar, M.D., M.P.H.
Meeting Recorder:	Gregory DiBernardo

FDA ATTENDEES

Office of Antimicrobial Products

Sunita Shukla, M.P.H., Ph.D.	Associate Director for Regulatory Science

Division of Anti-Infective Products

Sumathi Nambiar, M.D., M.P.H.	Director
Dmitri Iarikov, M.D., Ph.D.	Acting Deputy Director
Joseph Toerner, M.D., M.P.H.	Deputy Director for Safety
Abimbola Adebowale, Ph.D.	Associate Director for Labeling
Hiwot Hiruy, M.D., Ph.D.	Clinical Reviewer
Avery Goodwin, Ph.D.	Acting Clinical Microbiology Team Leader
Lynette Berkeley, Ph.D., MT (ASCP)	Clinical Microbiology Reviewer
Terry Miller, Ph.D.	Pharmacology/Toxicology Team Leader
Amy L. Ellis, Ph.D.	Pharmacology/Toxicology Reviewer
Maureen P. Dillon-Parker	Chief, Project Management Staff
Gregory DiBernardo	Regulatory Project Manager
Christopher Smith, Pharm.D., M.P.H.	Regulatory Project Manager

Deborah Wang, RPh., Pharm.D.	Regulatory Project Manager
Jaquelyn Rosenberger, RPh., Pharm.D.	Regulatory Project Manager

Division of Clinical Pharmacology IV

Amit Somani, Ph.D.	Clinical Pharmacology Reviewer
Yang He, Ph.D.	Clinical Pharmacology Reviewer

Division of Biometrics IV

Cheryl Dixon, Ph.D.	Biostatistics Reviewer

Office of Surveillance and Epidemiology

Elizabeth Everhart, M.S.N., R.N., ACNP	Team Leader, Safety Evaluator/DRISK
Otto Townsend, Pharm.D.	Team Leader/DMEPA
Sevan Kolejian, Pharm.D.	Safety Evaluator/DMEPA

SPONSOR ATTENDEES

Insmed Incorporated

Sandra Cottrell, M.A., Ph.D.	Vice President Regulatory Affairs
Gina Engle, M.D.	Vice President of Clinical Development
Diane Fiorenza	Executive Director, Regulatory Affairs
James Nezamis	Senior Director Biostatistics
Paul Streck	Chief Medical Officer
Eugene Sullivan	Chief Strategy Officer, Research
Angelique Braen	Senior Director Toxicology
Drayton Wise	General Manager, ALIS Program

1.0 BACKGROUND

Insmed Incorporated (Insmed) requested a type B Pre-NDA meeting on September 14, 2017. FDA granted the request on October 3, 2017, as a face to face meeting. The FDA provided Preliminary Meeting responses on November 9, 2017. Insmed informed FDA via email on November 13, 2017, that they would like to focus the discussion on Questions 6, 22, 23 and 8 and a clarification on the Agency's Additional Comments. A set of slides (attached) for the meeting were included in the email.

The meeting minutes include the preliminary FDA comments (**FDA Response**) followed by the discussion that took place at the meeting **(Meeting Discussion)**.

2.0 DISCUSSION

Following introductions, Insmed informed FDA of their proposed indication (the treatment of Nontuberculous Mycobacterial (NTM) lung infection caused by *Mycobacterium avium* complex) and a change in the acronym for their product from liposomal amikacin for inhalation (LAI) to [(amikacin liposome inhalation suspension (ALIS)] as part of the planned revision to their nonproprietary name. The Division acknowledged this information and the meeting proceeded to the discussion of questions.

Question 6: Does the Agency agree to the proposed tables and listings, and general strategies for side-by-side presentations and (b) (6) *in support of Insmed preparing the ISE?*

FDA Response:

Due to the differences in the study designs (i.e., duration of randomized treatment and the switch of "placebo" patients to receive active treatment) and (b) (6) .

Meeting Discussion:
Insmed stated they had reviewed the FDA Guidance for Industry Integrated Summary of Effectiveness (ISEs) Procedural, October 2015, which allowed for efficacy data to be presented in Module 2.7.3 as side-by-side comparisons and based on the FDA's preliminary meeting response proposed that an ISE would not be required as part of the NDA submission. Efficacy datasets would be provided in the individual CSR. FDA stated that (b) (6) so a side by side presentation of the efficacy data included in the Summary of Clinical Efficacy in Module 2.7.3 is sufficient.

Question 8: Does the Agency agree to the proposed approach for the 4-month safety update?

FDA Response:

We need additional information to respond to this question. You propose to provide a 4-month safety update for ongoing studies 212 and 312 based on data that would be available through February 28, 2018. Please clarify the rationale for selecting this date, estimated study completion dates for studies 212 and 312, time when you plan to submit the NDA and estimated time for a 4-month safety update submission. Regarding the structure of pooled data to be included in the 4-month safety update, the proposed approach seems reasonable.

Meeting Discussion:
Insmed clarified that they plan to submit the NDA at the end of the first quarter of 2018. Insmed explained that INS-212 will be completed in 2019 but the NDA will include efficacy results on the primary endpoint of culture conversion within the first 6 months of the study for all enrolled subjects. Insmed stated that efficacy analyses for culture conversion will be used to support approval under subpart H. Long term efficacy and safety results to support standard approval will follow once the study is completed. FDA asked if the data for non-converters would be included in the 4-month safety update. Insmed confirmed that the 4-month safety update would include safety data from non-converters and converters. Data from INS-312 would also be included. FDA agreed that the proposed data cutoff for a 4-month safety update was reasonable.

Question 22: Does the Agency agree with the general approaches to Sections 6.1 and 6.2 of the FPI, and does the Agency have any comments regarding the choice of 5% as the cut-off?

FDA Response:

It is premature to agree on a specific cutoff for reporting adverse reaction rates in the label. An appropriate cutoff will be determined upon review of the NDA, provided that the review supports the approval of the product. In general, the frequency cutoff for the listing of common

adverse reactions identified from clinical trials (usually the adverse reactions table) must be appropriate to the safety database (§ 201.57(c)(7)(ii)(A)). Factors that could influence selection of a frequency cut-off include the size of the safety database, the designs of the trials in the database, and the nature of the indication. The frequency cutoff should be noted in the listing or table header, in the text accompanying the listing or table, or in a footnote. See the FDA Adverse Reactions Sections of Labeling Guidance at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075057.pdf

Meeting Discussion:
Insmed stated that they will continue to analyze the safety data and evaluate the appropriateness of the initially proposed 5% cutoff. Insmed acknowledged the possibility that a lower frequency may be more informative. Insmed will assure the frequency cutoff is noted appropriately in the listing or table and/or text.

Question 23: Does the Agency agree that a single statement for routine pharmacovigilance (and not a RMP document) will be sufficient in Module 1.16.1 for the initial submission package, understanding that the need fora REMS remains an Agency review issue?

FDA Response:

At this time, the Office of New Drugs/Division of Anti-infective Products and the Office of Surveillance and Epidemiology/Division of Risk Management have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application.

Meeting Discussion:
Insmed proposed a plan to include the following routine pharmacovigilance text: “Insmed has proposed that routine pharmacovigilance processes would be used for post-marketing surveillance, rather than proposing a REMS. This approach would be consistent with other inhaled antibiotics.” This information would be placed in Module 1.16.1 of the original NDA. Insmed acknowledged that the determination for the need of REMS is a review issue but they wanted to be sure that their NDA includes all required information to avoid a Refuse to File response. FDA agreed with the proposed plan.

FDA Additional Comments Discussion:

Prescribing Information (PI)
Insmed stated that they agreed with the FDA comments on the PI, confirmed they would use the Selected Requirements for Prescribing Information (SRPI) checklist, and they would follow the Pregnancy, Lactation and Labeling rule (PLLR) including literature, database searches etc., to support the proposed Labeling. Insmed asked the FDA to direct them to the specific eCTD location within Module 1 where Insmed should include the PLLR supporting information requested by FDA.

FDA stated that this could be provided as an attachment to the submission cover letter, but would check if it is acceptable to include this in the Reviewer Guide.

Post Meeting Note: There is no designated area within Module 1 where the PLLR supporting documentation should appear. If the applicant plans to locate the information in a different module, then they would need to inform the FDA of that location.

Clinical
Insmed asked about the FDA's comments on programing changes for the vital signs and labs for INS-212 and the INS-312 study. Insmed wanted to know if FDA would expect the criteria that they listed to be a single rule in which all three criteria needed are to be met simultaneously, or if the Agency meant that there should be three separate rules for each listed criterion. FDA stated there should be 3 separate rules for each criterion and that all criteria need to be met at the same time. Insmed inquired about the FDA comment on changes in systolic and diastolic blood pressure from baseline. FDA stated that the 10 mm Hg changes in systolic and diastolic blood pressure refer to both increase and decrease.

Human Factors (HF) Report
Insmed stated that the HF validation study was the limiting part of their NDA submission and the data could only be submitted in the NDA. FDA stated they understood and had no follow-up questions.

Proprietary Name Request
Insmed stated that this information would be provided in a separate, concurrent submission at the time of NDA submission. FDA acknowledged Insmed's plan and had no follow-up questions.

505(b)(2) Regulatory Pathway
Insmed asked FDA about their comment on the tabular format template to be included in the NDA which allows FDA to identify selected sections of the application that are being cross referenced to literature sources. Insmed asked the FDA the specific location within the eCTD hierarchy where this table should be provided and suggested that it be appended to the Reviewer's Guide. FDA stated they expect that some sections of the NDA (e.g., Microbiology and Nonclinical Pharmacology/Toxicology) will include annotated summaries describing information from the public domain (including scientific literature) used to support the NDA.

Additional Meeting Discussion
Insmed inquired whether or not an Agency Committee meeting would occur for their product. FDA stated it was too early to provide information but at this time considered the potential for an Advisory Committee meeting to be very high but it could change.

Insmed stated the data from the NTM trial INS-212 were very encouraging and wanted to share with the FDA some ideas regarding (b) (4)

FDA stated that an understanding of the safety data collected

in the ongoing studies will also be important. FDA suggested a Type C meeting, preferably after the FDA has reviewed the data in the NDA data.

The FDA stated that the data from the INS-212 trial did not show a benefit on the 6MWT. Insmed confirmed this but stated that there was a separation of results in the 6MWT between patients that converted compared to those who did not convert. FDA encouraged Insmed to fully explain the interpretation of the 6MWT data, and to include the relationship of microbiologic outcomes to clinical benefit, as FDA would evaluate these data very closely.

3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. FDA emphasized the NDA would be complete based current NDA content and format regulations.

- 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.

- A preliminary discussion was held on the need for a REMS and it was concluded that the Sponsor will include routine pharmacovigilance text in Module 1.16.1 with their original NDA submission and the evaluation of a REMS plan will be determined during the NDA review.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

In addition, we note that a chemistry pre-submission meeting is scheduled for November 29, 2017. A summary of agreements reached at that meeting will be documented in the respective meeting minutes.

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.
Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. As of **May 5, 2017,** the following submission types: **NDA, ANDA,** and **BLA** must be submitted in eCTD format. **Commercial IND** and **Master File** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

SECURE EMAIL COMMUNICATIONS

Secure email is **required** for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

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.				

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the following items 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 field investigators who conduct those inspections (Item I and II). 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.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.
This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator

c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

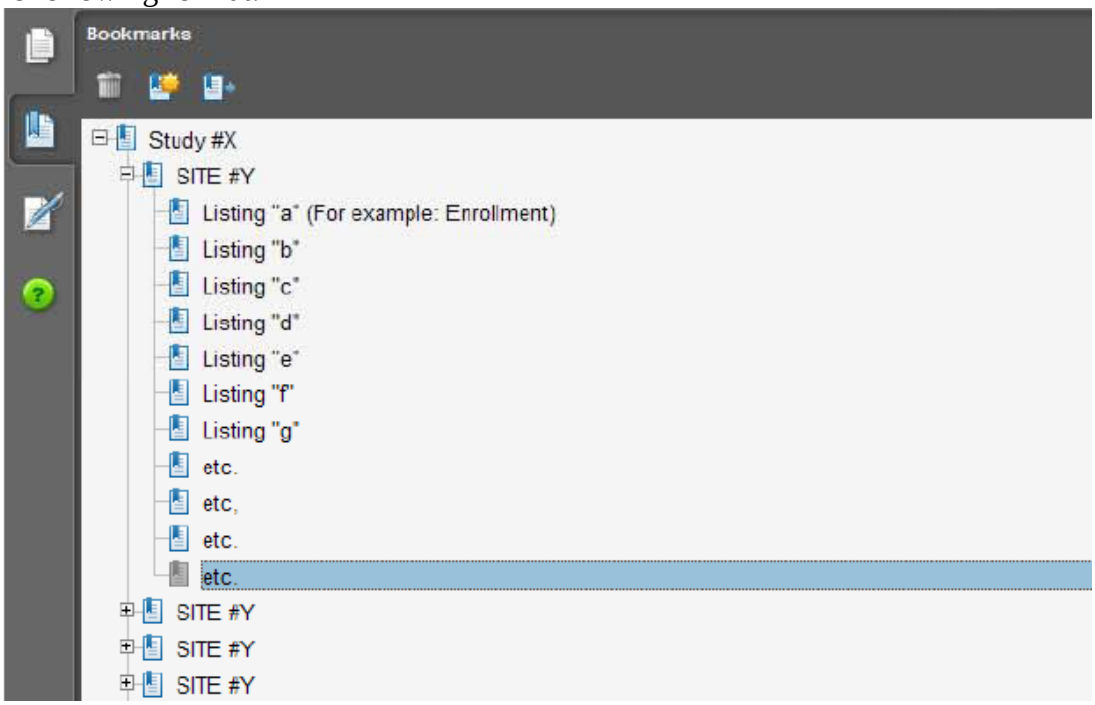
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)

c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
f. By subject listing, of AEs, SAEs, deaths and dates
g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link

http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None at this time.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Issue Meeting Minutes	FDA	December 15, 2017
Submit Meeting Presentation Slides to IND	Sponsor	Within 1 month of meeting

6.0 ATTACHMENTS

- Insmed November 13, 2017, email communication with meeting slides
- FDA November 9, 2017, Preliminary Meeting Comments

From:	Sandy Cottrell
To:	DiBernardo, Gregory
Cc:	Patrick Trefny
Subject:	IMPORTANT Replacement slides - RE: Insmed IND 108674 - pre-NDA meeting slides to display
Date:	Monday, November 13, 2017 5:26:01 PM
Attachments:	IND 108674 Pre-NDA Mtg Slides-non-CMC to FDA-replace.pdf mg_info.txt
Importance:	High

Dear Gregory
The slides I sent by accident were missing a slide regarding a question for 505(b)(2) .
Please distribute these instead if possible? :et me know please if you are ok?
Thank you
Sandy

From: Sandy Cottrell
Sent: Monday, November 13, 2017 3:41 PM
To: Gregory. DiBernardo (Gregory.DiBernardo@fda.hhs.gov) <Gregory.DiBernardo@fda.hhs.gov>
Cc: Patrick Trefny <Patrick.Trefny@Insmed.com>
Subject: Insmed IND 108674 - pre-NDA meeting slides to display

Dear Gregory,

As discussed, and in preparation for our face-to-face pre-NDA meeting on Wednesday, November 15, 2017, at 9am, please find the slide deck to be displayed at the meeting. We do not request specifically any resources of the review team as a pre-read, although of course they may choose to do so if you circulate them.

I do wish to confirm that these slides will be displayed by you, or do you require me to bring my computer to display at the meeting?

Thank you again for sending the preliminary written responses in such a timely manner as it truly allowed the team to discuss the guidance the team provided.

Kind regards,
Sandy

Sandra Cottrell, MA, PhD
Vice President, Global Regulatory Affairs
Insmed Inc.
Mobile 908-938-5344

19 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

From:	DiBernardo, Gregory
To:	"Sandy Cottrell"
Cc:	Patrick Trefny (Patrick.Trefny@Insmed.com)
Subject:	FDA Communication: IND 108674-ARICAYCE (LAI)-Insmed-FDA Preliminary Meeting Responses for 11/15/17 Pre-NDA Meeting
Date:	Thursday, November 09, 2017 4:35:26 PM
Attachments:	FINAL 11.09.17 108674 Pre NDA FDA Preliminary Meeting Responses.pdf
Importance:	High

Hello Dr. Cottrell,

I would like to provide the FDA Preliminary Meeting Responses for the November 15, 2017, Pre-NDA meeting scheduled for IND 108674. Please be aware that there will be **no paper/hardcopy** communication to follow this email communication.

Please let me know if after reviewing this material, if you plan to reduce the number of questions for discussion, change the format of the meeting to a teleconference, or cancel the scheduled meeting.

Thank you,

Gregory F. DiBernardo
Regulatory Project Manager
FDA/CDER/OND/OAP/Division of Anti-Infective Products
10903 New Hampshire Avenue
Building 22, Room 6223
Silver Spring, MD 20993
Telephone: (301) 796-4063

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Antimicrobial Products

COMMUNICATION SHEET

DATE: November 9, 2017

To: Sandra Cottrell, M.A., Ph.D. Vice President Regulatory Affairs	**From:** Gregory F. DiBernardo Regulatory Project Manager
Company: Insmed Incorporated	Division of Anti-Infective Products (DAIP)
Fax number: Communication sent via E-mail	**Fax number:** (301) 796-9882
Phone number: (908) 938-5344 E-mail: Sandra.Cottrell@Insmed.com Cc: Patrick.Trefny@insmed.com	**Phone number:** (301) 796-4063

Subject: IND 108674- Arikayce Liposomal Amikacin for Inhalation (LAI)

Total no. of pages including cover: 10

Comments:
FDA Preliminary Comments to questions outlined in your October 13, 2017, 2017, briefing document in preparation for the November 15, 2017, Pre-NDA meeting.

Confirm receipt of this communication at: gregory.dibernardo@fda.hhs.gov

Document to be mailed: ☐ YES ☑ NO

Investigational New Drug Application (IND) Number: 108674

Drug Name: Arikayce Liposomal Amikacin for Inhalation (LAI)

Re: FDA Preliminary Meeting Comments in Preparation for the November 15, 2017, Pre-NDA Meeting

This document provides our preliminary responses to the questions outlined in your briefing document dated October 13, 2017, and additional comments in preparation for the discussion at the meeting scheduled for November 15, 2017, at 9:00 A.M. between representatives for Insmed Incorporated (Insmed) and the Division of Anti-Infective Products (DAIP). We are sharing these in advance of the meeting to promote a collaborative and successful discussion. 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. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda for the meeting, again please contact the RPM. It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the premeeting communications are considered sufficient to answer the questions.

Question 1: Since all nonclinical studies will have TS datasets, and given the conduct dates of all nonclinical toxicology studies, does FDA agree that SEND datasets from nonclinical safety studies are not required in support of the NDA submission?

FDA Response: Yes, we agree that SEND datasets are not required for your NDA.

Question 2: Is the presentation of the histopathology data from the 2-year carcinogenicity study in rats, as collected by the Xybion Path/Tox System V.4.2.2, an acceptable electronic format submission to the Agency?

FDA Response: Yes, it is acceptable.

Questions 3: Based on the clinical development program and clinical exposures does the Agency consider this NDA to be an acceptable to file application?

FDA Response:

The clinical development program and clinical exposures appear to be acceptable to submit an NDA.

Question 4: Does the Agency agree to the proposed safety groups and subgroups as proposed?

FDA Response:

The safety subgroups are acceptable. Please refer to response to question 5 for additional comments on the proposed ISS pooling.

Questions 5: Does the Agency agree to the proposed tables and listings, and general strategies for pooling data in support of Insmed preparing the ISS?

FDA Response:

In addition to the proposed safety groups, we are interested in pooled safety data for patients enrolled in the randomized phases of studies 112 and 212.

Question 6: Does the Agency agree to the proposed tables and listings, and general strategies for side-by-side presentations (b) (4) *in support of Insmed preparing the ISE?*

FDA Response:

Due to the differences in the study designs (i.e., duration of randomized treatment and the switch of "placebo" patients to receive active treatment) and (b) (4)

Question 7: Does the Agency have any specific comments/guidance regarding the ISS and ISE SAPs?

FDA Response:

Please refer to the responses provided for questions 5 and 6.

Question 8: Does the Agency agree to the proposed approach for the 4-month safety update?

FDA Response:

We need additional information to respond to this question. You propose to provide a 4-month safety update for ongoing studies 212 and 312 based on data that would be available through February 28, 2018. Please clarify the rationale for selecting this date, estimated study completion dates for studies 212 and 312, time when you plan to submit the NDA and estimated time for a 4-month safety update submission. Regarding the structure of pooled data to be included in the 4-month safety update, the proposed approach seems reasonable.

Question 9: Does the Agency agree to the proposed placement of references with linking as described above?

FDA Response: This is acceptable.

Question 10: Upon review of the table of contents, proposed tables and listings, and general strategies for supporting the microbiology section of this NDA, does the Agency agree with the approach?

FDA Response: This is acceptable.

Question 11: Does the FDA agree that these available amikacin MIC data are sufficient to confirm the in vitro activity of amikacin against MAC?

FDA Response: This is acceptable.

Question 12: Does the Agency agree with the proposed list of adverse events of special interest?

FDA Response:

Please add exacerbation of underlying chronic obstructive pulmonary disease (COPD) to the list.

Question 13: Does the Agency agree to the proposed plan to submit the CRFs in compliance with 21 CFR 314.50(f)(2) as well as CRFs for the NTM Phase 3 subjects experiencing adverse events of special interest?

FDA Response:

Yes, we agree. Please also refer to responses to question 12.

Question 14: Will this proposal related to the datasets submission be acceptable to the Agency?

FDA Response:

Submission of SDTM and ADaM datasets for the NTM studies TR02-112, INS-212, and INS-312 is acceptable.

Regarding the datasets related to Clinical Pharmacology, we recommend that you submit the population PK model, related csv files, datasets and bioanalytical files for all relevant studies. Provide the related datasets as a SAS transport file (*.xpt). A description of each data variable should be provided in a define.pdf file. Follow the general guidance (https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm) to submit these datasets and relevant information.

Question 15: Would it be acceptable for Insmed to submit data in CDISC SDTM standard format and not include data listings?

FDA Response: Yes, this is acceptable.

Question 16: Insmed proposes to submit this NDA under 505(b)(1). Does the Agency agree the NDA should be submitted under 505(b)(1) and so designated on Item 17 FORM FDA 356h?

FDA Response:

No, we do not agree. You have indicated that you intend to rely on published literature to complete the required submission modules; hence, the NDA will need to be submitted as a 505(b)(2) application.

In addition, you are reminded that you will need to submit information that will permit amikacin liposome inhalation suspension to be labeled appropriately according to the Pregnancy and Lactation Labeling Rule (PLLR). As you have not conducted nonclinical reproduction toxicity studies with amikacin liposome inhalation suspension, we anticipate that this information will come from published literature and previous experience with other products that contain amikacin. Please see 505(b)(2) regulatory pathway comments below.

Question 17: Does the Agency agree to this approach to address PREA requirements in the NDA submission?

FDA Response: Yes, we agree.

Question 18: Does the Agency agree with Insmed's interpretation and the implications of QIDP for a priority review status to be granted?

FDA Response:

Yes, because your proposed NDA will be the first application for your QIDP-designated product, it will be eligible for priority review designation.

Question 19: Recognizing that the Agency acknowledged that amikacin is not a NME, will the Agency target the PDUFA review to be calculated from the NDA receipt date?

FDA Response:

The PDUFA goal date for NDA action will be calculated from the FDA receipt date.

Question 20: Does the Agency agree to this proposed eCTD placement of reports and the use of a Reference Leaf?

FDA Response:

In addition to the referred PK reports, provide any other relevant PK/population PK study reports (e.g., Study INS-212). We recommend you submit the study report for the gamma scintigraphy study as well at the time of NDA submission.

Question 21: Does the Agency agree to this proposal regarding the creation of "in-text" tables?

FDA Response: This is acceptable.

Question 22: Does the Agency agree with the general approaches to Sections 6.1 and 6.2 of the FPI, and does the Agency have any comments regarding the choice of 5% as the cut-off?

FDA Response:

It is premature to agree on a specific cutoff for reporting adverse reaction rates in the label. An appropriate cutoff will be determined upon review of the NDA, provided that the review supports the approval of the product. In general, the frequency cutoff for the listing of common adverse reactions identified from clinical trials (usually the adverse reactions

table) must be appropriate to the safety database (§ 201.57(c)(7)(ii)(A)). Factors that could influence selection of a frequency cut-off include the size of the safety database, the designs of the trials in the database, and the nature of the indication. The frequency cutoff should be noted in the listing or table header, in the text accompanying the listing or table, or in a footnote. See the FDA Adverse Reactions Sections of Labeling Guidance at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075057.pdf

Question 23: Does the Agency agree that a single statement for routine pharmacovigilance (and not a RMP document) will be sufficient in Module 1.16.1 for the initial submission package, understanding that the need fora REMS remains an Agency review issue?

FDA Response:

At this time, the Office of New Drugs/Division of Anti-infective Products and the Office of Surveillance and Epidemiology/Division of Risk Management have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application.

Additional Comments

A. Prescribing Information:

1. 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* and *Pregnancy and Lactation Labeling Final Rule* 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.

The application should include a review and summary of the available published literature

regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which 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* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

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

B. Clinical Pharmacology:

In your planned NDA, include a table to summarize all the relevant bioanalytical report(s) and the method validation report(s) along with the clinical/PK/Population PK study reports and enable the study/report number to be hyperlinked. In your bioanalytical report(s) and the method validation report(s), we recommend you include a summary table to indicate the acceptability of the bioanalyses and the method validations.

C. Clinical:

We do not agree with your definition of clinically meaningful changes for vital signs and laboratory investigations. Please note that we will consider the items listed below as clinically significant changes:

1. A body temperature below 35°C
2. A 50% increase from baseline or 0.3mg/dL increase from baseline in creatinine level
3. A systolic blood pressure ≤ 90mmHg, and a change from baseline by 10mmHg for systolic and diastolic blood pressure measurements
4. A heart rate above 120 beats per minute(bpm) or less than 60bpm
5. A change in body weight of 10%

D. Human Factors Report:

We are aware that your human factors (HF) validation study has commenced. The data from your human factors study will support approvability of your NDA. While we typically review HF study results during the application review cycle as that is when we would be completing a full review of the data to inform approval of an application, we are open to review the results under an IND given that the product has been granted fast track designation.

The following should be submitted at the time of human factors study result submission:

- A summary of preliminary analyses and evaluations, including formative studies;
    - Include in your summary a discussion of key findings and any changes made to your product or labeling, including how the findings were used to update the user interface and risk analysis

- An updated risk analysis for your product;
- Detailed HF validation study report. See Appendix A of Guidance *Applying Human Factors and Usability Engineering to Medical Devices*, available online at: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259760.pdf for a description of elements to include in the HF validation study report.
- Intend-to-market labels and labeling (including an editable word version of the IFU if an IFU is proposed)
- Five intend-to-market samples of product
- Summary of any changes made to the user interface (e.g., product design or label and labeling changes) after completion of the human factors validation study, including a description of how the changes were validated;
    - If changes to Instructions for Use (IFU) were made, a side-by-side comparison that points out the differences between the tested version and the intend-to-market version should be included

Human Factors study results should be placed in eCTD section 5.3.5.4 – Other Study reports and related information.

E. Proprietary Name Request:

We note that your proposed proprietary name for this product, Arikayce, was found conditionally acceptable under the IND. Please note that a request for proprietary name review for Arikayce should be submitted once the NDA is submitted.
If you require information on submitting a request for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)

- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

F. 505(b)(2) Regulatory Pathway

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry, *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had

challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s)

or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and effectiveness for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication A*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section B*
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

If you have any questions regarding this communication, please contact, Mr. Gregory DiBernardo, Regulatory Project Manager, at (301) 796-4063.

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/s/

SUMATHI NAMBIAR
12/15/2017