CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761163Orig1s000

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

IND 114856

MEETING MINUTES

Morphosys AG
C/O Catalyst Regulatory Services, LLC
Attention: Mark A. Ammann, PharmD
President
7444 Dexter-Ann Arbor Road, Suite J
Dexter, MI 48130

Dear Dr. Ammann:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MOR00208.

We also refer to the meeting between representatives of your firm and the FDA on July 1, 2019. The purpose of the meeting was to discuss and obtain agreement with the Division on the content and format of a complete application with regards to CMC, non-clinical, clinical and regulatory related topics, as well as a proposal for a rolling submission schedule.

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 Rachel McMullen, Senior Regulatory Project Manager at (240) 402-4574.

Sincerely,

{See appended electronic signature page}

Nicole Gormley, MD
Clinical Team Lead
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-BLA

Meeting Date and Time: July 1, 2019; 1:00-2:00PM (ET)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1311
Silver Spring, Maryland 20903

Application Number: IND 114856
Product Name: MOR00208
Indication: Humanized anti-CD19 antibody MOR00208 in combination with Lenalidomide is indicated for the treatment of patients with relapsed or refractory DLBCL who are not eligible for high-dose chemotherapy and autologous stem-cell transplantation (ASCT).
Sponsor Name: Morphosys AG

Meeting Chair: Nicole Gormley, MD
Meeting Recorder: Rachel McMullen, MPH, MHA

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)/Division of Hematology Products
Albert Deisseroth, MD, PhD, Supervisory Associate Deputy Director
Nicole Gormley, MD, Clinical Team Lead
Bindu Kanapuru, MD, Medical Officer
Yvette Kasamon, MD, Medical Officer
Rachel McMullen, MPH, MHA, Senior Regulatory Project Manager

OHOP/Division of Hematology Oncology Toxicology
Christopher Sheth, PhD, Supervisory Pharmacologist/Toxicologist

Office of Biostatistics/Division of Biometrics V
Kunthel By, PhD, Statistical Reviewer

Office of Clinical Pharmacology/Division of Clinical Pharmacology V
Amal Ayyoub, PhD, Clinical Pharmacology Reviewer

Office of Process and Facilities /Division of Microbiology Assessment (DMA)
Aimee Cunningham, PhD, Microbiology Reviewer

Office of Biotechnology Products
Bazarragchaa Damdinsuren, MD, PhD, Product Quality Team Leader
Ksenija Grgac, PhD, Product Quality Reviewer

SPONSOR ATTENDEES
Morphosys AG
Avril Mankel, PhD, Director Regulatory Affairs
Dominika Weinelt, MD, Senior Director, Safety & Pharmacovigilance
Guido Wuerth, MD, Head Clinical Development
Günter Fingerle-Rowson, MD, PhD, Business Team Head MOR208
Günter Gartenmaier, MD, Associated Drug Safety & Pharmacovigilance
Kai Rosport, PhD, Senior Director, CMC
Malte Peters, MD, Chief Development Officer
Mark Winderlich, PhD, Head of Biostatistics & Data Management
Philippe Serrano, PharmD, Global Head Regulatory Affairs
Stefan Härtle, PhD, Group Leader Pharmacokinetics & Immunogenicity
Stefan Steidl, PhD, Head of Preclinical Development
Sumeet Ambarkhane, MD, Clinical Program Leader MOR208

1.0 BACKGROUND

MOR00208 is a humanized Fc engineered, monoclonal antibody against CD19. It is being developed for the proposed indication of treatment of patients with relapsed or refractory DLBCL who are not eligible for high-dose chemotherapy and autologous stem-cell transplantation (ASCT). The Sponsor was granted Fast Track designation on October 29, 2014, Orphan Designation on December 1, 2014 and Breakthrough Designation on October 23, 2017.

On April 12, 2019, Morphosys, requested a pre-BLA meeting to discuss the content and format of their BLA with regards to CMC, non-clinical, clinical and regulatory related topics, as well as a proposal for a rolling submission schedule. The Sponsor intends to submit their BLA application in December 2019.

FDA sent Preliminary Comments to Morphosys on June 24, 2019.

2. DISCUSSION

CLINICAL

Question 1: *Does the Agency agree that the results of the L-MIND study (MOR208C203), together with the retrospective observational cohort study (RE-MIND study (MOR208C206)), and the NHL study (MOR208C201) are adequate to support the planned BLA for regular approval of the combination of tafasitamab plus Lenalidomide followed by MOR 208 monotherapy for the proposed indication?*

FDA Response to Question 1: We reiterate our previous concerns with the use of data from the retrospective observational cohort study MOR208C206 (RE-MIND). We also reiterate that time-to-event endpoints cannot be interpreted in a single arm trial and time-to-event endpoints in the context of the observational study are not acceptable.

Ultimately, whether the data from the external database lenalidomide monotherapy cohort and the results of the L-MIND study will be adequate to support the approval of MOR208 for the proposed indication will depend on the quality of data and will be a review issue.

The decision regarding accelerated approval versus regular approval will be a review issue. In general, overall response rate (ORR) endpoint has been used to support accelerated approval of drugs for relapsed or refractory diffuse large B cell lymphoma.

DISCUSSION: The decision to submit a BLA for MOR208 is at the Sponsor's discretion. The adequacy of the data to support filing of the BLA will be a review issue.

Question 2: *Does the Agency concur with the proposed safety database and its size for the BLA?*

FDA Response to Question 2: 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. See also response to question 3.

DISCUSSION: There was no discussion.

Question 3: *Does the agency agree with the proposed cut-off dates for the original BLA and Day 90 Safety Update, as well as the proposed content of the Day 90 safety update?*

FDA Response to Question 3: No. You should also include an analysis of deaths that occur on study treatment or within 30 days of last study treatment, regardless of attribution due to disease progression or AEs in the safety analysis.

We recommend you provide safety information for TEAES, deaths (due to disease progression or AEs), SAEs, AESI's and discontinuations due to AEs using the June 30, 2019 cut-off date.

Clarify how the updated safety information with a cut-off date of June 30, 2019 will be included in the BLA submission. Specifically, clarify if the AE datasets will include this updated data at the time of the original BLA submission.

DISCUSSION: The Sponsor clarified that the analysis of death will include death events regardless of cause. The Sponsor will submit a full ISS using the June 30,

2019 cut-off date in the original BLA submission. The proposal to submit SAEs and deaths in the 90 day safety update is reasonable.

Question 4: *Does the Agency have any comments related to the proposed analyses and agrees that the proposed analyses in the draft ISS SAP (Annex 2) and Summary of Safety (Module 2.7.4) are sufficient and adequate to support the BLA?*

FDA Response to Question 4: From a technical perspective (and not content related), it is acceptable to include summary of clinical safety in section 2.7.4 of the submission.

In general, the proposed ISS analysis plan and the draft Table of Contents for the Summary of Safety appears reasonable. The acceptability of the content of the ISS and SCS to support the BLA will be a review issue.

We have the following comments:

- As the datasets to be integrated for the ISS consist of various studies that took place over a number of years, please ensure that the integrated dataset uses a uniform CTCAE grading and event terms according to the same MedDRA version.

- You should preserve the individual preferred terms for infusion related reactions in the ADAE dataset for the pivotal trial and supportive trials. You should include a flag for infusion related reactions (as assessed by investigators). By doing so, you can provide more accurate analysis of types and severities of IRRs by PT, HLT and body system.

- Include also the epoch and cycle number for each adverse event.

- Include disposition data for patients who completed 12 or more cycles of treatment

- Include a flag for patients treated with MOR208 at the 12 mg/kg dose.

DISCUSSION: The Sponsor outlined a proposal to submit a separate dataset for infusion related reactions (see attached slides). The Sponsor's proposal is reasonable.

Question 5:

a) Does the FDA agree with the proposed dataset format for the BLA?

FDA Response to Question 5a: Yes, the proposed dataset format for the BLA is reasonable. Note, data from all relevant studies used to support the application must adhere to current CDISC standards. This includes observational data elicited in Study MOR208C206.

In addition,

- Submit an Analysis Data Reviewer's Guide (ADRG) and Study Data Reviewer's Guide (SDRG); refer to the *Study Data Technical Conformance Guide: Technical Specifications Document* for additional details.
- Provide sufficient comments, adequate bookmarks, and hyperlinks in the define files to ensure efficient review.
- Provide executable SAS programs with adequate documentation to allow FDA to duplicate the analysis datasets derivation from raw datasets.

b) Does the Agency agree that the analysis programs for L Mind and Re Mind studies are sufficient for the filing of the BLA?

FDA Response to Question 5b: No. You should also provide SAS programs for MOR208C201. It is not uncommon for the Agency to request SAS programs for any aspect of the submission. We recommend that you have analysis programs related to any aspect of your submission at the ready. Provide SAS programs as well as format library files used for efficacy and safety data analysis. If the SAS programs use any SAS macro, provide all necessary macro programs.

To facilitate review, please create a programs dictionary document that lists each SAS program file with a description of what that program file does. The document should contain a table with two columns: a column that provides the name of the SAS file, and another column that provides the description of what that SAS file does. For example, if the file creates the results for a particular Table or a particular Figure, the description should make that clear.

DISCUSSION: There was no discussion.

Question 6: *Does the Agency agree to the Sponsor's proposal to provide Images upon request for the BLA?*

FDA Response to Question 6: Yes. The proposal is reasonable.

DISCUSSION: There was no discussion.

Question 7: *Does the Agency agree to the narratives and CRFs planned for the BLA?*

FDA Response to Question 7: No. You should include narratives for all deaths that occur on study treatment or within 30 days of last study treatment, regardless of attribution due to disease progression or AEs. You should also include narratives and CRFs for adverse events of special interest of all grades. If additional narratives are needed, an information request will be sent during the review cycle.

DISCUSSION: The proposal to submit narratives for selected AESI's considering the grading is reasonable (See Sponsor slides). Additional narratives may be requested during the BLA review as needed.

Question 8: *Does the Agency agree with the proposed clinical pharmacology content, as summarized in section 10.2 of the Briefing Book, and with the dataset format to be included in the BLA?*

FDA Response to Question 8: The proposed clinical pharmacology data package appears to be sufficient to support filing of the BLA submission. Adequacy of the contents and results of the clinical pharmacology analyses will be determined upon review of the BLA. In the proposed exposure-response analyses for efficacy and safety, provide justification regarding the selection of trial results for inclusion in each analysis. Refer to the additional clinical pharmacology comments for details regarding the BLA submission.

DISCUSSION: There was no discussion.

CHEMISTRY, MANUFACTURING & CONTROLS

Question 9:

a) *Provided that the data support it, does the Agency agree on the proposed approach, to support a shelf life of* (b) (4) *months for tafasitamab drug substance?*

b) Provided that the data support it, does the agency agree on the proposed approach, to support a shelf life of (b) (4) months for tafasitamab drug product?

FDA Response to Questions 9 a & b: The expiration dating periods for MOR00208 drug substance (DS) and drug product (DP) will be assigned based on the totality of data available in the BLA.

Based on information provided in the Meeting Briefing Book:

a) The proposed approach with DS stability data (shown in Table 16) may support a shelf life of (b) (4) months for MOR00208 DS,
b) The proposed approach with DP stability data (Table 18) may not support a shelf life of (b) (4) months for MOR00208 DP.

The strategy to establish the commercial shelf life of MOR00208 materials (i.e., DS, DP) by leveraging stability data generated from non-commercial process (i.e., CMC2, CMC3) batches can be an acceptable approach, provided:

- information in the BLA demonstrates that CMC2 and CMC3 processes are fully representative of and simulating the commercial manufacturing process (CMC4),

- the container closure systems (CCS) of non-commercial process (i.e., CMC2, CMC3) materials are same or fully representative of the commercial CCS, and
- the data adequately support that non-commercial process batches and the process validation batches are comparable.

Information in your IND suggests that CMC2 and CMC3 processes are not fully representative of the proposed commercial manufacturing process, and the CMC2 and CMC3 process materials used a different container closure system than the container closure system for the commercial materials.

DISCUSSION: The Sponsor noted a preliminary shelf life of 24 months for DP will be proposed in the BLA based on datasets shown on slide 15. The Agency agreed that the Sponsor's proposal to support the DP shelf life of 24 months is acceptable and reiterated that the expiration dating periods for DS and DP eventually will be assigned based on the totality of data provided in the BLA.

The Sponsor noted that additional DS and DP stability data will be available in Q1 2020. The Agency stated that as agreed previously, we will request stability data update through information request during the BLA review.

Question 10: *Does the Agency concur with the proposed approach for the (i) presentation of the quality attributes of tafasitamab and their control strategy and (ii) the level and structure of information provided about relevant process parameters for the manufacture of tafasitamab and their control?*

FDA Response to Question 10:

I. The proposed presentation structure of the information on quality attributes and their control strategy appears adequate to facilitate the Agency's review. Please include specifics of process parameter control (e.g., process step, process parameter and control range, if applicable) for each critical quality attribute (CQA).

II. We recommend that you include the following information into the proposed presentation of the information on process parameters and their control strategy in section 3.2.S.2.6:
   - Summary data (e.g., ranges) obtained from process characterization studies and process validation to demonstrate how these data support the proposed proven acceptable ranges (PAR),
   - Rationale for "low risk" classification for CPPs that are not investigated experimentally.

Note that normal operating ranges of process parameters are not required to be included in sections 3.2.S.2.2 and 3.2.P.3.3 considering the Agency's current thinking for established conditions (see the FDA Draft Guidance for Industry "*Established Conditions: Reportable CMC Changes for Approved Drug and Biologic Products*" at https://www.fda.gov/media/92242/download).

DISCUSSION: There was no discussion.

Question 11:

a) *Does the Agency agree to the approach to include in eCTD sections 3.2.S.4.3 and 3.2.P.5.3, a detailed description of the validation data for the analytical procedures for the DS and DP?*

FDA Response to Question 11a: We agree with your formatting of the validation information of analytical methods to include in sections 3.2.S.4.3 and 3.2.P.5.3, however we request you to submit the method validation reports in module 3.2.R. Additionally, we recommend including representative degraded samples in the validation of stability-indicating methods.

b) *Does the Agency have any feedback on the submitted document outlining the ADCC bridging study?*

FDA Response to Question 11b: The information provided in report "Bridging Study MP1-01 ADCC Assays" supports that the (b) (4) ADCC method is more accurate and precise than the (b) (4) ADCC method, however data is insufficient to conclude that the results obtained by these methods would be comparable. In the BLA submission, provide scientific rationale on usage of (b) (4) ADCC assay data in defining the specification limits of potency by (b) (4) ADCC assay. The final assessment of suitability of the potency assay(s) will be performed during the BLA review based on information on the method, its validation, bridging, and available release and stability data.

DISCUSSION: The Sponsor clarified that the specification limit for the ADCC assay will be defined based on the (b) (4) ADCC data only. The Agency reiterated that the final assessment of suitability of the potency assay, including specification limits, will be performed during the BLA review based on information on the method, its validation, bridging data, and available release and stability data.

Question 12: *Does the Agency agree to the proposed rolling submission schedule, and the components to be submitted within 30 days after original submission?*

FDA Response to Question 12: Yes. The proposed rolling submission schedule appears reasonable. We also acknowledge that FDA agreed to receive a limited number of CMC documents related to MOR00208 DS PPQ no later than 30 days after submission of the original BLA.

DISCUSSION: The Sponsor clarified whether a submission of section 2.3.S.2 DS Manufacture (in Module 2) within 30 days following the initial BLA submission is acceptable. The Agency recommended that the Sponsor submit a preliminary section 2.3.S.2 with the initial BLA submission, then update the section 2.3.S.2 with information on DS process validation within 30 days of the BLA submission.

Question 13: *Does the Agency agree with the proposed presentation of the ISE / 2.7.3 and ISS / 2.7.4 in the planned eCTD?*

FDA Response to Question 13: No, we do not agree with your proposal to include the contents of the ISS in the SCS. In general, the SCS should provide a data summary, consisting mostly of text, but with tables and figures incorporated as needed. The ISS should be located in Module 5.3.5.3. and should contain a more detailed, in-depth analysis, including integrated analyses and summaries of all relevant data from the studies included in the ISS.

For completeness, you should prepare a separate ISE. If the information in the ISE and the SCE are the same, you may reference the SCE in your ISE.

The adequacy of the content of the ISE and ISS will be assessed during the filing review of the BLA submission.

DISCUSSION: The Sponsor's proposal as outlined in the presentation slides regarding the SCS and ISS appears reasonable.

The Sponsor's proposal for the ISE and SCE is reasonable.

Question 14: Does the Agency agree that the submission of a REMS is not needed for the BLA?

FDA Response to Question 14: At this time, the Office of New Drugs does not have sufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application.

DISCUSSION: There was no discussion.

Question 15: *Does the agency agree to the information planned for pediatric administrative information in Module 1?*

FDA Response to Question 15: The proposal appears reasonable for your BLA submission planned for December 2019 (as noted in the meeting package). We also refer you to the comment below regarding the PREA requirements for original marketing application for certain adult oncology drugs that are submitted on or after August 18, 2020.

DISCUSSION: There was no discussion.

Question 16: *Does the Agency agree to the plan for proposed tradename in the BLA?*

FDA Response to Question 16: Your approach appears reasonable.

DISCUSSION: There was no discussion.

Question 17: *Does the Agency agree with the proposal to submit the BIMO file for the pivotal L-MIND (MOR208C203) study only?*

FDA Response to Question 17: Yes. This is reasonable.

DISCUSSION: There was no discussion.

Question 18: *Does the Agency have any comment or see any potential issue that would prevent the filing of the Biologics license application?*

FDA Response to Question 18: The adequacy of the proposed package to support filing of the BLA will be determined at the time of submission.

We remind you to include the following:

- Detailed, up to date production schedules to facilitate planning of Pre-Licensure Inspections,
- Integrated Summary of Immunogenicity in eCTD section 2.7. Clinical Summary (refer to the FDA Guidance for Industry "Immunogenicity Testing of Therapeutic Protein Products – Developing and Validating Assays for Anti-Drug Antibody Detection" at https://www.fda.gov/media/119788/download).

DISCUSSION: The Sponsor's proposal provided on slide 26 is acceptable.

Question 19: *Could the Agency confirm that tafasitamab could be eligible to this pilot project? If yes, when would the Agency share the Assessment Aid template?*

FDA Response to Question 19: Yes, you may consider using the Assessment Aid pilot program. More information on this pilot program, including eligibility criteria and timelines, can be found at the following FDA website: https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project

DISCUSSION: There was no discussion.

Question 20: *Does the Agency agree to an orientation meeting?*

FDA Response to Question 20: An application orientation meeting will be scheduled following formal submission of the BLA. The regulatory project manager will facilitate all communication with the Applicant.

DISCUSSION: There was no discussion.

Additional Comments:

Clinical:

1. Provide details on your plan to include data and analyses based on NK cell levels in your proposed BLA submission.

DISCUSSION: The Sponsor agreed to include data and analysis based on NK cell levels in the BLA submission. The Sponsor's proposal is reasonable.

2. Include a simple data file that identifies the tests used to determine response in the L-MIND and Re-MIND study. This should include at least the following variables: study identification number, site identification number, subject identifier, histologic subtype, date of first dose of study drug, response category (i.e., CR, PR, etc.), date of response, cycle and day of response, date of progression, date of marrow used to identify response and date of imaging used to identify response.

Clinical Pharmacology:

Address the following questions in the Summary of Clinical Pharmacology:

1. What is the basis for selecting the doses and dosing regimen used in the registration trials to support your marketing application? Identify individuals who required dose modifications and provide time to the first dose modification and reasons for the dose modifications in support of the proposed dose and administration.
2. What are the exposure-response relationships for efficacy, safety and biomarkers?
3. How do extrinsic (e.g., other drugs) and intrinsic factors (such as sex, race, body weight, organ dysfunctions, and disease) influence the exposure, efficacy, or safety of your drug? What dose modifications are recommended?
4. What is the impact of immunogenicity on exposure, efficacy and safety?

Apply the following advice in preparing the clinical pharmacology sections of the original submission:

1. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials. Complete the bioanalytical method performance summary tables below (Tables 1), using one PK and/or biomarker method per analyte per table. This table is not applicable for anti-drug antibody method. Do not delete any rows from the tables. State "not applicable" if certain rows or columns are not applicable. Include any additional bioanalytical data that may be relevant to the submission in a separate table. We recommend that these tables be included as an Appendix in eCTD Module 2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods. In addition, we request that you also submit both

tables in docx format in Module 2.7.1.

2. In addition, please complete and submit Table 3 with the BLA submission to provide the information regarding the bioanalytical methods used in pivotal clinical pharmacology studies and its life-cycle information pertaining to the submission. The Agency recommends that this table be placed in eCTD 2.7.1 along with summary biopharmaceutics. Please include any additional bioanalytical information that might be relevant. Provide final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with range as appropriate.

3. Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The subjects' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.
   - Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
   - Identify individual subjects with dose modifications; the time to the first dose reduction, interruption or discontinuation; the reasons for dose modifications in the datasets.

4. Submit the following for the population pharmacokinetic analysis reports:
   - Standard model diagnostic plots
   - Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line
   - Model parameter names and units in tables.
   - Summary of the report describing the clinical application of modeling results.

   Refer to the following pharmacometric data and models submission guidelines http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm.

5. Submit the following information and data to support the population pharmacokinetic analysis:
   1. SAS transport files (*.xpt) for all datasets used for model development and validation
   2. A description of each data item provided in a Define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets
   3. Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submitted these files as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt)

6. Submit a study report describing exploratory exposure-response (measures of effectiveness, biomarkers and toxicity) relationships in the targeted patient population. Refer to Guidance for Industry at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf for population PK http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf for exposure-response relationships, and http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm for pharmacometric data and models submission guidelines.

7. Recommendation about labeling:
   We recommend that the content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support this application be consistent with FDA Guidance for Industry, "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" (available at https://go.usa.gov/xn4qB). Consider strategies to enhance clarity, readability, and comprehension of this information for health care providers through the use of text attributes, tables, and figures as outlined in the above guidance.

Table 1. Summary method performance of a bioanalytical method to measure [analyte] in [matrix]

Bioanalytical method validation report name, amendments, and hyperlinks			
Method description			
Materials used for calibration curve & concentration			
Validated assay range			
Material used for QCs & concentration			
Minimum required dilutions (MRDs)			
Source & lot of reagents (LBA)			
Regression model & weighting			
Validation parameters	**Method validation summary**		**Source location (hyperlinked)**
Standard calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	x	Eg. Table 1 of report # 123
	Cumulative accuracy (%bias) from LLOQ to ULOQ Product A Product B and/or C [Applicable for bioanalytical method in 351(k). Delete for other applications]	 x to y% x to y%	Table y of 2 report #123

	Cumulative precision (%CV) from LLOQ to ULOQ Product A Product B and/or C [Applicable for bioanalytical method in 351(k). Delete for other applications]	 ≤ x% ≤ x%	Table 4 of report #123
QCs performance during accuracy & precision	**Cumulative accuracy (%bias) in 5 QCs** QCs: Product A Product B and/or C	 x to y% x to y%	Table 5 of report #123
	Inter-batch %CV QCs: Product A Product B and/or C	 ≤ x% ≤ x%	Table 6 of report #123
	Total Error (TE) QCs: Product A Product B and/or C	 ≤ x% ≤ x%	Table 7 of report #123
Selectivity & matrix effect	Number of total lots tested. Range of observed bias. State any issue		
Interference & specificity	Number of total lots tested. Range of observed bias. State any issue		
Hemolysis effect	Number of total lots tested. Range of observed bias. State any issue		
Lipemic effect	Number of total lots tested. Range of observed bias. State any issue		
Dilution linearity & hook effect	Highest concentration tested and number of dilution factors. Range of observed bias		
Bench-top/process stability	Describe summary data here Product A Product B/C		
Freeze-Thaw stability	Describe summary data here Product A Product B/C		
Long-term storage	Describe summary data here Product A Product B/C		
Parallelism	Describe summary data here.		
Carry over	Describe summary data here		
Method performance in study number (In addition to the report name, also provide hyperlink to the report)			
Assay passing rate	(including incurred sample reanalysis (ISR))		
Standard curve performance	• Cumulative bias range: x to y% • Cumulative precision: ≤ x% CV		
QC performance	• Cumulative bias range: x to y%		

	• Cumulative precision: ≤ x% CV • TE: ≤ x% (LBA only)	
Method reproducibility	Incurred sample reanalysis was performed in x% of study samples and x % of samples met the pre-specified criteria	
Study sample analysis/ stability	Describe the length of storage stability for standard/QCs and study samples and the coverage	

If the method above was modified, describe the modification(s) and cross-validation results, with any additional information in Table 2 below.

Table 2. Summary of method [x] modification(s) and cross-validation results

Bioanalytical method validation report name and hyperlink			
Changes in method			
New validated assay range if any			
Validation parameters	**Cross-validation performance**		**Source location (hyperlinked)**
Standard calibration curve performance during accuracy & precision	Cumulative accuracy (%bias) in standard calibrators from LLOQ to ULOQ	x to y%	
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ x%	
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 5 QCs	x to y%	
	Inter-batch %CV	≤ x%	
	Percent total error (TE)	≤ x%	
Cross-validation	Numbers of spiked or incurred samples analyzed and result		
List other parameters			

Table 3. Summary life cycle information of bioanalytical method(s) used in submission of BLA/NDA to measure the analyte in matrix (including Ligand Binding Assay-based biomarker)

	Method validation #1	Method validation #2	Clinical Study x	Clinical Studies y-z
Analyte	Drug name	Drug x, Drug y	Drug x, and Drug y	Drug x, Drug z
Validation type	Full	Partial validation of method xx	NA	NA
• CTD ref #	Ref # in eCTD	x0000.0xxxxxxx	x0000.0xxxxxxx	x0000.0xxxxxxx
• method ID • BA site	Method ID xx (version)	SOP xxxx or Method xxx (v 1.0)	SOP xxxx or Method xxx (v 1.0)	SOP xxxx or Method xxx (v 1.0)
	Name of BA test facility	US Lab 1	US lab 1	Other lab
• Matrix	Serum/ Plasma/Urine/ whole blood			
• Platform	LC/MS, ELISA, ECL			
• Format	A validated sandwich format using x as capture and y as detection, a bridging format using z as both capture and detection, competitive assay using x as a capture and b as a competitor			
Stock reference & lot (expiry)	Drug 1, lot 1	Drug 1, lot 2 Drug 2, lot 1		
Calibration range (LLOQ -ULOQ) and levels validated	x- x000 ng/mL (Eg. 2, 5, 50, 250, 1000, 1500, 2000 ng/mL)	x- x000 ng/mL	x- x000 ng/mL	x- x000 ng/mL
Matrix/ study population	Normal or x diseased serum	Normal serum	Normal serum	x Diseased population
Relevant reference and applicable report amendment (s) and links -Amendment 1 -Amendment 2				
Amendment history				

DISCUSSION: The Agency clarified that the proposal for providing the basis for dose selection of MOR208 and not for lenalidomide is acceptable as lenalidomide was administered according to the dosing recommendations in the Revlimid label and clinical practice.

The proposed analyses for dose modifications and the respective reasons for dose modifications for tafasitamab in combination with lenalidomide as well as for tafasitamab monotherapy is acceptable.

MorphoSys stated that no formal pharmacodynamics biomarker(s) nor safety biomarker(s) were investigated in the pivotal study L-MIND, therefore, the exposure response analyses for efficacy and safety are proposed to exclude pharmacodynamic and safety biomarkers. FDA stated that the proposal to exclude biomarkers in the exposure-response analyses is acceptable from a fileability perspective. The final decision on the use of biomarkers would be assessed during review of the BLA. The proposal to exclude the biomarker assay data from the bioanalytical sections of the submission is also acceptable as no biomarker assays were applied in the clinical trials.

FDA also reiterated the recommendation to include a justification of the study datasets included in the exposure response analyses.

MorphoSys' proposal to include the study PK datasets under the corresponding clinical study reports is acceptable. Furthermore, MorphoSys stated that no information on lenalidomide PK assays will be listed as lenalidomide PK was not assessed during L-MIND. FDA stated that this proposal is reasonable.

3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.
    - 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.
    - **Additional information regarding CMC submission components were discussed. See discussion under Question 12**.
    - **See discussion regarding safety updates. See Question 3, 4 and 7.**
    - 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 this would be a review

issue.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application:

- **Some CMC elements will be submitted after the initial BLA submission and will be provided within 30 days. See discussion under Question 12.**

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

- **BLA NUMBER: LATE COMPONENT - QUALITY**

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 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 or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be “designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling” (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric

investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.

For the latest version of the molecular target list, please refer to FDA.gov.[1]

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020 or sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided. Meetings requests should be sent to the appropriate review division with the cover letter clearly stating, "MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA." These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult FDA's Guidance on Formal Meetings Between the FDA and Sponsors or Applicants [2] to ensure open lines of dialogue before and during their drug development process.

[1] https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm5 44641.htm

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[2]

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[3] and Pregnancy and Lactation Labeling Final Rule[4] websites, which include:

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

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and

[2] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm
[3] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm08 4159.htm
[4] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm09 3307.htm

summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

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

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

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

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

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

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

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

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

supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

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

COMPOUNDED DRUG PRODUCT REQUIREMENTS

As described at 21 CFR 210.2(c), a drug product, including a compounded product, intended for use in a clinical study must be prepared in accordance with the current good manufacturing practice requirements appropriate for the product. For questions or clarification, contact Compounding@fda.hhs.gov.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[5]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[6]

SECURE EMAIL COMMUNICATIONS

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

[5] http://www.fda.gov/ectd
[6] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments,

and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[7]

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR[8]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- AssessmentAid[9]

NONPROPRIETARY NAME

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

[7] https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRe quirements/UCM332468.pdf
[8] https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm61292 7.htm
[9] https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm61292 3.htm

meaning.

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

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

Your proposed 351(a) BLA would be within the scope of this guidance. As such, FDA intends to assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

NA

6.0 ATTACHMENTS AND HANDOUTS

A copy of the Sponsor's slide presentation is attached for reference.

32 Pages 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. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NICOLE J GORMLEY
07/03/2019 12:42:39 PM

CDER Breakthrough Therapy Designation Determination Review Template

IND/NDA/BLA #	114856
Request Receipt Date	24 August 2017
Product	MOR00208
Indication	MOR00208, a humanized anti-CD19 monoclonal antibody to be used in combination with lenalidomide for the treatment of patients with relapsed or refractory DLBCL who are not eligible for high dose chemotherapy and autologous stem-cell transplantation
Drug Class/Mechanism of Action	Humanized, monoclonal antibody against CD-19
Sponsor	MorphoSys AG
ODE/Division	DHP
Breakthrough Therapy Request(BTDR) Goal Date (within 60 days of receipt)	23 October 2017

Note: This document should be uploaded into CDER's electronic document archival system as a ***clinical review: REV-CLINICAL-24 (Breakthough Therapy Designation Determination)*** *and will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR)**.*** *Link this review to the incoming 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.

1. **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):**

   Humanized anti-CD19 antibody MOR00208 in combination with lenalidomide is indicated for the treatment of patients with relapsed or refractory DLBCL who are not eligible for high-dose chemotherapy and autologous stem-cell transplantation.

2. **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:**

   a. Is the condition serious/life-threatening[1])? ☒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:

   b. 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 adequeate and sufficiently complete to permit a substantive review?

[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

☒ 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):

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 therapy[2]/ 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 MPC review is not required, email Miranda Raggio and Sandy Benton as soon as this determination is made so that the BTDR can be removed from the MPC calendar.

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.

- *Information regarding the disease and intended population for the proposed indication.*
- *Disease mechanism (if known) and natural history (if the disease is uncommon).*

DLBCL, the most common subtype of non-Hodgkin lymphoma (NHL), is an aggressive lymphoma with 27,650 new cases expected in the US in 2016. Combination chemotherapy with CD20 monoclonal antibody rituximab (R-CHOP) is the standard of care for treatment of newly diagnosed patients with DLBCL. Despite good initial responses a significant proportion of patients relapse, and a small percentage are refractory to initial therapy. In this situation, treatment options are very limited, especially when autologous stem cell transplantation (ASCT) cannot be performed. The dismal prognosis of these patients, facing a very limited set of therapeutic alternatives, is reflected by

[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

a median progression-free survival (PFS) time of 3–6 months and a median overall survival of 10–12 months[1]. Thus, patients with R-R DLBCL represent a population with a serious and life-threatening condition with an unmet medical need.

The CD19 antigen is typically expressed in DLBCL cells, has a signaling function that contributes to the malignant phenotype and is not down-regulated in patients pre-treated with CD20-targeted agents. MOR00208 is an Fc-engineered, humanized, monoclonal antibody that binds to the human cell surface antigen and co-protein of the B-cell receptor, CD19. This antigen is highly expressed on most B cell malignancies, including DLBCL. Fc-engineering of MOR00208 results in enhanced antibody dependent cellular cytotoxicity (ADCC), antibody dependent cellular phagocytosis (ADCP) and direct cytotoxicity (apoptosis/inhibition of proliferation).

The combination of MOR00208 with lenalidomide (LEN), which has single agent activity in R/R DLBCL, may have synergistic potential, due to LEN's modes of action including immune modulation, antiangiogenesis, modulation of the microenvironment and direct antitumor activity. In animal models, the combination has demonstrated superior antitumor effects with respect to survival and tumor growth compared to either mono therapy. This new combination of MOR00208, a novel anti-CD-19 antibody, and LEN represents a new combinatory immunotherapeutic approach.

The investigation of MOR00208 for the treatment of relapsed or refractory diffuse large B cell lymphoma (DLBCL) was designated as a Fast Track development program on 29-OCT- 2014.

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

a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

The BTDR is based on objective response rate (ORR) rate (primary endpoint; a surrogate) and the secondary endpoints of duration of response (DOR) and progression free survival (PFS)

b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:

- *A clinical endpoint that directly measures the clinical benefit of a drug (supporting traditional approval).*
- *A surrogate/established endpoint that is known to predict clinical benefit of a drug (i.e., a validated surrogate endpoint that can be used to support traditional approval).*
- *An endpoint that is reasonably likely to predict clinical benefit of a drug (supporting accelerated approval), and the endpoint used in a confirmatory trial or trials to verify the predicted clinical benefit.*

Durable ORR could support accelerated approval in relapsed or refractory aggressive lymphoma. In a larger trial, depending on the magnitude and durability of the treatment effect, ORR could also be viewed as a direct measure of clinical benefit in the relapsed/refractory setting and support regular approval. PFS or OS benefit would support approval.

c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

None

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:

- *If the available therapies were approved under accelerated approval, provide the information for the endpoint used to support accelerated approval and the endpoint used to verify the predicted clinical benefit.*
- *In addition to drugs that have been approved by FDA for the indication, also identify those treatments that may be used off-label for that indication.*

There are no approved therapies for patients with relapsed or refractory DLBCL. Combination chemotherapy is the mainstay of treatment. There are no universally established treatment regimens for patients with rel/ref DLBCL who are ineligible for hematopoietic stem cell transplantation (SCT), are refractory to second-line salvage regimens, or relapse after SCT.

9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[3].

- Polotuzumab an IgG monoclonal antibody against CD79b conjugated to an anti-mitotic agent (MMAE), was granted BTD 9/ 2017 for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma who are not candidates for hematopoietic stem cell transplantation.
- CTL019, a CD19-directed CAR T-cell, was granted BTD 4/2017 for adult patients with relapsed and refractory DLBCL who have failed two or more prior therapies.
- JCAR017, a CD19-directed CAR T-cell, was granted BTD 12/2016 for relapsed/refractory aggressive large B-cell NHL, including DLBCL not otherwise specified, primary mediastinal B-cell lymphoma or grade 3B follicular lymphoma.
- KTE-C19, a CD19-directed CAR T-cell, was granted BTD 12/2015 for refractory, aggressive NHL.

10. Information related to the preliminary clinical evidence:

a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design[4], trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

b. Include any additional relevant information. Consider the following in your response:

- *Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness .*
- *Identify any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, troublesome and advantageous aspects of the design, missing data, any relevant nonclinical data, etc.*

[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.

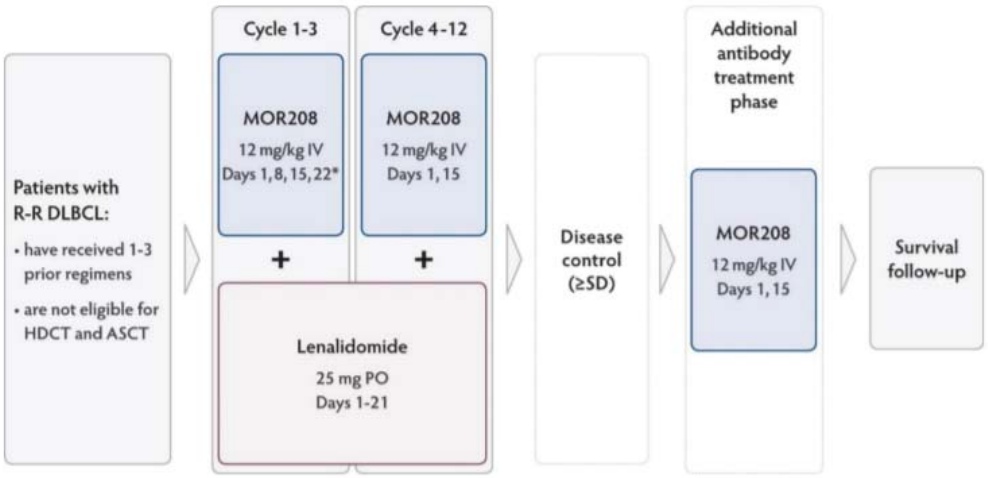
- *Safety data: Provide a brief explanation of the drug's safety profile, elaborating if it affects the Division's recommendation.*

This application is supported by the preliminary results of an ongoing phase II trial: L-MIND

ID: : NCT02399085

Study Design: Single-arm, multicenter, open-label phase II trial

Figure 1 Study Schema L-MIND



Source: IND114856 Request for breakthrough therapy designation Figure 1.

Primary endpoint : Objective response rate based on central, independent, radiological and clinical evaluations assessed according to the revised response criteria for malignant lymphoma as described in the guidelines of the International Working Group (Cheson et al., 2007). The outcomes of centrally and independently assessed radiological and clinical evaluations are not yet available. Preliminary response evaluations have therefore been based on investigator assessments.

Secondary endpoints: Disease control, duration of response, PFS, overall survival, time to progression, time to next treatment, safety, immunogenicity, pharmacokinetics and the investigation of possible correlations between efficacy parameters and candidate biomarkers (e.g., baseline tumor CD19 expression level, peripheral natural killer cell count, constitutional FCGR3A/FCGR2A polymorphism status, and cell of origin subtype).

As of June 2017, 51 of 80 planned had received at least one dose of study drug(safety population).

Median age of the study population was 74 years (range 47-82); 46% patients had received ≥2 prior lines of therapy; 35% had rituximab refractory disease and 41% were refractory to the last prior line; 60% had Ann Arbor stage ≥III disease; 55% had elevated lactate dehydrogenase level (>upper limit of normal), and 47% had a poor revised International Prognostic Index (3-5) at baseline.

Efficacy

44 patients qualified for a modified intention to treat (mITT) population-based investigator assessment of response, defined as having had at least one dose of MOR00208 and one dose of LEN, and one post-baseline response assessment or having discontinued treatment before that assessment.

Table 1 Preliminary Efficacy in Response Evaluable Population

	Response assessable N=44#
Best overall response	
Complete response	14 (32)
Partial response	9 (20)
Stable disease	6 (14)
Progressive disease	9 (20)
Not evaluable	6* (14)
Objective response rate (CR+PR)	23 (52)
Disease control rate (CR+PR+SD)	29 (66)

Source:IND 114856 Request for breakthrough therapy designation Table 2

The median duration of follow-up is currently 5.5 months for all efficacy evaluable patients (n=44). The median time to response was 1.8 months; the median time to CR was 2.3 months. The preliminary current median duration of response is 9.4 months,19 of 23 responses currently ongoing (13 complete, 6 partial).

The median PFS was 11.3 months (95% confidence interval: 5.4 months – not reached, the data are not yet fully mature).

As there is currently no FDA-approved treatment for R-R DLBCL, the potential for MOR00208 combined with LEN to improve outcomes over existing therapies in this difficult-to-treat patient population was made from comparisons of the preliminary LMIND data with previously published data from studies carried out in similar patient populations.

The results indicate that there is at least a doubling of the ORR and CR rates with the combination of lenalidomide and dexamethasone compared to single agent lenalidomide or the historical control (SCHOLAR-1).

Table 2 Comparison with Historical Studies

Parameter	L-MIND* MOR00208 + LEN	Witzig et al LEN alone	Czuczman et al LEN alone	Wang et al RTX + LEN	Vacirca et al RTX + BEN	Crump et al Meta-analysis
Evaluable patient population	R-R DLBCL N=44	R-R DLBCL N=108	R-R DLBCL N=51	R-R DLBCL N=32	R-R DLBCL N=59	Refractory DLBCL N=635
Objective response rate	52%†	28%†	27%†	28%†	46%†	26%
Complete response rate	32%	7%	10%	22%	15%	8
Median PFS, months	11.3	2.7	3.1	2.8	3.6	-
Median overall survival, months	-	-	7.1	10.2	-	6.6

*Preliminary data.
†Primary endpoint.
BEN, bendamustine; DLBCL, diffuse large B cell lymphoma; LEN, lenalidomide; PFS, progression-free survival; R-R, relapsed or refractory; RTX, rituximab.

Source:IND 114856 Request for breakthrough therapy designation Table 13

In the subgroups of patients with rituximab refractory and rituximab non-refractory disease, objective response rates were comparable between the two groups: 8 of 14 patients (57%) in the rituximab refractory group and 14 of 29 patients (48%) in the rituximab non-refractory group. The proportion of patients with a CR were 36% (5 out of 14), and 28% (8 out of 29), respectively.

In patients with disease refractory to the last prior line of treatment, the objective response rate was 53% (9 of 17 patients) compared with 50% (13 of 26 patients) for disease non-refractory to the last prior line of treatment. CR rates were 24% (4 of 17 patients) and 35% (9 of 26 patients), respectively.

Safety

The overall safety profile of the combination of MOR00208 and LEN is in line with the known safety profiles of the individual agents. The most common grade ≥3 TEAEs were neutropenia, reported in 18 (35%) of 51 patients, and thrombocytopenia and pneumonia, both reported in 5 (10%) patients. No infusion-related reactions were reported for MOR00208.

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

☒ GRANT :

Provide brief summary of rationale for granting:

DLBCL is a serious and life-threatening condition. Patients with relapsed or refractory DLBCL who are ineligible to receive hematopoietic stem cell transplantation have limited treatment options. MOR00208 in combination with LEN has preliminary clinical evidence of activity that may represent a substantial improvement over existing therapies.

- Efficacy data observed in the L-MIND study demonstrate that MOR00208 and LEN provide high overall and complete response rates in patients with R-R DLBCL who are not eligible for ASCT including patients with rituximab refractory disease or patients who are refractory to their last prior line of treatment.
- The responses appear durable, and the median PFS duration appears substantially longer as compared to results reported for alternative regiments in this setting.

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:

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):

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:

The Division had a Type C face to face meeting on June 28, 2017 with the Sponsor to discuss the revised protocol clinical study protocol MOR208C204 entitled "*A Phase III, Randomized, Multicenter Study of MOR00208 with Bendamustine versus Rituximab with Bendamustine in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma (R-R DLBCL) Who Are Not Eligible for High-Dose Chemotherapy (HDC) and Autologous Stem-Cell Transplantation (ASCT*)". The study is open in Europe and is planned to open in the US.

13. List references, if any:

1. Oral lenalidomide with rituximab in relapsed or refractory diffuse large cell, follicular and transformed lymphoma: a phase II clinical trial. Wang. 2013.
2. A Phase 2/3 Multicenter, Randomized, Open-Label Study to Compare the Efficacy and Safety of Lenalidomide Versus Investigator's Choice in Patients with Relapsed or Refractory Diffuse Large B Cell Lymphoma. Czuczman. 2017. An international phase II trial of single-agent lenalidomide for relapsed or refractory aggressive B cell non-Hodgkin's lymphoma. Witzig. 2011.
4. Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the International CORAL study, Gisselbrecht, 2016. https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf.
5. Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the International CORAL study. Neste. 2016.
6. Outcomes in refractory aggressive diffuse large b-cell lymphoma (DLBCL): Results from the international SCHOLAR-1 study. Crump. 2016.

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}

Revised 8/4/17/M. Raggio

Reference ID: 4651220

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/s/

BINDU N KANAPURU
10/19/2017

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10/22/2017

ANN T FARRELL
10/23/2017