

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761107Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 111015

MEETING MINUTES

Novimmune S.A.
c/o Advyzom LLC
Attention: Liz Lucini, PharmD
U.S. Agent, Senior Director
335 Snyder Avenue
Berkeley Heights, NJ 07922

Dear Dr. Lucini:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for NI-0501 (emapalumab).

We also refer to the meeting between representatives of your firm and the FDA on January 3, 2018. The purpose of the meeting was to gain Agency agreement that the results of the NI-0501-04 and NI-0501-05 studies are adequate to support a Biologic License Application (BLA) submission.

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 Natasha Kormanik, Regulatory Project Manager, at (240) 402-4227.

Sincerely,

{See appended electronic signature page}

Tanya Wroblewski, MD
Acting Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology 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: B
Meeting Category: Pre-BLA

Meeting Date and Time: January 3, 2018 from 1:00-2:00 PM (ET)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1315
Silver Spring, Maryland 20903

Application Number: IND 111015
Product Name: NI-0501 (emapalumab)
Indication: Primary hemophagocytic lymphohistiocytosis
Sponsor/Applicant Name: Novimmune S.A.

Meeting Chair: Tanya Wroblewski, MD
Meeting Recorder: Natasha Kormanik, MSN, RN, OCN

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)/ Division of Hematology Products

Albert Deisseroth, MD, PhD – Acting Supervisory Associate Director
Tanya Wroblewski, MD – Acting Clinical Team Leader
Angelo De Claro, MD- Clinical Team Leader
Margaret Merino, MD – Clinical Reviewer
Diane Leaman – Safety Regulatory Project Manager
Natasha Kormanik, MSN, RN, OCN® – Regulatory Health Project Manager

OHOP/ Division of Hematology, Oncology, Toxicology

Matthew Thompson, PhD – Reviewer

Office of Clinical Pharmacology/ Division of Clinical Pharmacology V

Liang Li, PhD – Reviewer

Office of Biostatistics/ Division of Biometrics V

Lei Nie, PhD –Team Leader

Office of Biotechnology Products/ Division of Biotechnology Research and Review I

Jennifer Swisher, PhD – Team Leader
Riley Myers, PhD – Reviewer

Office of Process and Facilities/ Division of Microbiology Assessment
Maria Candau-Chacon, PhD – Reviewer

Office of the Commissioner/Office of International Affairs
Mary Jo Salerno, MPH, CPH – International Policy Analyst
Tania Teixeira – European Medicines Agency Liaison to FDA

SPONSOR ATTENDEES

Novimmune S.A.

Maria Ballabio, MD – Head of emapalumab Clinical Development
Cristina de Min, MD – Chief Medical Officer
Walter Ferlin, PhD – Head of Exploratory Science and Translational Medicine
Ed Holdener, MD – Chairman of the Board and Chief Executive Officer
Marie Kosco-Vilbois, PhD – Chief Scientific Officer
Geneviève Lapeyre, MD – Safety Officer
Keith Wilson, PhD – Head of Bioprocess R&D
Monica Malerba, PhD – Bioprocess R&D Project Manager

Advyzom

Cynthia Dinella, PharmD – Regulatory Consultant
Elizabeth Lucini, PharmD – Regulatory Consultant

(b) (4)
(b) (4) – Statistical Consultant
(b) (4) – Statistical Consultant

Other Consultants

(b) (4) – Clinical Pharmacology Consultant
(b) (4)

1.0 BACKGROUND

Novimmune S.A. states that NI-0501 is a fully human high affinity anti-interferon gamma (IFN γ) monoclonal antibody (mAb) that binds to and neutralizes human IFN γ . NI-0501 binds to soluble and receptor (IFN γ R1)-bound forms of IFN γ . After binding to its receptor, IFN γ acts to produce a variety of physiological and cellular responses.

NI-0501 is being developed for the treatment of hemophagocytic lymphohistiocytosis (HLH) in pediatric patients, primary hemophagocytic lymphohistiocytosis (pHLH) with refractory disease or with recurrent or progressive disease during conventional HLH therapy or who are intolerant to conventional to HLH therapy.

On March 11, 2016, the Agency granted Breakthrough Designation for NI-0501 for the treatment of patients with primary HLH with refractory disease or with recurrent or progressive disease during conventional HLH therapy.

On October 19, 2017, the Sponsor requested a type B meeting to gain Agency agreement that the results of the NI-0501-04 and NI-0501-05 studies are adequate to support a Biologics License Application (BLA) submission.

FDA sent Preliminary Comments to Advizom on December 22, 2017.

2.0 DISCUSSION

Question 1: *Safety and Efficacy*

- a) *Does the Agency agree that the efficacy of emapalumab as demonstrated by the primary and secondary endpoints in NI-0501-04 and NI-0501-05, coupled with its safety profile as currently known, support a BLA filing of emapalumab for the treatment of patients with primary HLH?*
- b) *Does the Agency have any specific comments on the safety and efficacy results from the NI-0501-04 and NI-0501-05 studies?*
- c) *Does the Agency have any comments on the immunogenicity results to be included in the BLA from the NI-0501-04 and NI-0501-05 studies in addition to the data from NI-0501-03 and CU patients?*

FDA Response to Question 1a:

Based on our current understanding of the topline efficacy and safety data, it appears that you could support an application for patients who have primary hemophagocytic lymphohistiocytosis (HLH) with refractory disease or with recurrent or progressive disease during conventional HLH therapy. We will conduct our own independent analysis of the datasets submitted in the application to confirm the efficacy claims.

Based on your pre-specified primary analyses and current study population, we believe that the study results would only support a 2nd line treatment (primary hemophagocytic lymphohistiocytosis (HLH) with refractory disease or with recurrent or progressive disease during conventional HLH therapy) indication. The final determination for the indication will be made during the review process.

We note that single-arm trials do not adequately characterize time-to-event endpoints such as overall survival.

In the BLA submission, you will need to address all the concerns conveyed in the September 11, 2017, communication. A decision on filing will be based on the completeness of the data provided in the application during the filing review.

At the meeting, discuss the proposed timelines for BLA submission, including the timing of the 90 or 120 safety cutoff date.

In general, we recommend that the data cutoff date is within 6 months of the submission of the application.

Discussion:

The Sponsor's proposal to submit the BLA with the data cutoff of July 20, 2017, is acceptable. The Sponsor agrees to provide updated narratives for the five patients at the time of the BLA submission.

FDA Response to Question 1b:

Efficacy Analysis Comments

In the BLA submission include the following in the submission of the application.

- A. Descriptions for response assessments and duration of response to support the efficacy results (i.e., spleen size assessments, descriptions of physical exams, clinical criteria for response assessments).
- B. Descriptions for any objective assessments of CNS disease and improvements of neurologic findings to include radiographic findings, clinical exams, CSF assessments, and anti-seizure therapies.
- C. The protocol allows for the use of concomitant use of etoposide, T-cell depleting agents or other biological drugs for patients with unsustained or limited HLH improvement once maximum NI-0501 dose is achieved. Provide a description of rationale and dates of initiation of concomitant therapy and clarify if these patients were newly diagnosed or second line. We note use of concomitant medications in this group may confound the overall responses and isolation of drug effect will be uninterpretable. Conduct a sensitivity analysis for efficacy that excludes these patients.
- D. The durability of response will be an important review issue. Provide follow-up data for all patients enrolled in the study, include Day + 100 survival, engraftment rates, incidence of cGVHD and rates of post HSCT relapse for patients that proceed to transplantation.
- E. Include a swimmer plot for long-term follow-up using the proposed data cutoff date (July 20, 2017) in the BLA submission. Delineate the 2nd line from 1st line patients in the plot.
- F. Provide further description for the two patients who received emapalumab and experienced full control of HLH and did not proceed to HSCT to include if these patients had genetically confirmed HLH and any concomitant therapies these patients received.

- G. Clarify whether the primary efficacy endpoint and duration is assessed by investigator or an independent review committee (IRC).
- H. We sent you a written response on September 11, 2017. It is unclear whether you have addressed our specific comments with regard to your statistical analysis plan (SAP). Please see response to question 1a.

Safety analysis comments

We note the most common TEAE (occurring in 50% of patients) is classified as “condition aggravated.” This term is vague. Please include narratives for the patients who experienced this AE. A deeper understanding of this adverse event will be important in order to adequately describe and characterize the safety of emapalumab.

Discussion:

Please refer to Sponsor’s response to question 1b- D & E. The Sponsor provided clarification that they will provide three analyses of duration or response: DOR until EOT 04, DOR until HSCT, cumulative DOR until HSCT. The Agency requested that the Sponsor provide the SAS codes and data sets that generated the swimmers plots. The Sponsor will provide descriptions for the no response intervals for the patients.

Please refer to Sponsor’s responses to question 1b-G. The Sponsor clarified that there was no IRC assessment.

Please refer to Sponsor’s response to question 1b-H. The Agency agrees with the Sponsors proposal to not perform the competing risk analysis as there were only two deaths in the post-transplant period. The Sponsor will provide Day +100 survival, engraftment rates and description of the transplant morbidity at the time of the BLA submission.

FDA Response to Question 1c:

We refer you to the immunogenicity-related comments that were provided on September 11, 2017; we have no additional comment at this time. The acceptability of immunogenicity data is a review issue and will depend on validation of the immunogenicity assays. If the assays have not been appropriately validated, re-validation and re-testing of clinical samples may be needed during the review cycle.

Discussion:

No discussion.

Question 2: *Chemistry, Manufacturing and Controls (CMC)*

- a) *Does the Agency have any further comment on how Novimmune is addressing the CMC feedback from the Type B meetings held in December 2016 and May 2017?*
- b) *Does the Agency have any comment on the planned manufacturing schedule and potential dates for pre-approval inspections?*
- c) *Does the Agency agree with the proposal for additional stability to be submitted during the BLA review period?*

FDA Response to Question 2a:

The suitability of the control strategy to mitigate possible (b) (4) is a review issue and will depend, in part, on characterization (b) (4). In addition to the mitigation measures identified on page 43, we recommend that (b) (4)

You state in Table 19 that “For (b) (4) DP, a shelf life of 36 months will be proposed in the BLA (b) (4)

Your response to the Type B meetings appears appropriate, however the information will be evaluated during the review process

Discussion:

No discussion.

FDA Response to Question 2b:

It appears that the manufacturing schedule does not support a prelicense inspection within the review timeline. If the BLA is submitted in (b) (4), the inspection should occur approximately between (b) (4) for a standard submission and between (b) (4) for a priority submission. The inspection cannot be conducted until the BLA is filed.

Discussion:

For Drug Substance, the proposed inspection

(b) (4)

inspection of (b) (4) **appears acceptable.**

For Drug Product, the proposed

FDA Response to Question 2c:

The acceptability of a stability update in May 2018 will be dependent on its timing within the BLA review cycle.

Discussion:

No discussion.

Question 3: *Regulatory*

- a) *Can FDA provide feedback on the review process and any recommendations to facilitate review of the BLA?*
- b) *Can FDA provide their current thinking on the need for an Advisory Committee during the BLA review?*
- c) *Can FDA provide guidance on the process for requesting a rare pediatric disease voucher and anything additional that needs to be provided in the BLA?*

FDA Response to Question 3a:

1. During the review process, we will assess the criteria that prompted dose increases and the actual dosing of NI-0501 in the clinical trial to clearly define the most appropriate dosage recommendation for the prescribing information. We would like to emphasize the following comment regarding the proposed dose regimen for emapalumab conveyed to you on September 20, 2017:

To facilitate the review of emapalumab, we recommend that you provide a table comparing the clinical and laboratory criteria used to guide dose increases for Versions 1 to 4 vs Version 5 (Table 3 in EOP2A meeting package) for all patients. Include revised Tables 4 and 5 from the EOP2A meeting package in which comparisons of the dose regimens applied in Trial NI-0501-04 and of the retrospective review of the dose regimen administered under previous versions of the protocol were summarized. Provide the subject identification number for patients whose dose would be increased more or earlier (Table 5 from EOP2A meeting package) based on the implementation of Version 5 vs. Versions 1 to 4. We also recommend that you provide a patient-by-patient dose regimen, as provided in the EOP2A meeting package, to facilitate the understanding of the impact of the revised dose regimen (Version 5) on the dose regimen of the patients treated under earlier versions of the protocol (Versions 1 to 4).

2. Given the complexity of this disease and competing risks, assessment of individual narratives will be an important part of this review. Include narratives for all patients (n=34). Provide descriptions for both duration of response for patients on study NI-0501-04 and duration of response for patients on study who continue to long term follow-up (NI-0501-05).
3. Please confirm that the proposed BLA will contain a mock-up define file to show the variables which will be included in the derived datasets for the primary and key secondary efficacy analyses including, but not limited to, variables used for sensitivity and/or subgroup analyses, including reasons of missing and censoring data. In addition, please include in your submission (a) SAS programs that produced all efficacy results, (b) all raw as well as derived variables in .xpt format, (c) SAS programs by which the derived variables were produced from the raw variables, and (d) results of any interim analysis if ever performed.
4. The summary tables in the SCE and CSR should include columns for the all treated population (m=34) and the second line all treated populations(n=27) (i.e., concomitant medications, disposition table, confirmed genetic mutation).
5. For combined data sets include flags in the data sets for those patients who were treated as second line and those that received emapalumab as first line therapy.
6. To facilitate the selection of the clinical sites for inspection, you may submit a dataset (1 site per row) with the following information from clinical trial NI-050104 prior to the submission of the Application. Submit this information as a SAS transport file, and include a define.pdf file.
 - Site number
 - Principal investigator
 - Location: Address, City, State, Country
 - Contact Information: Name, Phone, Fax, Email
 - Number of subjects screened
 - Number of subjects enrolled
 - Number of subjects who received NI-0501
 - Number of subjects who achieved complete response (CR) or partial response (PR), partial HLH response per investigator
 - Number of major protocol violations
 - Number of deaths
 - Number of subjects who experienced serious adverse events (SAEs)
7. In addition, see response to question 2.

Discussion:

No discussion.

FDA Response to Question 3b: A decision regarding the need for an Advisory Committee will be determined during the review of the BLA.

Discussion:

No discussion.

FDA Response to Question 3c: Please refer to the “*Rare Pediatric Disease Priority Review Vouchers, Guidance for Industry*” found at:

<https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM423325.pdf>

Discussion:

No discussion.

Additional Comments

In reference to the November 29, 2017, submission providing a proposed plan to determine the potential effects of emapalumab on metabolic cytochrome P450, we have the following comments:

- We realize that TP-DI cocktail studies conducted in pediatric or adult patients with HLH may not be feasible due to the severity of the disease and the high number of required co-medications and procedures in this patient population. We also agree that the extent of the DDI might not be similar if conducted in non-HLH populations given that inflammatory cytokine levels are expected to be much higher in HLH population vs. non-HLH populations.
- We recommend that you collect PK data of commonly used concurrent medications, that are the substrates of CYP enzymes, and monitor the effectiveness of these drugs before, during and after treatment of emapalumab in all your proposed trials in order to have sufficient information that is useful to guide the dose adjustments for the substrates of CYP enzymes in your proposed label, if necessary. The adequacy of your assessments of potential effects of emapalumab on metabolic CYP enzymes will be a review issue after your BLA submitted.

Discussion:

No discussion.

3.0 OTHER IMPORTANT INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. The Sponsor plans to submit a complete application in late March 2018.

- 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, other risk management actions and, where applicable, the development of a Formal Communication Plan and it was concluded that a REMS is not expected at this time.
- 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.

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.

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](#) 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.

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>.

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).

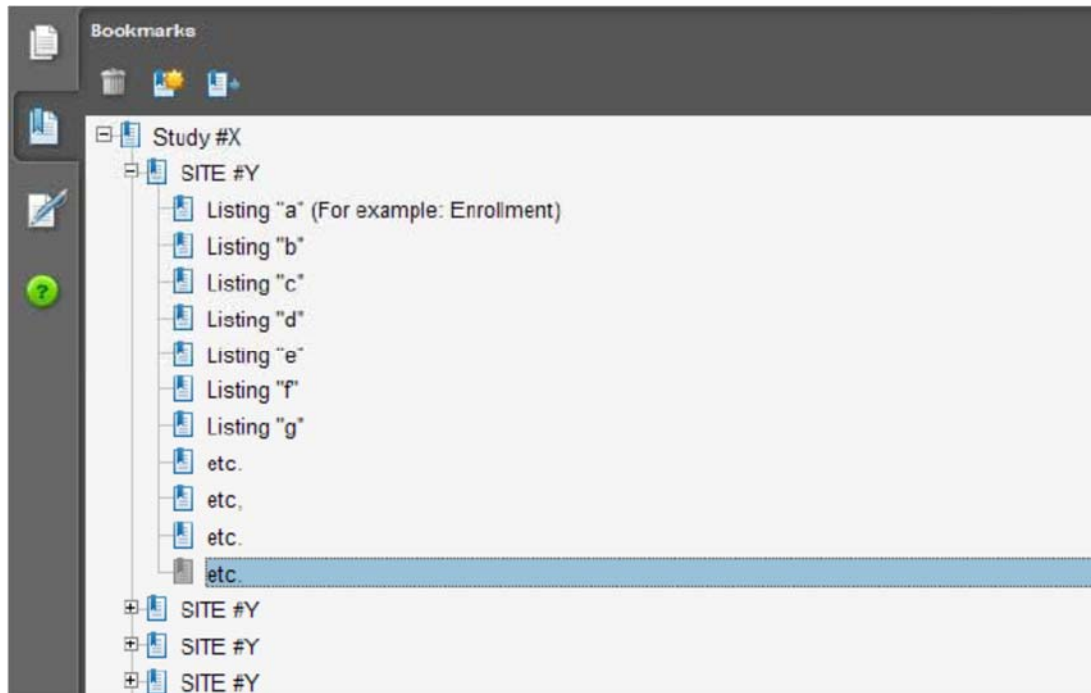
I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

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 Item¹	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

No issues were identified.

5.0 ACTION ITEMS

No action items were identified.

6.0 ATTACHMENTS AND HANDOUTS

- Sponsor's PowerPoint presentation.
- Sponsor's responses to the preliminary comments.
- Sponsor's revised SAP.

175 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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

/s/

TANYA M WROBLEWSKI
01/04/2018



IND 111015

MEETING MINUTES

Novimmune S.A.
c/o Advyzom LLC
Attention: Angela Windt, PharmD
U.S. Agent, Senior Director
335 Snyder Avenue
Berkeley Heights, NJ 07922

Dear Dr. Windt:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for NI-0501.

We also refer to the meeting between representatives of your firm and the FDA on December 19, 2016. The purpose of the meeting was to discuss PK/PD analyses generated in support of the proposed dosing schema for NI-0501; review and confirm FDA's understanding and agreement with the data parameters utilized in support of dosing decisions for NI-0501 in study NI-0501-04; and discuss the proposed approach to labeling for dosage and administration of NI-0501.

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, please call Kimberly Scott, Regulatory Project Manager at (240) 402-4560.

Sincerely,

{See appended electronic signature page}

R. Angelo de Claro, MD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology 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: B
Meeting Category: End of Phase 2

Meeting Date and Time: December 19, 2016 from 1:00-2:00 PM (ET)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1315
Silver Spring, Maryland 20903

Application Number: IND 111015
Product Name: NI-0501
Indication: Primary hemophagocytic lymphohistocytosis (pHLH) with refractory disease or with recurrent or progressive disease during conventional HLH therapy or who are intolerant to conventional to HLH therapy
Sponsor Name: Novimmune S.A.

Meeting Chair: R. Angelo de Claro, MD
Meeting Recorder: Kris Kolibab, PhD

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)/ Division of Hematology Products

Ann T. Farrell, MD – Division Director

Albert Deisseroth, MD, PhD – Acting Supervisory Associate Director

R. Angelo de Claro, MD – Clinical Team Leader

Tanya Wroblewski, MD – Clinical Reviewer

Lori Ehrlich, MD, PhD – Clinical Reviewer

Margaret Merino, MD – Clinical Reviewer

Nicholas Richardson, DO – Clinical Reviewer

Natasha Kormanik, MSN, RN, OCN® – Regulatory Health Project Manager

Kris Kolibab, PhD – Senior Regulatory Health Project Manager

Office of Clinical Pharmacology/ Division of Clinical Pharmacology V

Nitin Mehrotra, M Pharm, PhD – Pharmacometrics Team Leader

Jee Eun Lee, PhD – Pharmacometrics Reviewer

Yuhong Chen, MD, PhD – Reviewer

Office of Biostatistics

Yuan-Li Shen, DrPH – Statistics Team Leader

Lola Luo, PhD –Reviewer

SPONSOR ATTENDEES

Cristina de Min, MD, Chief Medical Officer
Maria Ballabio, MD, Clinical Science Leader
Geneviève Lapeyre, MD, Safety Officer
Walter Ferlin, PhD, Head of Exploratory Science and Translational Medicine
(b) (4) Pharmacometrics Consultant, MnS

(b) (4) Statistical Consultant
Cynthia Dinella, PharmD, Regulatory Consultant, Advyzom
Angela Windt, PharmD, Regulatory Consultant, Advyzom
Ed Holdener, MD, Chairman of the Board and Chief Executive Officer

1.0 BACKGROUND

Novimmune S.A. states that NI-0501 is a fully human high affinity anti-interferon gamma (IFN γ) monoclonal antibody (mAb) that binds to and neutralizes human IFN γ . NI-0501 binds to soluble and receptor (IFN γ R1)-bound forms of IFN γ . After binding to its receptor, IFN γ acts to produce a variety of physiological and cellular responses.

NI-0501 is being developed for the treatment of hemophagocytic lymphohistiocytosis (HLH) in pediatric patients, primary hemophagocytic lymphohistiocytosis (pHLH) with refractory disease or with recurrent or progressive disease during conventional HLH therapy or who are intolerant to conventional to HLH therapy.

On March 11, 2016, the Agency granted Breakthrough Designation for the treatment of patients with primary HLH with refractory disease or with recurrent or progressive disease during conventional HLH therapy.

On October 13, 2016, Novimmune S.A. requested an end-of-phase 2 meeting to discuss PK/PD analyses generated in support of proposed dosing schema for NI-0501; review and confirm FDA's understanding and agreement with the data parameters utilized in support of dosing decisions for NI-0501 in study NI-0501-04; and discuss the proposed approach to labeling for dosage and administration of NI-0501.

FDA sent Preliminary Comments to Novimmune S.A. on December 13, 2016.

2. DISCUSSION

Question 1:

Does the Agency have any comments regarding the PK and PD analyses performed in HLH patients treated with NI-0501? In particular, does the Agency agree that the outcome of the analyses supports the rationale for NI- 0501 dose adjustments?

FDA Response to Question 1:

The ability of the PK/PD modeling to support the dosing regimen and dose adjustment scheme will be a review issue once you submit the BLA. However, we have the following suggestions regarding the PK/PD analyses that you may intend to use to support the NI-0501 dosing regimen and dose adjustment scheme.

- *Justify the target concentration of NI-0501 and the target level of PD markers from an efficacy endpoint of clinical response (e.g., MAS remission), utilizing the data from Study 04 and Study 05.*

... and the target level of PD markers from an efficacy endpoint of clinical response (e.g., MAS remission), utilizing the data from Study 04 and Study 05.

Discussion:

In principle, FDA agreed that the sponsor proposal is reasonable. Whether or not the target NI-0501 range is appropriate will be a review issue.

- *Perform additional modeling and simulation with a revised popPK model (including TMDD) to compare predicted and the observed concentrations of NI-0501 in patients to justify your dose adjustment scheme with the predicted C_{end}/C₄₈ hours postinfusion.*

Discussion:

FDA cannot comment on the adequacy on the approach at this time. Sponsor should justify the modeling and simulation strategy.

- *There were 7 subjects out of 41 who received the maximum dose of 10 mg/kg. Clarify what condition led to exceeding 6 mg/kg cap for dose increase and why you do not propose 10 mg/kg as a cap for your dosing scheme.*

... and why you do not propose 10 mg/kg as a cap for your dosing scheme.

Discussion:

The Agency would be open to consider the 10mg/kg dose level if supported by clinical data.

Question 2:

Does the FDA agree with the company's dosing strategy for NI-0501? In particular, does FDA agree that dose adjustments can be based on the patients' clinical and laboratory data?

FDA Response to Question 2:

Your rationale and proposed dosing strategy based on clinical and laboratory parameters appears acceptable. During the review of the application, the Agency will

assess the criteria that prompted dose increases and the actual dosing of NI-0501 in the clinical trial to clearly define the most appropriate dosage recommendations for the labeling.

We have the following additional comments regarding the clinical and laboratory parameters:

- We recommend that you define fever in your clinical parameters.*
- We also note that one dimensional spleen measurements are non-evaluable.*

Discussion:

The Agency provided their perspective on the use of spleen size information to inform the response assessments and the dosing recommendation, which will be taken within the context of the entire clinical data.

Question 3:

Does the Agency agree with Novimmune’s plans for how to approach Section 2 “Dosage and Administration” for the proposed prescribing information?

FDA Response to Question 3:

No, we recommend that a starting point for your approach to Section 2 (Dosage and Administration) is to incorporate a tabular format similar to Table 3 (page 23) from meeting background documents. Revisions may occur during the review process based upon review of the actual patient data.

We recommend that you submit a pre-BLA meeting request prior to submission of BLA to agree on format and content of the application.

Discussion:

The Sponsor and Agency had a general discussion about application and submission timelines. The Agency would be open to grant a separate meeting to discuss development in other HLH settings.

3.0 OTHER IMPORTANT INFORMATION

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.

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 (cdeler-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 start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or 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 start 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.

Additional information can be found at

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>.

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 <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm>.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. Beginning **May 5, 2017**, the following submission types: **NDA, ANDA, BLA** and **Master Files** must be submitted in eCTD format. **Commercial IND** 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>.

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).

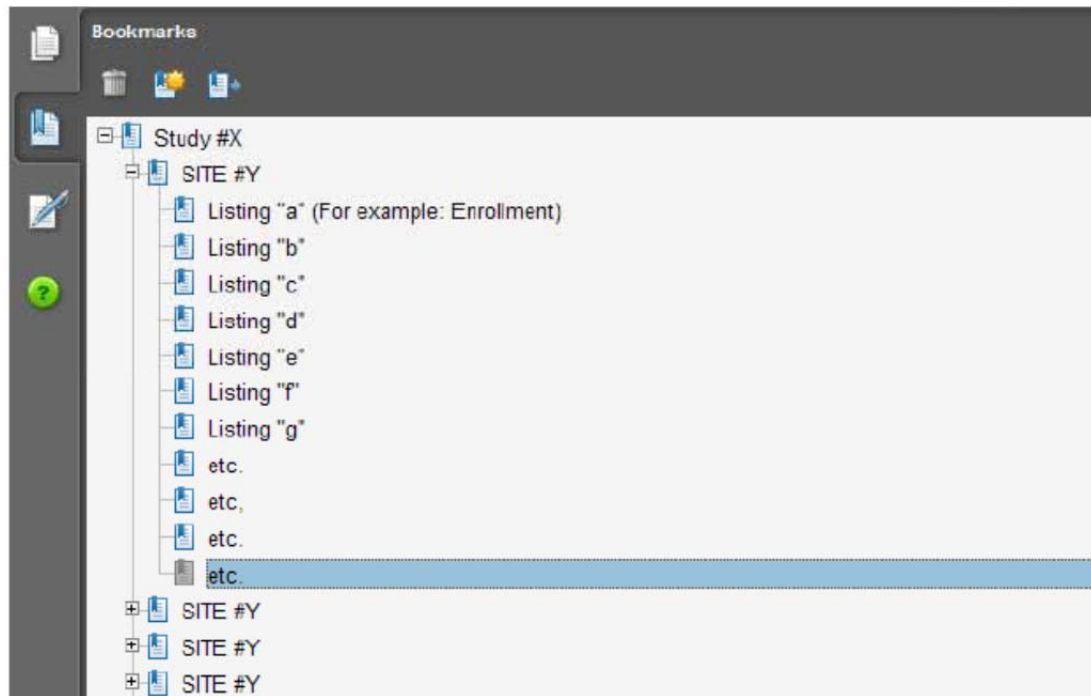
I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

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

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
 - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
 - Other significant changes
 - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

The Sponsor provided the attached response document for the meeting.



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: December 19, 2016 from 1:00-2:00 PM (ET)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1315
Silver Spring, Maryland 20903

Application Number: IND 111015
Product Name: NI-0501
Indication: Primary hemophagocytic lymphohistocytosis (pHLH) with refractory disease or with recurrent or progressive disease during conventional HLH therapy or who are intolerant to conventional to HLH therapy

Sponsor/Applicant Name: Novimmune S.A.

FDA ATTENDEES (tentative)

Office of Hematology and Oncology Products (OHOP)/ Division of Hematology Products

Ann Farrell, MD – Director

Edvardas Kaminskas, MD – Deputy Director

Albert Deisseroth, MD, PhD – Acting Supervisory Associate Director

R. Angelo de Claro, MD – Clinical Team Leader

Tanya Wroblewski, MD – Clinical Reviewer

Lori Ehrlich, MD, PhD – Clinical Reviewer

Emily Jen, MD, PhD – Clinical Reviewer

Aviva Krauss, MD – Clinical Reviewer

Margaret Merino, MD – Clinical Reviewer

Nicholas Richardson, DO – Clinical Reviewer

Kimberly Scott, BSN, RN, OCN® – Regulatory Health Project Manager

Office of Clinical Pharmacology/ Division of Clinical Pharmacology V

Stacy Shord, PharmD – Team Leader

Yuhong Chen, PharmD – Reviewer

Office of Clinical Pharmacology/ Division of Pharmacometrics

Nitin Mehrotra, PhD – Team Leader

Jee Eun Lee, PhD – Reviewer

Office of Biostatistics

Yuan-Li Shen, PhD – Team Leader

Lola Luo, PhD – Reviewer

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for December 19, 2016, 1:00-2:00 PM (ET), White Oak Campus Building 22, between Novimmune S.A. and the Division of Hematology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. 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 and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Novimmune S.A. states that NI-0501 is a fully human high affinity anti-interferon gamma (IFN γ) monoclonal antibody (mAb) that binds to and neutralizes human IFN γ . NI-0501 binds to soluble and receptor (IFN γ R1)-bound forms of IFN γ . After binding to its receptor, IFN γ acts to produce a variety of physiological and cellular responses.

NI-0501 is being developed for the treatment of hemophagocytic lymphohistiocytosis (HLH) in pediatric patients, primary hemophagocytic lymphohistiocytosis (pHLH) with refractory disease or with recurrent or progressive disease during conventional HLH therapy or who are intolerant to conventional HLH therapy.

On March 11, 2016, the Agency granted Breakthrough Designation for the treatment of patients with primary HLH with refractory disease or with recurrent or progressive disease during conventional HLH therapy.

On October 13, 2016, Novimmune S.A. requested an end-of-phase 2 meeting to discuss PK/PD analyses generated in support of proposed dosing schema for NI-0501; review and confirm FDA's understanding and agreement with the data parameters utilized in support of dosing decisions for NI-0501 in study NI-0501-04; and discuss the proposed approach to labeling for dosage and administration of NI-0501.

2.1 DISCUSSION

Question 1:

Does the Agency have any comments regarding the PK and PD analyses performed in HLH patients treated with NI-0501? In particular, does the Agency agree that the outcome of the analyses supports the rationale for NI- 0501 dose adjustments?

FDA Response to Question 1:

The ability of the PK/PD modeling to support the dosing regimen and dose adjustment scheme will be a review issue once you submit the BLA. However, we have the following suggestions regarding the PK/PD analyses that you may intend to use to support the NI-0501 dosing regimen and dose adjustment scheme.

- *Justify the target concentration of NI-0501 . . .*

Novimmune Response: We acknowledge FDA's request and will justify for PK-PD analyses the target concentration of NI-0501 utilizing CXCL9.

Rationale:

Target concentrations of NI-0501 will depend on IFN γ production levels which vary inter and intra HLH patients. Therefore, NI-0501 target concentrations cannot be identified without taking into consideration IFN γ production. We have identified and demonstrated the biomarker CXCL9 reflects both production and neutralization of IFN γ in HLH patients. Therefore, NI-0501 target concentrations will be defined by simulations using the PK and PK-PD models for different levels of IFN γ production using CXCL9 as a biomarker of the latter.

Does FDA agree?

. . . and the target level of PD markers from an efficacy endpoint of clinical response (e.g., MAS remission), utilizing the data from Study 04 and Study 05.

Novimmune Response: Analyses are planned to explore the relationship between PD markers (e.g. CXCL9) and clinical response, details of which will be provided for FDA comment in a SAP.

- *Perform additional modeling and simulation with a revised popPK model (including TMDD) to compare predicted and the observed concentrations of NI-0501 in patients to justify your dose adjustment scheme with the predicted Cend/C48 hours post-infusion.*

Novimmune Response: As per your request, we can perform additional modeling and simulation with a revised popPK, including TMDD. (b) (4)

Does FDA agree?

- *There were 7 subjects out of 41 who received the maximum dose of 10 mg/kg. Clarify what condition led to exceeding 6 mg/kg cap for dose increase . . .*

Novimmune Response: The dose of 10 mg/kg was administered in 7 subjects because of clinical conditions, as noted in table 3 of our package, supported by PK. Of these patients, 2 received NI-0501 in compassionate use, and 2 of the 5 patients enrolled in the clinical study were first line patients.

. . . and why you do not propose 10 mg/kg as a cap for your dosing scheme.

Novimmune Response: We are open to this and accordingly, the current study does not have a cap.

Question 2:

Does the FDA agree with the company's dosing strategy for NI-0501? In particular, does FDA agree that dose adjustments can be based on the patients' clinical and laboratory data?

FDA Response to Question 2:

Your rationale and proposed dosing strategy based on clinical and laboratory parameters appears acceptable. During the review of the application, the Agency will assess the criteria that prompted dose increases and the actual dosing of NI-0501 in the clinical trial to clearly define the most appropriate dosage recommendations for the labeling.

We have the following additional comments regarding the clinical and laboratory parameters:

- *We recommend that you define fever in your clinical parameters.*

Novimmune response: The protocol defined fever as oral temperature ≥ 37.5 °C,

(b) (4)

- *We also note that one dimensional spleen measurements are non-evaluable.*

Novimmune response: We would like to discuss this point further with FDA. Please note we have amended the protocol to include 3-dimensional ultrasound as recommended by FDA.

(b) (4)

Question 3:

Does the Agency agree with Novimmune’s plans for how to approach Section 2 “Dosage and Administration” for the proposed prescribing information?

FDA Response to Question 3:

No, we recommend that a starting point for your approach to Section 2 (Dosage and Administration) is to incorporate a tabular format similar to Table 3 (page 23) from meeting background documents. Revisions may occur during the review process based upon review of the actual patient data.

Novimmune response: We agree to incorporate a tabular format similar to Table 3 as a starting point for the approach to Section 2 of labeling.

We recommend that you submit a pre-BLA meeting request prior to submission of BLA to agree on format and content of the application.

Novimmune response: We agree our next step is to submit a pre-BLA format and content meeting request. Does FDA agree this can be a face-to-face meeting?

Does FDA agree we can submit the SAP(s) separately, in advance of a meeting package, to allow additional time for FDA to review prior to the meeting?

3.0 OTHER IMPORTANT INFORMATION

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.

DATA STANDARDS FOR STUDIES

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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>).

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<http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team (cdcr-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 start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or 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.

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For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>.

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 <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm>.

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).

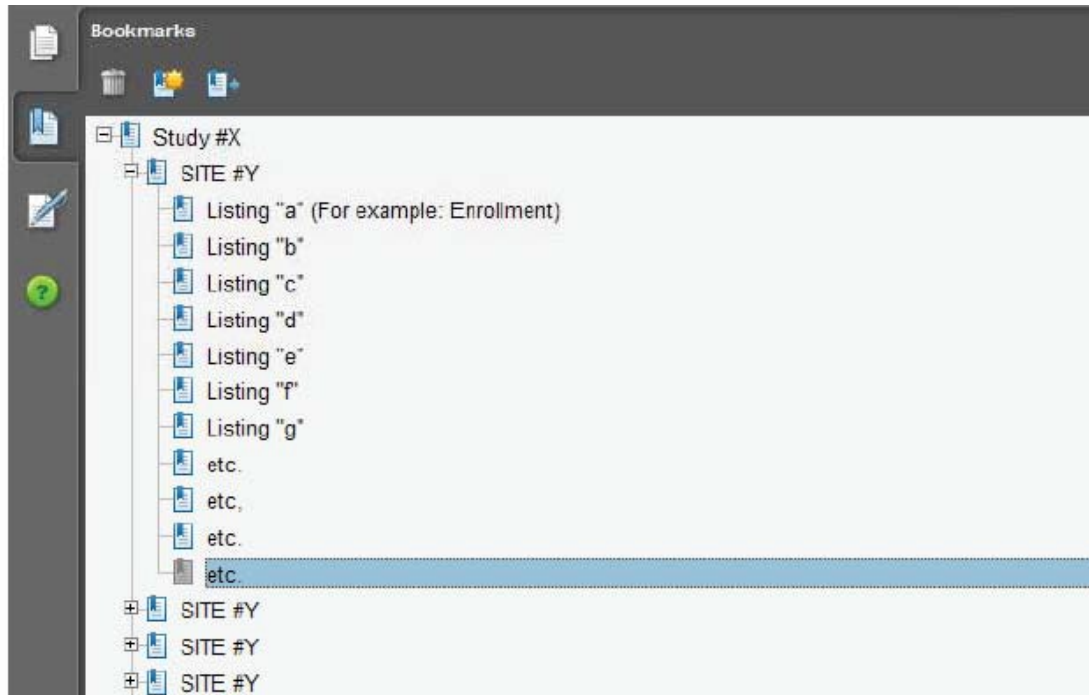
I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

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 Item¹	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

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
 - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
 - Other significant changes
 - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

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

/s/

KIMBERLY L SCOTT
12/13/2016

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/s/

ROMEO A DE CLARO
12/20/2016

CDER Breakthrough Therapy Designation Determination Review

IND/NDA/BLA #	IND 111015
Request Receipt Date	January 14, 2016
Product	NI-0501
Indication	For the treatment of primary hemophagocytic lymphohistiocytosis(HLH) in pediatric patients
Drug Class/Mechanism of Action	Monoclonal antibody that binds to interferon gamma
Sponsor	NovImmune SA
ODE/Division	CDER/OHOP/DHP
Breakthrough Therapy Request Goal Date (within <u>60</u> days of receipt)	March 14, 2016

Note: This document should be uploaded into CDER's electronic document archival system as a clinical review and will serve as the official Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Note: Signatory Authority is the Division Director.

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.*Section I to be completed within 14 days of receipt for all BTDRs*

- Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):** Treatment of patients with primary HLH with refractory disease or with recurrent or progressive disease during conventional HLH therapy.
- Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** ☐ YES ☒ NO

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

3. Consideration of Breakthrough Therapy Criteria:

- Is the condition serious/life-threatening¹? ☒ YES ☐ NO

If 3a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

- Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?
 - ☒ YES the BTDR is adequate and sufficiently complete to permit a substantive review
 - ☐ Undetermined
 - ☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):

¹ For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

- i. Only animal/nonclinical data submitted as evidence ☐
- ii. Insufficient clinical data provided to evaluate the BTDR
(e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
- iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐
- iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐
- v. No or minimal clinically meaningful improvement as compared to available therapy²/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

4. Provide below a brief description of the deficiencies for each box checked above in Section 3b:

If 3b is checked “No”, BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC’s input is desired. If this is the case, proceed with BTDR review and complete Section II). If 3b is checked “Yes” or “Undetermined”, proceed with BTDR review and complete Section II, as MPC review is required.

5. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}

Team Leader Signature: {See appended electronic signature page}

Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

6. A brief description of the drug, the drug’s mechanism of action (if known), the drug’s relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

Brief Description of the Drug

NI-0501 is a fully human anti-interferon gamma monoclonal antibody that binds to and neutralizes human IFN{gamma}. IFN{gamma} is produced predominately by natural killer and natural killer T cells as part of the innate immune response and by CD4⁺ Th1 and CD8⁺ Cytotoxic T Lymphocyte effector T cells once antigen-specific immunity develops. The rationale for the use of NI-0501 in Hemophagocytic Lymphohistiocytosis (HLH) is based on animal models that demonstrates neutralization of the high levels of IFN{gamma} and correction of the biochemical and hematological abnormalities associated with HLH.

² For a definition of available therapy refer to Guidance for Industry: “Expedited Programs for Serious Conditions—Drugs and Biologics” <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

Brief Description of the disease and intended population

Hemophagocytic lymphohistiocytosis(HLH) is a rare and severe disorder characterized by overwhelming hyperactivation of the immune system. A defect in the triggering of apoptosis results in decreased NK cell function and T-cell cytotoxicity leading to an unbridled activation of the immune system. The ensuing hypercytokine storm results in damage to tissues which can lead to systemic infections, multi-organ failure and death. The clinical scenario of HLH consists of hepatomegaly, fever, splenomegaly, neurological symptoms and rash. Common laboratory abnormalities include cytopenias, hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia and lymphohistiocyte infiltrate of the bone marrow and meninges, elevated levels of soluble IL-2 receptor (CD25), elevated IL-6 levels, and decreased NK cell function.

HLH is primarily a pediatric disorder(infancy and early childhood) but it can be diagnosed in all ages including adults. HLH occurs as either a genetic disorder(primary HLH) or as an acquired disorder associated with underlying triggers(autoimmune disease, malignancies, infections). Most commonly an inheritable gene mutation that affects proteins such as perforin or munc 13-4 can be identified in primary HLH. The diagnosis of HLH is based on a molecular diagnosis of HLH or a demonstration of clinical(fever, splenomegaly, cytopenias, hepatitis) and laboratory parameters(increased ferritin, increased serum IL-2 levels, absent or decreased NK function, or demonstration of hemophagocytosis).

If untreated, most patients will die within 2 months due to systemic infections, uncontrolled systemic inflammation, and multi-organ failure. The goal of therapy is to suppress the immune reaction and allow the patient to proceed to hematopoietic stem cell transplantation(HSCT). HLH-94 was the first prospective international treatment study for HLH and the cumulative experience from the HLH-94 protocol led to the development of the HLH-2004 protocol. The HLH-2004 protocol consists of 8 weeks of induction chemotherapy in combination with corticosteroids and immunosuppressive drugs(etoposide 150mg/m², dexamethasone 10mg/m², cyclosporine 3mg by mouth twice daily and intrathecal methotrexate). Induction therapy is followed by continuation therapy(weeks 9 to week 40 or longer) with the same drugs given at longer intervals. Continuation treatment is continued until hematopoietic stem cell transplantation(HSCT) is performed if donor available. If patients have disease reactivation or recurrent disease during continuation, re-intensification therapy with the initial intensity of protocol regimen is given. HSCT is the only potential curative therapy for patients with primary HLH (identified genetic deficiency and in very severe cases with no disease-associated mutations).

The five year survival of patients with primary HLH treated with the HLH-94 protocol is 54% with 29% of patients dying during initial or continuation therapy. Approximately 40% of the initial responses to treatment are complete responses. The five year survival for patients with primary HLH treated with HLH-94 protocol followed by a HSCT was 66% (Trottestam 2011). ATG in combination with corticosteroids, and cyclosporine is sometimes used as initial treatment and has reported initial complete response of 73%(Mahlaoui 2007) however early relapses are common and 25% of patients died before HSCT. Additional immunosuppressive therapy is frequently employed in patients with suboptimal responses including alemtuzumab with only partial responses of 64% and no complete responses(Marsh 2013). There are no approved therapies for the treatment of refractory HLH.

- a. The intended population for NI-0501 is for patients with primary HLH who have refractory disease or with recurrent or progressive disease during conventional HLH therapy. The response criteria used are described below per the modified HLH response criteria.(Henter JI 2007)
 - Complete Response: Normalization of HLH diagnostic clinical and laboratory abnormalities
 - No fever

- No splenomegaly(by ultrasound)
- No cytopenia (ANC > 1.0 x 10⁹/L and platelet count > 100 x 10⁹/L(absence of G-CSF and transfusion support documented)
- No hyperferritinemia (serum level < 1000 ug/L)
- No hypofibrinogenemia (> 1.5 g/dL)
- Serum CD 25 < 1000ug/mL
- No CNS abnormalities
- Partial Response: Normalization of at least 3 HLH diagnostic and laboratory abnormalities
 - For patients with reactivated disease(normalization of at least 2 criteria)
- HLH Improvement Improvement(> 50% change from baseline of at least 3 HLH criteria or improvement of 2 criteria and CNS alterations).
- Lack of Improvement: < 30% change from baseline of no more than 2 criteria and no improvement in other aspects of disease pathology

7. Information related to endpoints used in the available clinical data:

- a. Endpoints considered by the Sponsor as supporting breakthrough therapy designation: The endpoint considered by the Sponsor as supporting breakthrough therapy designation include overall response rate which includes complete response, partial response and HLH improvement as defined by the modified HLH response criteria.(Henter JI 2007)
 - i. Overall response(complete response, partial response, and HLH improvement) defined using the following criteria
 - ii. Percentage of subjects able to decrease their glucocorticoid dose
- b. Endpoint accepted by the Division as a clinically significant endpoint(outcome measure) for patients with the disease:
 - i. Overall Response(complete response and partial response). Exclusion of HLH improvement as this response as magnitude of improvement may be only marginal.
 - ii. Overall Survival rate and survival at 30 days, 100 days, and 180 days after HSCT
- c. Any other biomarkers the division would consider likely to predict a clinical benefit even if not yet a basis for accelerated approval.
 - i. CXCL9 levels and assessment of total IFN{gamma}(free IFN{gamma} plus IFN{gamma} bound to NI-0501). IFN{gamma} neutralization as demonstrated by the decrease in IFN{gamma} inducible chemokines (CXCL9, CXCL10, CXCL11). CXCL9 appears to be produced upon the presence of biologically active IFN{gamma} and may be the most reliable marker of IFN{gamma} neutralization. Preliminary analysis of data from patients in the phase 2 study demonstrate a correlation between baseline CXCL9 concentrations and the production of IFN{gamma}. If the preliminary observations are confirmed, CXCL9 could be a response biomarker(marker for IFN{gamma} neutralization) as well as a new diagnostic criteria for HLH

8. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s)

used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

- HLH-94 treatment protocol: Initial Therapy consists of etoposide(150mg/m²), dexamethasone 10mg/m² + cyclosporine(3mg/kg bid) +/- intrathecal methotrexate for 8 weeks then weekly followed by continuation therapy(same drugs given every 2 weeks). For patients with primary HLH, continuation therapy is continued until HSCT.
 - Five year survival: 54%+/-6%(127/249)
 - 29% of patients died before HSCT(64 within 1 year, 97% who had active disease)
 - 124 patients underwent HSCT and the 5 year survival was 66% +/- 8%
 - Survival with active disease at time of HSCT: 58%
 - Survival with no active disease at time of HSCT: 72%
- No available therapy for refractory HLH(either primary or secondary)

9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation³.

- None

10. Information related to the preliminary clinical evidence:

Overview of clinical development program for NI-051

- a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design⁴, trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

The breakthrough therapy designation request is based primarily on the Phase 2 study with supporting data from the compassionate use protocol and extended treatment protocol.

Table 1 Overview of Clinical Development Plan

Study	Phase	Population	Number of Subjects	Endpoints
NI-0501-04 Study	Phase 2	Pediatric patients with primary HLH as first-line or second-line treatment.	16 subjects enrolled(13 evaluable) 2 excluded due to newly diagnosed and 1 patient without adequate follow-up for evaluation	Overall Response Rate(CR, PR) Survival rate at 30 days and 100 days post-HSCT and overall survival(data not yet submitted on these endpoints)

³ Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

⁴ Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

Study	Phase	Population	Number of Subjects	Endpoints
NI-0501-05 Study	Phase 1 /2 Study	Long-term follow-up study with monitors patients after treatment with NI-0501	11 enrolled(6 received treatment with NI-0501)	Long-term safety
Compassionate Use Protocol	Compassionate Use	Adult and pediatric patients with primary or secondary HLH	6(3 evaluable)	Overall Response Rate

Study NI-0501-04 is the main source of data to support the request. The study is a multicenter, open-label, phase 2 study of NI-0501 as first-line or second-line treatment for pediatric patients(≤18 years of age at the time of HLH diagnosis) with suspected or confirmed primary HLH. First-line patients must not have previously received conventional therapy for HLH. Second line patients include those who have received prior conventional therapy for HLH and either did not respond, did not achieve or did not maintain a satisfactory response or were intolerant to conventional therapy due to toxicities.

The primary efficacy endpoints defined in the protocol are overall response rate(complete response, partial response and HLH improvement defined using the criteria).

NI-0501 is administered on a background of dexamethasone which can be tapered depending upon the patient's condition. The dose schedule is as follows: dose of NI-0501 is 1mg/kg every 3 days.

A total of 16 patients(8 females and 8 males enrolled in Study NI-0501-04). Median age was 1.2 years(range 0.2 years to 13.9 years). Thirteen patients are evaluable for efficacy with a minimum of 30 days of follow-up after last NI-0501 treatment. Two patients were excluded as they received NI=-5-1 as first line therapy and 1 patient excluded due to lack of adequate follow-up. Three pediatric patients from the compassionate use protocol were included in the efficacy analysis with a median age of 1.3 years(range 4 months to 10 years). At study entry, 8 patients had refractory disease and 8 patients had disease progression or recurrence during initial therapy or reintensification therapy for HLH. The following table describes the baseline demographics for Study NI-0501-04 and the compassionate use protocol subjects.

Table 2 Baseline Demographics and Disease Characteristics in Study NI-0501-04 and Compassionate Use Pediatric Cases

	NI-0501-04	Compassionate Use
Number of Patients enrolled	16	3
Median Age	1.2 year	1.3 year
Range	(2.5 mo-13.9 years)	(4 mo-10 years)
Gender	8 female 8 males	1 female 2 male
Presence of documented HLH mutation	13 patients	None(one de novo gain of NLCR4 gene mutation)
NI-0501 as second-line therapy	14	3
NI-0501 as first-line therapy	2	0
Prior HLH treatments	13	3
dexamethasone	2	2
methylprednisone	13	1
etoposide	4	0
ATG	6	2
cyclosporine	5	0
other		

Efficacy results are presented for a total of 16 patients: 13 pediatric patients who received NI-0501 for refractory disease or progression or recurrent disease during conventional therapy for primary HLH in the NI-0501-04 protocol and 3 pediatric patients who received NI-0501 in compassionate use. The following table describes the efficacy results for NI-0501.

Table 3 Efficacy Results for all evaluable patients in Study NI-051-04 and the Compassionate Use Study

	NI-0501-04 N=13* n(%)	Compassionate Use N=3 n(%)	Total N=16 n(%)
CR	6(46%)	2	8(50%)
PR	2(15%)	0	2(12%)
HLH Improvement	2(15%)	1	3(19%)
No Improvement	3(23%)	0	3(19%)
ORR (CR+PR)	8(62%)	2(67%)	10(62%)

*Evaluable population

- **An overall response rate was documented in 10/16 (62%)evaluable patients with 8/16 (50%) complete responses**
 - **Refractory (4/8): ORR 50%**
 - **Recurrence during conventional therapy (6/8): 75%**
- **Follow-up for a minimum of 30 days after last NI-0501 dose**
- **Median duration of treatment was 7 weeks.**
- **In NI-0501-4, 7 of 8 patients(88%) with CR or PR proceeded to HSCT**
 - **At time of HSCT 6 were still in CR or PR**

Safety Data: Overall a total of 21 patients have received NI-051 for treatment duration of up to 32 weeks (range< 2 weeks to 32 weeks). Study NI-0501-05 is the extended treatment study and there have been 5 patients with at least one serious adverse event (SAE) and 1 death reported on Study NI-0501-05.

Table 4. Summary of Serious Adverse Events for Study NI-0501-04, Compassionate use and NI-0501-05

	Total N=21* N (%)
Adverse reactions leading to withdrawal	0
Number of deaths	6(18%)
Patients with at least one SAE	15(45%)
Total number of SAEs	36(88%)

*Includes 6 patients who went onto Study 05 (extended treatment) after completion of study 04.

Two potential risks with NI-0501-04 include infusion related reactions and infections (specifically pathogens favored by IFN{gamma} neutralization).

Infections:

- The presence of an active infection did not prevent treatment initiation of NI-051 treatment. Of the 12 patients who had preexisting active infections at the time of enrollment in NI-0501 treatment, all infections resolved except in one patient with an EBV infection still present at time of patient's death.
- No infections favored by neutralization of IFN{gamma} have been reported in any of the patients who received NI-0501(atypical mycobacteria, *Varicella Zoster*, *Salmonella*).

Infusion Reactions: Fifteen out of 21 patients had uneventful infusions. In 3/16 patients mild non-serious and transient adverse reactions (recurrent sweating, isolated transient fever, and localized erythematous rashes) were reported during the initial infusions. Similar erythematous rashes were reported in study patients in 3 patients treated in the compassionate use protocol.

11. Division's recommendation and rationale (pre-MPC review):

☒ GRANT: Grant Breakthrough Designation for "Treatment of patients with primary HLH with refractory disease or with recurrent or progressive disease during conventional HLH therapy."

Rationale: Primary HLH is a rare and serious condition and substantial clinical evidence demonstrates an overall response rate of 62% and a CR rate of 50%. The demonstration of a 50% CR rate by itself in a highly refractory group of patients represents a meaningful clinical benefit for whom no available salvage therapy exists.

Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.

☐ DENY:

Provide brief summary of rationale for denial:

Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:

12. Division's next steps and sponsor's plan for future development:

- Sponsor's plan: The Sponsor intends to submit the results from the single arm trial(study NI-0501-04) as a new biological licensing application(BLA). A single arm trial in a refractory population is acceptable given the rare nature of the disease. Conducting a randomized control trial in a refractory setting is not feasible. (b) (4)

[REDACTED]

- a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program): The Agency and Sponsor had a type B meeting in December 2015 to discuss the level of data need to support an initial registration. Depending upon the magnitude of benefit, durability of response, peritransplantation safety data a traditional approval may be considered for a refractory primary HLH population. Further advice to the Sponsor will include an appropriate sample size for their single arm trial to support registration taking into consideration efficacy and safety, adequate follow-up for patients, collection of peri-transplantation safety data(graft failures, GVHD) and survival data after transplantation. Additional comments to the Sponsor include appropriate dosing regimen/dosing strategy for each age group and clarification of the dose-escalation criteria.

- b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

13. List references, if any:

Trottestan H., Horne A., Maurizio A. et al. Chemoimmunotherapy for hemophagocytic lymphohistiocytosis: long-term results of the HLH-94 treatment protocol. Blood 2011 118(17):4577-4584.

Marsh R., Allen C., McClain K. et al. Salvage therapy of Refractory Hemophagocytic Lymphohistiocytosis with Alemtuzumab. Pediatr Blood Cancer 2013; 60:101-109.

Mahlaoui N. Ouachee-Chardin M, de Saint Basile G. et al. Immunotherapy of familial hemophagocytic lymphohistiocytosis with antithymocyte globulin: A single-center retrospective report of 38 patients. Pediatrics 2007; 120:e622-e628.

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14. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

15. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☒
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

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

/s/

TANYA M WROBLEWSKI
03/10/2016

ROMEO A DE CLARO
03/10/2016

ANN T FARRELL
03/10/2016