CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761328Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 118524

MEETING MINUTES

AstraZeneca Pharmaceuticals LP
Attention: Leslie Sands
Director, Global Regulatory Affairs
One MedImmune Way
Gaithersburg, MD 20878

Dear Ms. Sands:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MEDI8897.

We also refer to the telecon between representatives of your firm and the FDA on July 26, 2022. The purpose of the meeting was to discuss the content and format of the BLA submission.

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

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

If you have any questions, call me, at (240) 402-9953 or at the mainline at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Saebyeol Jang, PhD, RAC-US
Regulatory Project Manager
Antivirals Group
Division of Regulatory Operations for Infectious Diseases
Office of Regulatory Operations
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-BLA
Meeting Date and Time:	July 26, 2022, 9:30 – 11:00 AM (ET)
Meeting Location:	Teleconference
Application Number:	IND 118524
Product Name:	MEDI8897 (nirsevimab)
Proposed Indication:	To immunize infants and children for the prevention of Respiratory syncytial virus (RSV) lower respiratory tract disease in (i) infants from birth entering their first RSV season and (ii) children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season, (b) (4) chronic lung disease (CLD) (b) (4) congenital heart disease (CHD), (b) (4)
Sponsor Name:	AstraZeneca Pharmaceuticals LP
Regulatory Pathway:	351(a) of the Public Health Service Act

FDA ATTENDEES

Office of New Drugs (OND)/Office of Infectious Diseases (OID)

- John Farley, MD, MPH, Director

OND/OID/Division of Antivirals (DAV)

- Debra Birnkrant, MD, Director
- Wendy Carter, DO, Acting Deputy Director
- Poonam Mishra, MD, MPH, Deputy Director of Safety
- Mary Singer, MD, PhD, Medical Team Leader
- Melisse Baylor, MD, Medical Officer
- Samer El-Kamary, MD, Medical Officer

- Julian O'Rear, PhD, Clinical Virology Team Leader
- Michael Thomson, PhD, Clinical Virology Reviewer
- Sheli Radoshitzky, PhD, Clinical Virology Reviewer

OND/OID/Division of Pharmacology/Toxicology for Infectious Diseases
- Laine Peyton Myers, PhD, DABT, Pharmacology/Toxicology Team Leader
- Ilona Bebenek, PhD, DABT, Pharmacology/Toxicology Reviewer

OND/Office of Regulatory Operations/Division of Regulatory Operations for Infectious Diseases
- Maureen Dillon Parker, MS, RAC, Director, Regulatory Project Management Staff

OND/Office of Regulatory Operations/Division of Regulatory Operations for Infectious Diseases, Antivirals Group
- Karen Winestock, Chief, Project Management Staff
- Saebyeol Jang, PhD, RAC-US, Regulatory Project Manager

OND/Office of Translational Sciences (OTS)/Office of Clinical Pharmacology/Division of Infectious Disease Pharmacology
- Kunyi Wu, PharmD, Clinical Pharmacology Team Leader
- Justin Earp, PhD, Pharmacometrics Team Leader
- Yang Zhao, PhD, Clinical Pharmacology Reviewer
- Jiajun Liu, PharmD, MSc, Pharmacometrics Reviewer

OND/OTS/Office of Biostatistics/Division of Biometrics IV
- Thamban Valappil, PhD, Statistics Team Leader
- Fraser Smith, PhD, Statistics Reviewer

OND/Office of Pharmaceutical Quality/Office of Biotechnology Products
- Willie Wilson, PhD, Product Quality Team Leader
- Jens Fricke, PhD, Product Quality Reviewer
- Jeanne Fringer, PhD, Drug Product Microbiology Reviewer

OC/Office of Clinical Policy and Programs/Office of Combination Products
- Bindi Nikhar, MD, Associate Clinical Director

Office of Surveillance and Epidemiology/Office of Medication Error Prevention and Risk Management/Division of Medication Error Prevention and Analysis 1
- Murewa Oguntimein, PhD, MHS, CPH, MCHES, Human Factors Team Lead

SPONSOR ATTENDEES
- Alexander Currie, Senior Director, Statistics
- Amanda Leach, Global Clinical Head

- Amy Grenham, Senior Director, Regulatory Affairs
- Amy Scott-Billman, Vice President, Global Regulatory Affairs
- Anna Berglind, Executive Director, Statistics
- Beth Kelly, Senior Director, Clinical Virology
- Christine Wood, Regulatory Affairs Group Director, Global Labeling
- Leslie Sands, Director, Global Regulatory Affairs
- Melia Grim, CMC Regulatory Affairs Senior Director
- Manish Shroff, Medical Director, Senior Patient Safety Physician
- Therese Takas, Director, Clinical Operations
- Tonya Villafana, Vice President, Global Franchise Head
- Ulrika Wahlby-Hamren, Senior Director, Clinical Pharmacology and Pharmacometrics
- Vaishali Mankad, Global Development Medical Director
- Jon Heinrichs, Associate Vice President and Segment Head at Sanofi
- Denise Ecker, Regulatory Affairs Development-US at Sanofi

1.0 BACKGROUND

AstraZeneca Pharmaceuticals LP (AstraZeneca) is developing MEDI8897 (nirsevimab) for the prevention of lower respiratory tract illness caused by RSV in all infants entering their first RSV season and in children with certain chronic diseases [chronic lung disease (CLD), congenital heart disease (CHD), (b) (4) entering their first and second RSV season.

The MEDI8897 development program was granted Fast Track and Breakthrough Therapy designations on March 27, 2015, and February 1, 2019, respectively. An Agreed Initial Pediatric Study Plan (iPSP) was finalized on April 28, 2017.

AstraZeneca had an End of Phase 2 (EOP2)/Initial Comprehensive Breakthrough Therapy meeting on February 26, 2019, to reach agreement with the Agency on key aspects of the development program for MEDI8897 and to discuss the phase 3 clinical development plan prior to initiation of the trials planned for the 2019-2020 Northern Hemisphere respiratory virus season.

AstraZeneca also had a Type B, Chemistry, Manufacturing, and Control (CMC) meeting on March 12, 2020, to obtain FDA's advice and agreement on AstraZeneca's approach to bridging MEDI8897 from the current registrational trial presentation (vial) to the proposed commercial presentation (prefilled syringe).

On May 15, 2020, the FDA determined that Sponsor did not need to submit the results of the human factors (HF) validation study as part of the MEDI8897 BLA based on the review of the submitted use-related risk analysis and justification for not submitting HF validation study results.

On December 2, 2020, AstraZeneca had a Type B, Breakthrough Therapy Guidance Meeting to discuss and reach agreement on a proposal for an updated clinical package for MEDI8897 to be submitted to support a marketing application and to obtain advice on the proposed changes to the statistical analysis plans for the ongoing phase 3 Trial 004 (MELODY) and the phase 2/3 Trial 005 (MEDLEY).

On August 10, 2021, the proprietary name, Beyfortus was conditionally granted.

On August 17, 2021, the FDA's written responses regarding the final drug product comparability strategy were provided in response to Type B CMC, Breakthrough Therapy Guidance Meeting Request.

AstraZeneca submitted the Type B, pre-BLA meeting request on June 1, 2022, to discuss the content and format of the BLA submission. FDA granted this request on June 14, 2022, as a Type B Meeting. FDA sent Preliminary Comments to AstraZeneca on July 20, 2022. Upon receiving FDA's preliminary comments, AstraZeneca sent the enclosed presentation slides on June 24, 2022, and requested to focus the meeting discussion on the FDA responses to Questions 5a and 6. Subsequently, AstraZeneca sent responses to additional comments in Preliminary Comments letter on July 25, 2022. The Pre-BLA meeting was held on July 26, 2022, via teleconference.

2.0 DISCUSSION

Questions submitted by AstraZeneca in the June 17, 2022 meeting background package are in **bold** font, followed by the July 20, 2022 Division's preliminary responses in *italics* font, followed by a summary of the meeting discussion pertinent to the given question in normal font.

2.1. Clinical

Question 5a: In addition to efficacy results for individual studies (b) (4) does the Agency agree that the results of pooled analyses (MELODY [Primary Cohort]/Study 3 [Proposed Dose] Pool) add value (b) (4)?

FDA Response to Question 5a:

(b) (4) *Efficacy for prevention of RSV hospitalization cannot be pooled from these two studies because of the different risks for hospitalization in the populations studied in Trials 003 and 004. Trial 003 enrolled infants born at 29 weeks to 35 weeks gestational age, while Trial 004 enrolled infants born at 35 weeks gestational age or later. As shown in the results of these studies, the risk of hospitalization varies in these two populations. In*

Trial 003, the incidence of hospitalization in the placebo arm (4.1%) was 2.6-fold higher than the incidence of hospitalization in the placebo arm (1.6%) of Trial 004. In addition, differences in hospitalization by gestational age ≥ 35 weeks and < 35 weeks are also described in Table 1 of the AAP Updated Guidance for Palivizumab Prophylaxis Among Infants and Young Children at Increased Risk of Hospitalization for Respiratory Syncytial Virus Infection, Technical Report.

Discussion:

Pooling efficacy data of Trial 004 (MELOLDY) and Trial 003
AstraZeneca presented slides which detailed their justification for pooling efficacy data of Trial 004 (MELOLDY) and Trial 003 (See attached slides 5-7).

FDA acknowledged AstraZeneca's position but reiterated that they do not agree with pooling the efficacy data from the two trials because the risk-benefit assessments for preterm and term infants are very different.

- Risk assessment:
The study populations in Trial 003 (pre-term infant) and Trial 004 (term and late pre-term infants) are different populations with different risk profiles as shown in Slide 5. The rates of MA RSV LRTI and of MA RSV-associated hospitalization are higher in preterm infants; the percentage of affected MA RSV LRTI with hospitalization is 4.1% in the placebo arm of pre-term infants. That is higher than the incidence of MA-LRTI in both time periods that are shown for the Trial 004.

- Benefit assessment:
FDA agreed that there is evidence of efficacy in both populations as shown in Slide 6. However, given the efficacy for hospitalization was statistically robust in preterm infants and was not statistically significant in term infants, pooling the efficacy data from Trial 003 and from Trial 004 could be misleading, showing apparently lower efficacy in preterm infants and higher efficacy in term infants compared to the results for the separate populations. FDA stated that while 62.1% of the subjects were observed to have MA RSV LRTI with hospitalization in the Trial 004 (primary cohort), the confidence interval was -8.6 to 86.8, which did not reach statistical significance since it overlapped zero.

AstraZeneca pointed out the efficacy results in Slide 6. The sponsor stated that the results for prevention of RSV-associated hospitalization in Trial 004 (Melody) were statistically significant when analyzed for the entire study population. AstraZeneca also stated that the efficacy (for prevention of MA-LRTI and of hospitalization) results were similar in the Melody trial, all subject population, and in the pooled efficacy population (Melody primary cohort and Trial 003). AstraZeneca also stated that these data show that there the study populations

are similar and that that the results are statistically significant for preterm and term infants.

FDA asked for clarification regarding which subjects were included in the "all subject" population for the Melody trial compared to the "primary cohort" population for Melody. AstraZeneca stated that they had succeeded in collecting efficacy data in the safety cohort in the Melody trial and combined the efficacy data from both the primary cohort and from the safety cohort to make a new category including "all subjects". They now proposed pooling efficacy data from the primary cohort or efficacy population of Trial 004 (Melody), the safety population of Trial 004, and Trial 003.

FDA replied that at the last meeting, AstraZeneca had suggested, and DAV had agreed that the population of Trial 004 (Melody) would include a primary efficacy population and a safety population. AstraZeneca had proposed the two populations because of the lower RSV incidence during COVID and difficulty enrolling subjects. If AstraZeneca is planning on using efficacy data from the safety cohort, AstraZeneca will have to justify it in the BLA submission and demonstrate that there was no difference in the way that efficacy data was collected in the safety cohort and efficacy cohort. The use of efficacy data from the safety cohort will be a review issue.

AstraZeneca asked for clarification for what FDA expects in labeling. FDA replied that they expect to see results for the primary endpoints of Trial 003 and for 004 (Melody) presented separately in Section 14. The efficacy data presented from Melody should be from the efficacy cohort. The safety data from Trial 003 and from the entire study population of Melody should described in Section 6. AstraZeneca acknowledged.

In conclusion, from clinical and statistical point of view, FDA does not agree with pooling data of Trial 003 and Trial 004 (b) (4)

<u>Question 6:</u> Does the agency agree with the proposed data presentations for safety in Module 2.7.4?

<u>FDA Response to Question 6:</u>
We agree with the planned presentation of safety data.

We do not agree with the pooling of safety data of all subjects in Trials 003 and 004; however, we agree with pooling of safety data from the proposed dose cohort of Trial 003 and all subjects in Trial 004. In the clinical study report for Trial 003, please provide safety data for all subjects in Trial 003 as well as providing safety data

separately for subjects in Trial 003 who weigh < 5 kg and for those who weigh ≥ 5 kg.

We agree with your planned analyses of adverse events related to the skin. In your analyses of Trials 002 and 003, please attempt to separately describe skin AEs that are local injection site reactions from those that are not injection site reactions. Please provide a summary of local injection site reactions from all studies. Please note that we may request additional analyses during the review.

Please provide the following safety data in Module 2.7.4 and/or the integrated summary of safety (ISS):

- *Narratives for all the following AEs, regardless of drug relatedness: deaths, discontinuations due to AEs, SAEs, and new onset chronic diseases*
- *Autopsy reports, if available, for all subjects who died with 30 days of receipt of MEDI8897 (nirsevimab)*
- *Analyses of all AEs by time periods ≤ 48 hours, ≤ 7 days, ≤ 14 days, ≤ 6 weeks, and for the entire safety follow-up period*
- *Analyses of safety by gestational age (<29 weeks, ≥ 29 weeks to < 35 weeks, and ≥ 35 weeks)*
- *Safety by gender and race*
- *Summary (description and tabular) of SAEs and of LRTIs in subjects in Trial 004 for Days 360 to 511.*

Please provide information from the safety of other monoclonal antibodies used in infants, if needed, to provide a context for MEDI8897 (nirsevimab) safety results.

Discussion:

Pooling Safety Data

AstraZeneca presented Slide 9 stating that they had used all subjects in Trial 004 and all subjects in Trial 003 as the primary pooled safety population for analyses in the Module 2.7.4 Clinical Summary of Safety asked if FDA agree with the proposed approach.

FDA did not agree with the approach, stating that safety data from subjects who receive the to-be-marketed dose should be reported as the primary safety population. If safety data from a dose higher than the to-be-marketed dose, the safety risk could be overestimated; If safety data from a lower dose than the to-be-marketed dose, the safety risk could be underestimated. Therefore, FDA expects the focus on the Clinical Summary of Safety to be the safety data from the Trial 004 and the Trial 003 (proposed dose).

AstraZeneca agreed.

Safety analysis in Trial 003 by weight < 5 kg
The most relevant Safety Analysis for study participants in subjects weighing less than 5 kg would be in those who received the to-be-marketed dose to support the safety of the proposed dose.

AstraZeneca asked if FDA agrees with the proposed plan to present safety for subjects < 5kg for Trial 003. FDA replied that they expect to see the safety analysis for the entire study population and a separate analysis of safety for subjects < 5 kg in the Clinical Study Report for Trial 003.

AstraZeneca agreed.

Safety data presentation by Time Period and Gender & Race
FDA stated that they agree with the proposed plan for analyses of safety data by time period and by gender and race.

2.2. Additional Comments in the Meeting Preliminary Comments

Clinical Pharmacology

Low percentage of ADA and PK data availability for Day 361
FDA asked why ADA and PK data availability for Day 361 (i.e. Season 2) is significantly lower than that for Baseline and Day 151 (Refer to Table 1 in the response to FDA additional comments). AstraZeneca responded that the study is still ongoing, and they expect to collect the similar percentage of ADA and PK data for Day 361 when the study is completed.

PK measurement
FDA asked whether the PK measurement has been conducted for the total serum concentration or the free serum concentration of MEDI8897. AstraZeneca will provide a written follow-up response to this question.

Exposure response
FDA recommended that if AstraZeneca pools the data for E-R analysis, it treats the study as a covariate because of slightly different patient populations across studies.

Statistics

AstraZeneca's clarification question regarding raw dataset (Refer to Page 7, the response to FDA additional comments)
FDA stated if SDTM datasets replicate the key variables in the ADaM dataset, the submission of RAW datasets would not be necessary. However, SDTM variables are sometimes not quite the same as some of the variables in the RAW datasets, and if the

SDTM datasets cannot be used to derive the key variables in the ADAM/analysis datasets, then FDA needs to have both the SDTM and the RAW datasets.

AstraZeneca clarified that they used the RAW database to create the SDTM. FDA will provide a written response (response sent on August 3, 2022).

AstraZeneca's clarification question regarding the pilot dataset (Refer to Page 7, the response to FDA additional comments)
FDA clarified that they are asking for mock datasets as examples to show the proposed contents of the datasets in the BLA submission so that FDA would be able to provide advice prior to the BLA submission as to whether there are any potential issues associated with dataset contents. FDA will provide a written response (response sent on August 3, 2022).

2.3. Additional Discussion

AstraZeneca informed the current target date for the BLA submission is the end of September 2022.

3.0 ADDITIONAL INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed in the meeting preliminary comments.

- 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.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You confirmed via email communication dated August 9, 2022 that you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

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]

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.

[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

- 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.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing

of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

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

[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

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]

NONPROPRIETARY NAME

On January 13, 2017, FDA issued a final guidance for industry *Nonproprietary Naming of Biological Products*, stating that, for certain biological products, the Agency intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning.

Please note that certain provisions of this guidance describe a collection of information and are under review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (PRA). These provisions of the guidance describe the submission of proposed suffixes to the FDA, and a sponsor's related analysis of proposed suffixes, which are considered a "collection of information" under the PRA. FDA is not currently implementing provisions of the guidance that describe this collection of information.

However, provisions of the final guidance that do not describe the collection of information should be considered final and represent FDA's current thinking on the nonproprietary naming of biological products. These include, generally, the description of the naming convention (including its format for originator, related, and biosimilar biological products) and the considerations that support the convention.

To the extent that your proposed 351(a) BLA is within the scope of this guidance, FDA will assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Provide a written response on AstraZeneca's clarification questions for statistics.	FDA	Completed on August 3, 2022

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

Submit mock datasets.	Sponsor	Prior to the BLA submission
Provide a written follow-up response to FDA clinical pharmacology question regarding PK measurement.	Sponsor	Completed on August 12, 2022

6.0 ATTACHMENTS AND HANDOUTS

A copy of presented slides and AstraZeneca's response to FDA additional comments in meeting preliminary comments letter.

24 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SAEBYEOL JANG
08/18/2022 03:06:47 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 118524

MEETING MINUTES

MedImmune LLC
Attention: Amy Grenham, MS, RAC
Director, Regulatory Affairs
1 MedImmune Way
Gaithersburg, MD 20878

Dear Ms. Grenham:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MEDI8897.

We also refer to the meeting between representatives of your firm and the FDA on February 26, 2019. The purpose of the meeting was to reach agreement with the Agency on key aspects of the development program for MEDI8897 and to discuss the phase 3 clinical development plan prior to initiation of the trials planned for the 2019-2020 Northern Hemisphere respiratory virus season.

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 Saebyeol Jang, Regulatory Project Manager at 240-402-9953 or 301-796-1500.

Sincerely,

{See appended electronic signature page}

Saebyeol Jang, PhD
Regulatory Project Manager
Division of Antiviral 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:	End of Phase 2/Breakthrough Therapy-Initial Comprehensive
Meeting Date and Time:	February 26, 2019, 3:00-4:30 pm
Meeting Location:	10903 New Hampshire Avenue White Oak Building 21, Conference Room 1537 Silver Spring, MD 20903
Application Number:	IND 118524
Product Name:	MEDI8897
Indication:	Prevention of lower respiratory tract infection caused by RSV
Sponsor/Applicant Name:	MedImmune, LLC
Meeting Chair:	Melisse Baylor, MD
Meeting Recorder:	Saebyeol Jang, PhD

FDA ATTENDEES

OND/Office of Antimicrobial Products (OAP)
John Farley, MD, MPH, Deputy Director

OND/OAP/Division of Antiviral Products (DAVP)
Debra Birnkrant, MD, Director
Jeffrey Murray, MD, MPH, Deputy Director
Mary Singer, MD, PhD, Medical Team Lead
Melisse Baylor, MD, Clinical Reviewer
Prabha Viswanathan, MD, Medical Officer
Julian O'Rear, PhD, Clinical Virology Team Lead
William Ince, PhD, Clinical Virology Reviewer
Christopher Ellis, PhD, Pharmacology/Toxicology Team Lead for Biologics
Karen Winestock, Chief, Project Management Staff
Saebyeol Jang, PhD, Regulatory Project Manager

Office of Translational Sciences (OTS)/Office of Biostatistics (OB)/Division of Biometrics (DBIV)
Thamban Valappil, PhD, Biometrics Team Lead
Fraser Smith, PhD, Biometrics Reviewer

OTS/Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology (DCPIV)

Qin Sun, PhD, Acting Clinical Pharmacology Team Lead
Jenny Zheng, PhD, Clinical Pharmacology Reviewer
Lilian Adeojo, PharmD, ORISE Fellow

OTS/Office of Clinical Pharmacology (OCP)/Division of Pharmacometrics(DPM)
Ruojing Li, PhD, Pharmacometrics Reviewer

Office of Pharmaceutical Quality (OPQ)/Office of Biotechnology Products (OBP)
Willie Wilson, PhD, Product Quality Team Lead
Jens Fricke, PhD, Product Quality Reviewer

Independent Contractor team, PDUFA VI IND communications assessment
Jason Hsiao

SPONSOR ATTENDEES
MedImmune, LLC
Gary Cline, MS, PhD, Vice President, Biostatistics and Data Management
Filip Dubovsky, MD, MPH, Vice President, Clinical Development
Mark Esser, PhD, Director, Translational Medicine
Pam Griffin, MD, Senior Director, Clinical Development
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Beth Alley, BA, Director, Regulatory Affairs
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Sanofi Pasteur
Jon Heinrichs, MS, PhD, Associate Vice President and Segment Head
Alison Rameau, PharmD, Regulatory Product Manager

1.0 BACKGROUND

MedImmune, LLC (MedImmune) requested a Type B, End of Phase 2 (EOP2) meeting with the Division of Antiviral Products (DAVP) to discuss their proposed Phase 3 development plans for MEDI8897, an extended half-life monoclonal antibody directed against Respiratory Syncytial Virus (RSV) fusion (F) protein. MedImmune intends to develop MEDI8897 for the prevention of medically attended lower respiratory tract infection (MALRTI) caused by RSV in infants

entering their first RSV season and in children with chronic lung disease (CLD) or congenital heart disease (CHD) entering their first and second RSV season.

The MEDI8897 development program was granted Fast Track and Breakthrough Therapy designations on March 27, 2015 and February 1, 2019, respectively. An Agreed Initial Pediatric Study Plan (iPSP) was finalized on April 28, 2017.

MedImmune has completed the phase 2b Study D5290C00003, a trial that evaluated safety, efficacy, and pharmacokinetics (PK) of MEDI8897 in healthy preterm infants. MedImmune is now planning to initiate their phase 3 program which is planned as follows:

- **D5290C00004**: A phase 3 randomized, double-blind, placebo-controlled trial to evaluate the safety and efficacy of MEDI8897 in healthy late preterm and term infants

- **D5290C00005**: A phase 2/3 randomized, double-blind, palivizumab-controlled trial to evaluate safety of MEDI98897 in pediatric patients for whom palivizumab is currently recommended.

The primary goal of this EOP2/Initial Comprehensive Breakthrough Therapy meeting was to reach agreement with the Agency on key aspects of the development program for MEDI8897 and to discuss the phase 3 clinical development plan prior to initiation of the trials planned for the 2019-2020 Northern Hemisphere respiratory virus season.

MedImmune submitted the EOP2 meeting request on December 18, 2018, and the Division granted this request on December 28, 2018, as a Type B Meeting.

FDA sent preliminary comment to MedImmune on February 19, 2019. Upon receiving FDA's preliminary comments, MedImmune requested that the meeting discussion be focused on the FDA responses to Questions 1, 3, 4 and 5.

2. DISCUSSION

2.1. Dose Selection

Question 1

Does the Agency agree with the rationale for MEDI8897 dose selection for the pivotal Phase 3 and Phase 2/3 studies?

(a) A stratified dosing regimen for infants in the first year of life and entering their first RSV season based on body weight at time of dosing:
- a single fixed 50-mg dose for infants < 5 kg
- a single fixed 100-mg dose for infants ≥ 5 kg

(b) A single fixed 200-mg dose for children in the second year of life and entering their second RSV season

FDA Response to Question 1

Clinical Pharmacology Comment

(a) Based on available data, we agree with the proposed stratified dosing regimen based on body weight at time of dosing for infants in the first year of life and entering their first RSV season. We have some comments for you to fine tune the model for BLA submission. It is not clear whether age/body weight is associated with time to medically attended lower respiratory tract infection (MALRTI) based on your Kaplan-Meier curves of MALRTI across the quartiles of age and weight at baseline from subjects in the placebo arm. The highest age or body weight quartile of subjects showed the highest incidence of a MALRTI after 90 days in your plot, but the third quartile of body weight had the lowest incidence of a MALRTI. As additional PK, safety, and efficacy data are collected in phase 3 and phase 2/3 trials, we recommend that you re-analyze the association between age/body weight and the time to MALRTI. We also noted that your proposed target AUC of 13.4 day*mg/mL (the target AUC at the time of dosing) was calculated based on baseline clearance.

(b) We agree with the proposed single fixed 200-mg dose for children in the second year of life and entering their second RSV season. We note that given the 10 mg/kg efficacious dose threshold, a 200-mg dose would be expected to be efficacious for body weights up to 20 kg in the second year of life. We have some comments for you to fine tune the model for BLA submission. We recommend that you analyze the exposure-response based on the association between demographic characteristics/geographic location and the time to MALRTI in the second RSV season as well.

Clinical Comment

We are concerned that weights of infants with chronic lung and chronic heart disease may vary considerably and that a single dose of 200 mg in the second year of life may not be appropriate for all infants with CLD and CHD. Please provide growth curves that have been accepted for use in these two populations. In the absence of established growth curves, please provide any information on average weights and weight ranges for these two populations during the second year of life.

MedImmune Response:

There is very limited information on growth curves for children with CLD or CHD. We do have information on those populations that was collected in previous clinical studies. Based on data from the motavizumab clinical studies, the mean weight for children 12 – 24 months of age with CLD was 9.29 kg (range 5.55 to 14.35 kg). The mean weight for children 12 – 24 months of age with CHD was 9.67 kg (range 4.89 to 15.0 kg). For CLD, 24/316 (7.6%) children had a weight < 7 kg on Day 1. For CHD, 18/352 (5.1%) of children had a weight that was < 7 kg on Day 1.

In the Phase 2b study of MEDI8897, there were a number of infants with lower weights who would have received a higher exposure. Two hundred eighty two (19.5%) infants had a weight ≤

2.5 kg on the day of dosing: 96 in the placebo group and 186 in the MEDI8897 group. Of those 186 infants in the MEDI8897 group, 59 infants had weights ranging from 1.6 kg to ≤ 2 kg on the day of dosing. The safety analysis was performed by weight bands with the lowest weight band ≤ 2.5 kg on the day of dosing, and the information provided is for that weight group. Treatment emergent adverse events were reported in 148/186 (79.6%) of infants who received MEDI8897 and 75/96 (78.1%) infants who received placebo.

Treatment emergent serious adverse events occurred in 39 (21%) infants in the MEDI8897 group and 21 (21.9%) infants in the placebo group. Adverse events of special interest (AESI) were reported in 1 infant (petechiae) who received MEDI8897 and no infants who received placebo. The petechiae that was reported as an AESI was 1-day duration and was reported by the site investigator based on parental description. There were no laboratory assessments for the petechiae. There were 5 deaths (2 MEDI8897 and 3 placebo), and neither of the 2 deaths in the MEDI8897 group were in infants ≤ 2.5 kg on the day of dosing. Based on this safety information for the lowest weight infants, there is no evidence of a safety concern.

Table 1 Comparison of IM-equivalent Weight-normalized Dose Levels in Phase 1 Adults, Phase 2b and Proposed Phase2/3 Infant Populations

Study	Route	Population	Bodyweight Range (kg) [min, max]	Nominal Dose	Equivalent IM Dose[a] (mg/kg) [min, max]
D5290C00001	IV	Adults	[60.5, 110]	3000 mg	[35.3, 64.4]
D5290C00003	IM	Infants	[1.6, 11.1]	50 mg	[4.5, 31.3]
D5290C00005	IM	Infants	[4.8[b], 20]	200 mg	[10, 41.7]

[a] Equivalent IM Dose for the administered IV in adults calculated as the quotient of Nominal Dose and Bioavailability (0.77)

[b] Lowest expected bodyweight range in season 2 for CHD/CLD population based on previous motavizumab clinical trial

IM-equivalent body weight-normalized MEDI8897 dose in the Phase 1 study (Study D5290C00001) in adults, who had received the highest dose of 3000 mg IV, ranged from 35.3 to 64.4 mg/kg which was well tolerated with no safety concerns (Table 1). The observed highest weight-normalized IM dose in the Phase 2b trial was 31.3, which was well tolerated with no safety concerns. Additionally, the highest expected weight-normalized IM dose in the Phase 2/3 trial is 41.7, which is well below the maximum doses in adults. The doses studied in adults provide supportive evidence for the proposed dosing strategy in infants because 1) MEDI8897 does not bind to any internal targets, 2) to date, there is no clinical or preclinical evidence of dose-dependent adverse events or toxicity.

The safety exposure coverage and available safety data from clinical studies support the proposed dosing strategy with consideration of the anticipated weights for children with CHD and CLD. In addition, we plan to implement increased monitoring for the smaller children. We will flag children with weights < 7 kg and have the blinded medical monitor review adverse

events frequently for those children. If there are SAEs or grade 3 or 4 AEs in the first month after dosing, then those would be sent to the IDMC immediately for review.

Meeting Discussion

MedImmune asked to confirm whether FDA's concern regarding the 200 mg dose for the second season was safety, e.g, because the lowest weight infants have higher drug exposures. FDA responded that since there will be a wide range of possible body weights (5.6 -14.4 kg) for children 12-24 months of age enrolled in the second year of the Phase 2/3 trial, the FDA has concerns with safety in the smaller infants and with efficacy in larger infants. FDA stated that safety and efficacy in infants who receive the 200 mg dose should both be analyzed by weight bands, and MedImmune agreed to do so.

MedImmune asked to confirm that FDA agrees with the proposed 200 mg dose, for the second season in the CHD/CLD population with provision for increased monitoring for the smaller children (weight < 7 kg). FDA responded that the proposed dosing plan with increased monitoring, as proposed, was acceptable.

2.2. Phase 2/3 Palivizumab Comparison Study Design

Question 3

(a) Does the Agency agree that the design of the Phase 2/3 study with the extrapolation plan is adequate to support an indication for use of MEDI8897 in pediatric populations currently recommended to receive Synagis® (palivizumab)?

(b) MedImmune intends to include the Phase 2/3 study information, specifically information on the exposure-response relationship in the Pharmacodynamic Section 12.2 of the label supported by study PK results in the Pharmacokinetics Section 12.3 and observed efficacy in Section 14 Clinical Studies section, respectively. Does the Agency agree with this approach?

FDA Response to Question 3

(a) We agree with the use of the incidence of RSV medically attended lower respiratory tract infection (MALRTI) as the primary endpoint in the phase 2/ 3 trial in high risk infants. However, the proposed definition of MALRTI has not been previously studied in this population, and it is not clear whether the proposed definition of MALRTI will adequately capture cases of RSV lower respiratory tract disease in this population.

Additionally, while you hypothesize that an $AUC_{0-\infty} > 13.4$ day*mg/mL correlates with efficacy, the relationship between MEDI8897 serum concentration and efficacy was based on a post-hoc subgroup analysis from the phase 2 trial, and additional PK and efficacy data from phase 3 would be helpful to confirm this relationship. Therefore, we recommend that you conduct the phase 3 trial in healthy infants prior to this phase 2/ 3 trial in high risk infants.

We would suggest that the phase 2/3 trial data are not necessary for submission of your initial BLA. Rather, submission of the phase 2b and phase 3 trial data in healthy infants may be sufficient to support a BLA for prophylaxis in healthy infants > 29 weeks gestational age.

In general, extrapolation of efficacy from the phase 3 trial in healthy subjects to subjects with chronic lung or chronic heart disease may be acceptable (assuming the MEDI8897 exposures in CLD or CHD subjects correspond to exposures associated with efficacy in healthy subjects in the phase 3 trial), and in general we agree with your plan to evaluate PK and safety as primary endpoints, with efficacy in this population evaluated as a secondary endpoint.

(b) Although we can't provide definite agreement at this time, your proposed approach to labeling the phase 2/3 exposure-response, pharmacokinetic and efficacy data generally seems reasonable; however, specifics regarding inclusion and location this information in the package insert will be a review issue.

Meeting Discussion

MedImmune changed their timeline to conduct the phase 3 and phase 2/3 trials during the same season because of the positive efficacy results from the Phase 2b trial and after discussions with other regulatory agencies.

FDA expressed concerns regarding conducting the trials in parallel. Since the phase 3 trial will have new, unstudied elements (including term infants and a new unstudied dosing regimen for MEDI8897), and the phase 2/3 trial will also use the new, unstudied dosing regimen as well as a new definition of MALRTI, there are some risks involved in conducting each of the trials. FDA suggested several options to decrease MedImmune's risks of having useful results of these trials as follows:

- To conduct an interim analysis of PK/PD and safety of MEDI8897 for the phase 3 trial and then conduct the phase 2/3 trial
- To conduct interim analyses in both the phase 3 and phase 2/3 trials to confirm PK/PD of MEDI8897 and that the definitions of MALRTI are appropriate for the study populations
- To have lead-in period for either or both trials, using adaptive design principles

MedImmune asked whether FDA was more concerned with the proposed dosing or with the MALRTI definition in the CLD or CHD population in the phase 2/3 trial. MedImmune stated that phase 2/3 study will include the palivizumab-eligible population, i.e., pre-term infants (<35 weeks) who were included in the phase 2b study in which efficacy was demonstrated. MedImmune expressed their confidence on the dose (200 mg) which was selected based on the PK/PD data from the 50 mg for infants < 5 kg in the completed phase 2b trial. FDA responded that we were concerned with the new dose in both populations and with the new definition for MALRTI in the CLD/CHD population. FDA reiterated that neither the new dose nor the new MALRTI definition had been studied in phase 2, FDA stated that without an additional Phase 2 trial to test these, an interim analysis might prevent the risk associated with the use of the weight-based dose, the proposed second year dose, and the new MALRTI definition.

MedImmune stated that they were not planning to conduct an interim analysis in the Phase 3 trial, because of concerns regarding maintaining study integrity and because of sample size considerations. MedImmune stated that they understood FDA's concerns and would like to confirm whether FDA would be in agreement if MedImmune decided to start the phase 2/3 trial in parallel with the phase 3 trial. FDA reiterated that we would prefer an interim analysis to confirm that the appropriate dose and definitions have been selected.

MedImmune stated that the definition of MALRTI was based on advice from expert pulmonologists and key external experts which was captured in Medimmune's white paper. FDA reiterated that a trial for registrational purposes that uses untested factors always has a risk involved and the acceptability of the trial results will be a review issue for FDA. Ultimately the company must decide whether to accept that risk. MedImmune stated that they noted FDA's concerns.

2.3. Clinical Safety

Question 4

Does the Agency agree that the planned safety assessments including the size of the planned safety database are adequate to fully characterize the safety profile of MEDI8897 in support of marketing authorization for the proposed indication?

FDA Response to Question 4

We agree with your safety monitoring plans in the draft protocols submitted with the meeting package. Comments regarding your proposed safety monitoring may be communicated to you after review of the final protocols for both studies.

Please clarify how many term and preterm infants in the proposed safety database will have received MEDI8897 at the targeted serum concentration.

Please also note that in the teleconference of April 7, 2016 to discuss the phase 2 and phase 3 clinical development of MEDI8897, you agreed to include approximately 1,000 infants from the phase 2b trial, approximately 2,000 from the phase 3 trial in healthy infants, and approximately 666 infants from the high risk, phase 2/ 3 trial in the safety database. (See response to Question 5 on page 35 of the meeting minutes). We recommend increasing the safety database in healthy subjects to 3000, as previously agreed. If you conduct the phase 3 trial in healthy infants prior to the phase 2/ 3 trial in high-risk infants and if the safety database from the phase 2b trial and phase 3 trial includes approximately 3,000 infants, a BLA based on the safety and efficacy of these two pivotal trials could be discussed with the FDA, as noted in response to Question 3. The results of the proposed phase 2/ 3 trial could be submitted in a supplemental BLA. This would allow for assessment of the dose response data from the phase 3 trial prior to the initial of the phase 2 /3 trial in high risk infants. Because high risk infants may have more complicated disease courses or recoveries and may have more illness during safety follow-up, this would also minimize the risks associated with inclusion of safety data from high risk infants in the pivotal safety database.

If any safety signals(s) should arise during the clinical development of MEDI8897, the size of the safety database needed may change.

Meeting Discussion

MedImmune noted that FDA suggested increasing the safety database to 3000 healthy infants exposed to MEDI8897. MedImmune stated that there will be approximately 3000 subjects overall who will receive MEDI8897 at proposed dose/exposure, including 572 healthy subjects weighing < 5 kg from the phase 2b trial, 1400 healthy subjects from the phase 3 trial, and 1000 palivizumab-eligible subjects from the phase 2/3 trial. Medimmune asked whether FDA expected the 3000-subject number to be a sum of subjects from only the phase 2b and phase 3 trials.

FDA noted that the safety database issue had been discussed at the End of Phase 1 (EOP1) meeting. FDA first stated that the safety database should include subjects who received the same dose/exposure of the drug as that recommended in proposed labeling. Because MEDI8897, if approved, may be indicated for use in normal healthy term infants, which could result in potential widespread use, a large safety database in healthy infants would be necessary, as agreed at the EOP1 meeting. FDA recommended against inclusion of premature subjects and subjects with CLD and CHD from the phase 2/3 trial in the total safety database size of 3000. Subjects in the phase 2/3 trial will probably experience more adverse events (AEs) and serious adverse events (SAEs). These AEs and SAEs may not reflect the safety profile for MEDI8897 in normal, healthy term infants, but may be included in labeling, which could affect prescribing practices. The FDA recommended a safety database of 3000 heathy, term infants to best characterize the safety of the product in this population.

MedImmune stated that one of the reasons that they reassessed the sample size was the FDA RSV draft guidance which stated that a 'minimum 1500' subjects could be included in the safety database. FDA clarified that the recommendation for a safety database of '1500' subjects was intended to define the size of the safety database needed for preterm infants, e.g. palivizumab-eligible infants and not healthy, term infants and stated that this would be revisited and clarified in the final version of the guidance.

MedImmune thanked FDA for the clarification and background information on the RSV draft guidance. MedImmune added that their change in safety database size was also based on the lack of a safety signal in the phase 2b trial in healthy, late preterm infants. They stated that increasing the safety database to 3000 healthy subjects would likely delay BLA filing, but they would consider FDA's recommendations. Finally, MedImmune stated that the safety results from the phase 2/3 trial in palivizumab-eligible subjects would provide an advantage in interpreting the safety data for MEDI8897 in this population, as palivizumab will be used as the comparator.

FDA reiterated the recommendation to increase the safety database in healthy subjects to 3000; however, if there are no safety issues, the proposed database size might be sufficient. In the end, this will be a review issue, depending on whether a safety signal is identified.

2.4. Immunogenicity Assessments

Question 5

Does the Agency agree that the proposed immunogenicity testing strategy, methods and analyses described in the Company's position are adequate for assessing ADA responses to MEDI8897?

FDA Response to Question 5

The proposed multi-tiered immunogenicity testing strategy (Figure 8) and approach for collecting serum samples appears reasonable to support the assessment of anti-drug antibody (ADA) response to MEDI8897 in the proposed phase 3 and phase 2/3 studies. The suitability of the analytical methods (i.e., ADA bridging assays, anti-YTE ADA assay, and neutralizing antibody assay) that will be used to assess ADA response to MEDI8897 during the proposed phase 3 and phase 2/3 studies will be determined upon review of the final method validation reports and data generated from the clinical samples.

MedImmune Response

MedImmune thanks DAVP for their feedback on this question. Following submission of the briefing document, we received feedback from the EMA and as a result have revised our immunogenicity assessments to include a Day 0 (predose) timepoint and to remove the Day 8 sample. To limit the total number of blood draws in the infants to 4 and collect early timepoints for PK analysis we now plan to collect a day 15 (PK only) or day 31 (PK and ADA) for the second blood draw for the EU and US-international subjects, respectively. For the US and non-EU countries, the revised serum collection timepoints for ADA testing now include a Day 0, Day 31, Day 151, and Day 361. For the EU, the revised serum collection timepoints now include a Day 0, Day 15, Day 151, and Day 361.

Meeting Discussion

MedImmune asked FDA to confirm that the proposed immunogenicity assessment plan for phase 2/3 and phase 3 trials is agreeable. FDA agreed with the plan. MedImmune confirmed that the revised serum collection strategy will be applied to both trials and that the pre-dose serum samples will be used to determine post-baseline ADA response.

2.5. Other Meeting Discussion

MedImmune inquired when the new version of the FDA guidance on RSV product development would be available. FDA stated that they are currently working on revisions based on the public comments obtained thus far and do have a specific date yet for issuance of the final guidance document.

MedImmune stated that the resistance monitoring and analysis plan is being developed and will be submitted to the IND for review. The FDA stated that they would provide written feedback on the plan. If a meeting is needed, MedImmune can submit a meeting request.

MedImmune asked if FDA had additional questions on their written response. FDA noted that EMA requested inclusion of populations with Down Syndrome and Cystic Fibrosis. Although FDA thinks that inclusion of these subjects might affect efficacy and safety results of the phase 3 trial, the FDA agreed to the inclusion of those subjects since the number of infants with those conditions would be small. FDA will look forward to receiving the final study protocol.

2.6. Post-Meeting FDA Comments

Please submit the "white paper", which was referenced in the meeting discussion, to this IND.

3.0 DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data

standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site. When submitting sample data sets, clearly identify them as such with SAMPLE STANDARDIZED DATASETS on the cover letter of your submission.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

4.0 DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

5.0 LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf.

6.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

7.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Submit Final Protocols for the Phase 3 and Phase 2/3 trials	Sponsor	When available
Submit the virology analysis plan	Sponsor	When available

8.0 ATTACHMENTS AND HANDOUTS

None

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SAEBYEOL JANG
03/19/2019 03:38:06 PM