CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761145Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 125541

MEETING MINUTES

Janssen Research & Development, LLC.
Attention: Brian J Maloney, RPh, MS
Director, Regulatory Affairs
920 US Highway 202 South
Raritan, New Jersey 08869

Dear Mr. Maloney:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for, daratumumab (DARZALEX®, HuMax®-CD38) and recombinant human hyaluronidase (rHuPH20).

We also refer to the meeting between representatives of your firm and the FDA on February 23, 2017. The purpose of the meeting was to discuss and obtain agreement on the Phase 3 study design to support the use of daratumumab co-formulant administered by subcutaneous (SC) injection.

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}

Nicole Gormley, 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:	Thursday, February 23, 2017 1:00PM – 2:00PM (ET)
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1309 Silver Spring, Maryland 20903
Application Number:	IND 125541
Product Name:	daratumumab (DARZALEX®, HuMax®-CD38) and Recombinant Human Hyaluronidase (rHuPH20)
Indication:	Treatment of patients with multiple myeloma
Applicant Name:	Janssen Research & Development, LLC.
Meeting Chair:	Nicole Gormley, MD
Meeting Recorder:	Kimberly Scott, BSN, RN, OCN®

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)/Division of Hematology Products:
Albert Deisseroth, MD, PhD, Supervisory Associate Division Director
Nicole Gormley, MD, Clinical Team Leader
Vishal Bhatnagar, MD, Clinical Reviewer
Kimberly Scott, BSN, RN, OCN®, Regulatory Health Project Manager

Office of Clinical Pharmacology (OCP)/Division of Clinical Pharmacology V
Stacy Shord, PharmD, Team Leader
Sriram Subramaniam, PhD, Clinical Pharmacology Reviewer

Office of Biostatistics (OB)/Division of Biometrics V
Lei Nie, PhD, Team Leader
Kyung Yul Lee, PhD, Reviewer

Office of Medication Error Prevention and Risk Management/Division of Medication Error Prevention and Analysis (DMEPA)
Hina Mehta, PharmD, Team Leader
Leeza Rahimi, PharmD, Safety Evaluator

Office of Biotechnology Products (OBP)/Division of Biological Review and Research I
Rachel Novak, PhD, Team Leader
Eric Hales, PhD, Reviewer
Nina Brahme, PhD, Reviewer

SPONSOR ATTENDEES
Adam Dinerman, PhD, CMC Team Leader
Christoph Heuck, MD, Study Responsible Physician
Richard Jansson, PhD, Compound development Team Leader
Lillian Li, PhD, Clinical Pharmacology Lead
Brian Maloney, RPh, MS, North America Regulatory Affairs
Duncan Nickless, Global Regulatory Leader
Ming Qi, MD, PhD, Clinical Leader
Mark Rashkin, PhD, CMC Regulatory Affairs
Steven Sun, PhD, Director, Biostatistics
Yu-Nien (Tom) Sun, PhD, Global Clinical Pharmacology
Kevin Wanczyk, CMC Regulatory Affairs
Zhilong Yuan, PhD, Biostatistics Leader
Sen Hong Zhuang, MD, PhD, Vice President, Oncology Clinical Research
Michael Karl Bauer, PhD, Head Clinical Development (Genmab)
Mary Wilhelm, MS, Regulatory Affairs (Halozyme)

1.0 BACKGROUND

Multiple myeloma is a malignant disorder of the plasma cells, characterized by uncontrolled and progressive proliferation of a plasma cell clone.

The Sponsor, Janssen Research & Development, LLC, has been granted an end of phase 2 meeting to discuss their proposed plan for development of a subcutaneous (SC) formulation of daratumumab.

FDA sent Preliminary Comments to Janssen Research & Development, LLC on February 17, 2017.

2.0 DISCUSSION

Question 1:
Does the Division agree with the dose selection strategy for the SC development program?

FDA Response to Question 1:
The overall dose selection strategy appears reasonable. However, you should justify that the proposed dose of rHuPH20 (*i.e.,* 30, 000 U) with 1800 mg daratumumab SC dose in proposed commercial drug product (Dara-CF) (b) (4)

Discussion:
Janssen clarified that they conducted two non-clinical studies to support co-formulation and the route of administration.

Janssen agreed to submit the safety and PK data of the co-formulated product to the Agency for review before starting the Phase 3 trial.

Question 2:
Does the Division agree that the proposed Phase 3 study design could support registration of daratumumab SC formulation?

FDA Response to Question 2:
No. We do not agree with the patient population, primary endpoint and statistical assumptions. See responses to questions 3 and 4.

The protocol for the proposed Phase 3 trials should include a sparse pharmacokinetic (PK) sampling plan that is adequate to conduct population PK analysis and exposure-response analyses for efficacy and safety.

Discussion:
Janssen agrees to include sparse PK sampling and conduct population PK analysis and exposure-response analyses for efficacy and safety.

Question 3:
Does the Division agree that the proposed primary endpoint in Study MMY3012 is appropriate and could form the basis of a regulatory approval for Dara-CF SC in multiple myeloma?

FDA Response to Question 3:
Overall response rate (ORR) with an adequate median duration of response has been used to support accelerated approval in multiple myeloma. The Agency recommends that you consider ORR and the trough serum concentrations as co-primary endpoints. See Question 4 regarding the statistical analysis plans for trough concentrations.

Discussion:
The Sponsor agreed to add C3D1 C_{trough} as co-primary endpoint for Study MMY3012.

Question 4:
Does the Division agree that the statistical assumptions, sample size calculation, effect size, and proposed analyses are acceptable?

FDA Response to Question 4:
No. You currently propose to demonstrate non-inferiority of IV daratumumab vs. SC daratumumab using a non-inferiority margin that corresponds to 60% retention of the effect size of IV daratumumab in ORR. We have concerns with regard to the determination of this margin that could prohibit a conclusion of non-inferiority. Given slight differences in the patient populations, we discourage you from combining MMY2002 and Gen501 efficacy data and suggest using MMY2002 efficacy data alone for the purposes of statistical assumptions. Furthermore, the trial population for MMY3012 should be the same (prior lines of therapy, refractoriness, baseline disease characteristics, etc.) as MMY2002 for alignment with the current daratumumab IV monotherapy indication.

Additionally, you should modify the statistical analysis plan to include the ratio of the trough concentrations measured on cycle 3, day 1 of daratumumab following IV and SC administration, two-sided 90% confidence intervals, and the proposed bioequivalence limits (e.g., 80%, 125%).

Discussion:
The Agency requested clinical justification for 60% retention of effects size.

The Sponsor will modify the protocol and statistical analysis plan based on the Agency recommendations as outlined in responses 2 through 4.

The Agency agreed with the Sponsor's proposal to include C3D1 C_{trough} as a co-primary endpoint and to use a non-inferior analysis as the primary analysis. The Agency agreed to Janssen's proposal to include the two sided 90% CI ratio without formal hypothesis testing for bioequivalence.

Question 5:
Does the Division agree that the size of the safety database is acceptable to support a BLA for an SC formulation of daratumumab for the treatment of patients with multiple myeloma?

FDA Response to Question 5:
The Agency does not agree to the adequacy of the safety database in advance. The adequacy of the proposed safety database will be a review issue.

Discussion:
The Sponsor accepted FDA's response, no discussion occurred.

Question 6:

Does the Division agree that the proposed development program including the Phase 2 study of Dara-CF SC in combination with several background regimens for treatment of newly diagnosed/relapsed myeloma will provide sufficient evidence for approval across the multiple myeloma continuum where IV daratumumab is approved?

FDA Response to Question 6:
Discussion of Phase 2 study of daratumumab CF in combination with background regimens is premature at this time, as there is incomplete information regarding (1) the safety and effectiveness of any daratumumab product (IV or SC) in the NDMM population and (2) the safety and effectiveness of daratumumab CF in any myeloma population beyond the results of MMY1004. Therefore, the Agency is unable to determine of the adequacy of the proposed combination study plan at this time and we suggest requesting a meeting when more information is available. The data from early phase trials and MMY3012 will inform appropriate trial designs for Dara-CF in combination with other therapies.

Discussion:
The Sponsor accepted FDA's response, no discussion occurred.

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 (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that 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).

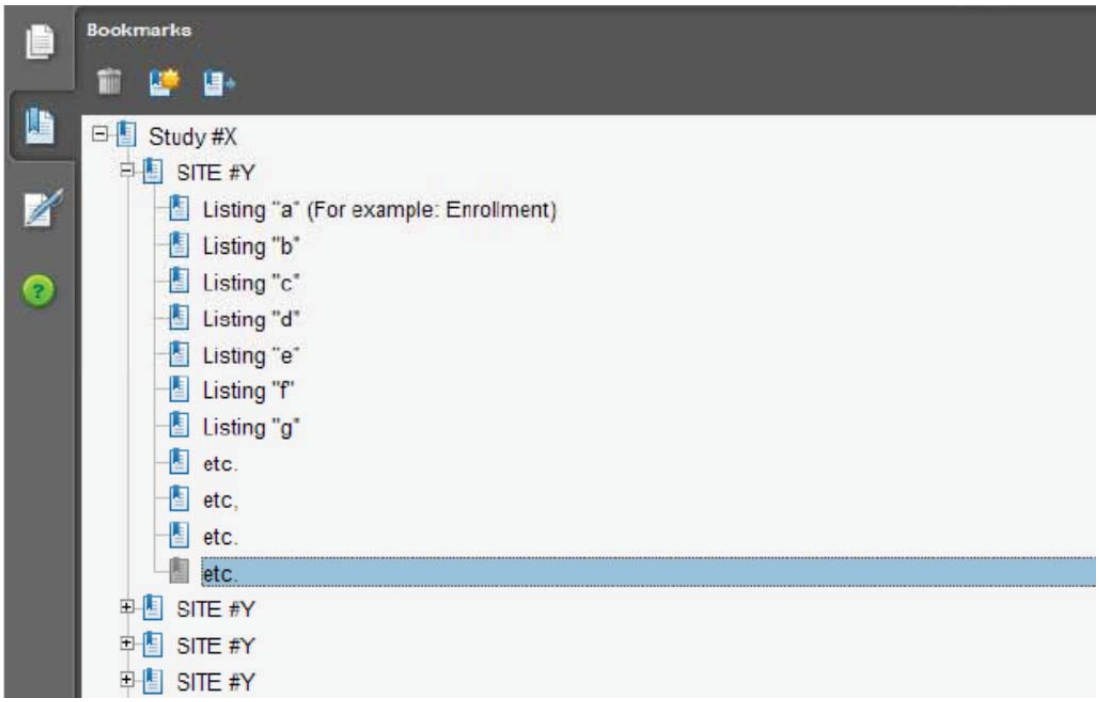
5. For each pivotal trial, provide original protocol and all amendments (or identify the location and/or provide a link if provided elsewhere in the submission).

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.

APPEARS THIS WAY ON ORIGINAL

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

No issues requiring further discussion.

5.0 ACTION ITEMS

No action items identified.

6.0 ATTACHMENTS AND HANDOUTS

Janssen's slides and handouts for the meeting.

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

/s/

NICOLE J GORMLEY
03/02/2017