CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761352Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND156484

MEETING MINUTES

Merus N.V.
Penny Ng, DRSc, MBA, RAC
Executive Director, Global Regulatory Affairs
139 Main Street, Suite 301
Cambridge, MA 02142

Dear Dr. Ng:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MCLA-128.

We also refer to the video conference between representatives of your firm and the FDA on December 7, 2023. The purpose of the meeting was to obtain feedback on the zenocutuzumab clinical development plan to support submission of an initial Biologics License Application (BLA), in addition to the proposed structure, content, and timing of the zenocutuzumab BLA, for two tumor specific indications (NRG1+ NSCLC under IND 156484, and NRG1+ PDAC under PIND 165120).
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A copy of the official minutes of the video conference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact me via telephone at 240-402-2691 or via email at Bamidele.aisida@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Florence Aisida, Pharm. D, BCPS
Senior Regulatory Health Project Manager
Division of Oncology 2
Division of Regulatory Operations for Oncologic Diseases
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:
- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre BLA

Meeting Date and Time: December 7, 2023, 3:00 PM – 4:00 PM, EST
Meeting Location: ZOOM MEETING INFORMATION will be provided by FDA

Application Number: IND 156484
Product Name: MCLA-128
Indication: Non-Small Cell Lung Cancer
Sponsor: Merus N.V.
Regulatory Pathway: 351(a) of the Public Health Service Act

Meeting Chair: Gautam Mehta, MD
Meeting Recorder: Maritsa Stephenson, PharmD, BCPS

FDA ATTENDEES

Harpreet Singh, MD ., Division Director, Division of Oncology 2 (DO2)
Steven Lemery MD., M.H.S., Division Director, Division of Oncology 2 (DO3)
Gautam Mehta, MD, PhD., Cross Disciplinary Team Lead, DO2
Yufan Liu, MD., Clinical Reviewer, DO2
Laure Price, PhD., Clinical Pharmacology Team Lead, Division of Cancer PharmacologyII (DCPII)
Anand Om, PhD., Clinical Pharmacology Reviewer, DCPII
Anup Amatya, PhD., Biometrics Team Lead, Division of Biometrics V (DBV)
Michelle Marcovitz, PhD., Biometrics Reviewer, DBV
Amy Sessums, Pharm D., Senior Regulatory Health Project Manager, DO3
Maritsa Stephenson, PharmD, BCPS, Division of Regulatory Operations

SPONSOR ATTENDEES

Shola Adeyemi, PhD, Senior Director, Clinical Biostatistics
Noémie Braekeveldt, PhD, Senior Manager, Regulatory Affairs
Lokesh Jain, PhD, VP, Clinical and Bioanalytical Sciences, Clinical Development
Shekeab Jauhari, MD, Medical Director, Clinical Development
Andrew Joe, MD, Chief Medical Officer, Clinical Development
Kees-Jan Koeman, Clinical Trial Lead, Clinical Operation
Penny Ng, DRSc, MBA, RAC, Executive Director, Regulatory Affairs
Ashley Pereira, PharmD, Senior VP, Regulatory Affairs
Peter Silverman, Chief Operating Officer
Viktoriya Stalbovskaya, PhD, VP, Biometrics, Clinical Biostatistics

Program Lead for Zenocutuzumab
Ernesto Wasserman, MD, Senior VP, Clinical Development

BACKGROUND

Meeting Purpose

On October 6, 2023, FDA received a Type B meeting request to obtain feedback on the zenocutuzumab clinical development plan to support submission of an initial Biologics License Application (BLA), in addition to the proposed structure, content, and timing of the zenocutuzumab BLA, for two tumor specific indications (NRG1+ NSCLC under IND 156484, and NRG1+ PDAC under PIND 165120).

Regulatory

On July 3, 2023, FDA granted Breakthrough Therapy designation (BTD) to zenocutuzumab for the treatment of advanced unresectable or metastatic non-small cell lung cancer following progression with prior systemic therapy or who have no satisfactory alternative treatment options. FDA had previously granted BTD for zenocutuzumab for the treatment of patients with advanced unresectable or metastatic pancreatic adenocarcinoma harboring a neuregulin 1 (NRG1) gene fusion (NRG1-positive PDAC) following progression with prior systemic therapy or who have no satisfactory alternative treatment options on May 17, 2023.

On September 12 and 25, 2023, Type B BTD meetings were held to discuss the planned efficacy analyses, estimated safety database, proposed format, content and regulatory timelines of a potential BLA. FDA advised Merus that patients who are identified as having non-measurable disease by investigator or had no baseline scans available, should be included in the primary analysis population. Merus should also summarize a plan to inform selection of patients in product labeling as part of the pre-BLA submission. It was agreed that the data from Study eNRGy and the expanded access program would not be pooled and would be analyzed separately. FDA also advised Merus that the safety database cutoff should be no more than 6 months prior to submission and that they should continue to enroll PDAC and NSCLC patients in Study eNRGy.

Clinical

Zenocutuzumab is a bispecific antibody that targets the transmembrane receptor tyrosine kinases HER2 and HER3, putatively preventing HER3 from associating with HER2, blocking NRG1 (or NRG1 fusion protein) from binding to HER3, and inhibiting the subsequent NRG1-driven PI3K and MAPK signaling pathways. NRG1 gene fusions have been reported at an incidence of 0.2% across a wide range of tumor types including PDAC, gallbladder cancer, renal cell cancer (RCC), ovarian cancer, NSCLC, breast cancer, sarcoma, bladder cancer, and colorectal cancer (CRC). Zenocutuzumab is being studied as a single agent in a Phase 1/2 study (MCLA-128-CL01) and an expanded access program (EAP). Zenocutuzumab in combination with other therapies has also been investigated in two clinical trials (Study MCLA-128-CL02 [completed] and Study MCLA-128-CL03 [ongoing]).

Study MCLA-128-CL01
Study MCLA-128-CL01 (NCT02912949) is an ongoing, open label, single-arm, dose-escalation and expansion study in patients with solid tumors evaluating the safety, tolerability, pharmacokinetics, immunogenicity, and preliminary efficacy of zenocutuzumab as a single agent in patients with NRG1-positive and NRG1-negative tumors. Study eNRGy is a subset of Study MCLA-128-CL01 and contains three cohorts of patients with NRG1-positive tumors (NSCLC, PDAC, other solid tumors) who are being treated with zenocutuzumab 750 mg IV once every 2 weeks (Q2W) until disease progression. The primary endpoint of Study eNRGy is overall response rate (ORR) per RECIST v1.1 as determined by local investigators. Key secondary endpoints include ORR and duration of response (DOR) per central independent radiologist review, progression free survival (PFS), overall survival (OS), and safety.

As of a data cutoff date of July 31, 2023, 75 patients with NRG1-positive NSCLC have been enrolled in Study eNRGy, including 64 patients who were previously treated. Of the 64 patients, 61 (81%) received prior chemotherapy and 41 (64%) received prior immunotherapy. Of the 64 previously treated patients, 21 patients had a confirmed response by investigator assessment and blinded independent central review (BICR) (ORR 33% [95% CI: 22; 46]). The median DOR was 13 months (95% CI 7, 21) and 7 months (95% CI, 4 to 17) by investigator assessment and BICR, respectively. Of the 11 treatment naïve patients, 4 patients had a confirmed response by investigator assessment and BICR (ORR 36% [95% CI: 11; 69]).

In addition, 29 patients with NRG1-positive PDAC have been enrolled in Study eNRGy. Patients had received a median of 2 prior systemic therapies and 19 (70.4%) patients had disease progression on FOLFIRINOX (2 in the neoadjuvant or adjuvant setting) and/or a gemcitabine/taxane combination. Of the 29 patients, 13 patients had a confirmed response by investigator assessment (ORR 45% [95% CI: 26; 64]) and 12 by BICR (ORR 41% [95% CI 24, 61]). The median DOR was 7 months (95% CI 6, 11) and 17 months (95% CI, 3.7 to NC) by investigator assessment and BICR, respectively.

An overview of the safety data is provided below.

	NRG1+ NSCLC (N=99) N (%)	NRG1+ PDAC (N=39) N (%)	All NRG1+ Tumors (N=175) N (%)
Patients with ≥Grade 3 AEs	31 (31)	20 (51)	64 (37)
Patients with SAEs	25 (25)	9 (23)	42 (24)
Patients with Grade 5 AEs	5 (5)	2 (5)	8 (5)
Patients with AEs leading to discontinuation	10 (10)	2 (5)	14 (8)
Patients with AEs leading to drug interruption	29 (29)	13 (33)	53 (10)

The most frequent adverse events (AEs) (≥10%) across all NRG1 tumors include diarrhea (28%), anemia (17%), nausea (17%), fatigue (15%), dyspnea (13%), constipation (13%), infusion-related reactions (13%), vomiting (12%), ALT increased (11%), hypomagnesemia (11%), and abdominal pain (10%).

Identification of NRG1 Fusions for zenocutuzumab and CDx Development
NRG1+ cancer patients were enrolled in Study eNRGy and the EAP on the basis of a locally documented functional NRG1 gene fusion identified through a molecular assay such as NGS based assays (DNA or RNA) as routinely performed at clinical laboratory improvement amendments (CLIA) or other similarly certified laboratories. A process to assess NRG1 functionality and the occurrence of additional driver alternations against pre-defined criteria was formalized in the "NRG1 Functionality Plan" document, which will be included with the BLA.

Prior to each patient being enrolled, a translational scientist from Merus reviewed the patient specific pathology report for the NRG1 gene fusion and completed a review form. This was subsequently reviewed by an NRG1 fusion review team at (b) (4) to assess functionality, after which the patient could be enrolled in the study. For the data analyses in Study eNRGy, the final decision about NRG1 fusion functionality was made using retrospective evaluation of pathology reports by an Independent Reviewer. This reviewer, who was blinded to patient outcomes, assessed NRG1 functionality (and the presence of other concomitant genetic tumor alterations) and captured the overall functionality assessment in the electronic Case Report Form.

Merus intends to support the development of a companion diagnostic (CDx) assay (b) (4), to identify known and unknown NRG1 gene fusions. However, Merus anticipates seeking approval of zenocutuzumab without contemporaneous approval of a CDx. (b) (4)

Proposed BLA Filing
Merus plans to submit a BLA to support accelerated approval via a rolling submission and will submit a formal request for Priority Review at the time of the initial BLA submission. Merus plans to submit nonclinical and CMC packages initially January 2024, and clinical documents and Module 1 documents by the beginning of March 2024 (no later than 08 March 2024) to complete the BLA submission, which would be approximately 7 months from the data cutoff date.

Merus plans to provide a 90-Day Safety Update Report with a data cutoff date of January 31, 2024, which would provide an additional 6 months of follow-up. Merus would include updated safety data from Study eNRGy, the EAP, and the zenocutuzumab combination study, along with updated efficacy data for the patients included in the initial BLA submission. If any new, important safety findings from pharmacology or toxicology studies become available, these data would also be submitted to FDA.

SPONSOR QUESTIONS AND FDA RESPONSES

1. Clinical Data Package for BLA Filing - Does the Agency agree that the available clinical data package provides sufficient clinical evidence to characterize the benefit and risk of zenocutuzumab in the proposed indications to support a BLA filing?

   FDA Response: We generally agree that the data provided appears adequate to support filing a BLA. However, we recommend you address the following in your planned BLA submission:

   - Patients who did not have measurable disease at baseline should be included as part of the assessment of response by both BICR and investigator. If available, please provide these data before BLA submission for FDA review.

- We note that there are patients who are excluded from the primary efficacy set (PES) as they were treated less than 24 weeks prior to the data cutoff date. Please also perform a sensitivity analysis with inclusion of these patients
- Please clarify the number of patients with NSCLC who received prior platinum chemotherapy, prior immunotherapy and both prior platinum chemotherapy and immunotherapy. Table 10 of your meeting materials states that 41 patients received prior immunotherapy while Section 10.2.2.4 states 36 patients received prior immunotherapy. We expect that the efficacy results would also be provided for these patient population subgroups.
- In the BLA submission, provide an analysis of the discrepancy between BICR and investigator's assessment of duration of response in patients with PDAC.

Sponsor's Response:

Merus acknowledges FDA comments. The points noted by the FDA will be addressed in the BLA submission. Merus would also like to provide responses and clarifications before the BLA submission for FDA review and discussion:

A. Patients who did not have measurable disease at baseline should be included as part of the assessment of response by both BICR and investigator. If available, please provide these data before BLA submission for FDA review.

As agreed with the FDA at the September 2023 Initial Comprehensive, Multidisciplinary Breakthrough (Type B) Meetings, patients with non-measurable disease by BICR but measurable disease by investigator at baseline were included in the BICR ORR analysis. Overall, 75 NRG1+ NSCLC and 29 NRG1+ PDAC patients were included in the BICR ORR analysis.
As shown in Table 1 below, only 1 NSCLC patient in the PES in the eNRGy Study did not have measurable disease at baseline by investigator, but this patient was assessed as having measurable disease at baseline by BICR, hence they were included in the BICR ORR analysis. Overall, no patient was assessed as non-measurable by both investigator and BICR. No patients were excluded from BICR ORR analysis based on measurability.

Table 1 Number of NRG1+ NSCLC Patients in PES of Study eNRGy Assessed as Measurable/Non-Measurable Disease at Baseline

NSCLC (N=75*)		BICR	
		Measurable	Non-measurable
INV	Measurable	72	2
	Non-measurable	1	0

* All N=75 is used in the calculation of ORR by BICR

No PDAC patients were judged as having non-measurable disease by both investigator and BICR (Table 2).

Table 2 Number of NRG1+ PDAC Patients in PES of Study eNRGy Assessed as Measurable/Non-Measurable Disease at Baseline

PDAC (N=29)		BICR	
		Measurable	Non-measurable
INV	Measurable	29	0
	Non-measurable	0	0

B. We note that there are patients who are excluded from the primary efficacy set (PES) as they were treated less than 24 weeks prior to the data cutoff date. Please also perform a sensitivity analysis with inclusion of these patients.

Patients treated less than 24 weeks prior to the data cutoff are excluded from the PES but included in the supportive efficacy set (SES) per the Statistical Analysis Plan of the eNRGy Study.

Definition of Supportive Efficacy Set (SES)

All patients:

- received at least one infusion of the study treatment at 750 mg Q2W
- had documented functional NRG1 fusion,
- had no other known driver mutations,
- had at least one post-baseline response assessment or early discontinuation due to toxicity or disease progression (including death due to underlying disease)
- have not been exposed to anti-HER3 targeting antibodies.

APPEARS THIS WAY ON ORIGINAL

Efficacy analyses of SES are provided below and will also be provided in the BLA:

Table 3 Overall Response Rate in NRG1+ NSCLC and NRG1+ PDAC in SES (eNRGy Study)

	BICR Assessment		Investigator Assessment	
	NSCLC (N=87)	**PDAC (N=33)**	**NSCLC (N=87)**	**PDAC (N=33)**
Number of patients with measurable disease at baseline, n (%)	84 (96.6)	33 (100)	86 (98.9)	33 (100)
Number of patients with non-measurable disease at baseline, n (%)	2 (2.3)	0	1 (1.1)	0
Number of patients non-evaluable at baseline [1], n (%)	1 (1.1)	0	NA	NA
Number of patients assessed for response [2], n(%)	87	33	86	33
ORR, n (%)	26 (29.9)	13 (39.4)	25 (29.1)	13 (39.4)
95% CI	20.5 ; 40.6	22.9 ; 57.9	19.8 ; 39.9	22.9 ; 57.9

C. Please clarify the number of patients with NSCLC who received prior platinum chemotherapy, prior immunotherapy and both prior platinum chemotherapy and immunotherapy. Table 10 of your meeting materials states that 41 patients received prior immunotherapy while Section 10.2.2.4 states 36 patients received prior immunotherapy. We expect that the efficacy results would also be provided for these patient population subgroups.

Prior immunotherapy was received by 41 NSCLC patients, irrespective of other therapies received, as per Table 10 of the Meeting Package. Out of these 41 patients, 36 patients also received prior platinum-based therapy (either sequentially or concurrently with immunotherapy), with efficacy data on the 36 patients included in Section 10.2.2.4 of the Meeting Package.

Table 4 below describes the distribution of NSCLC patients who were previously treated with platinum-based chemotherapy or immunotherapy (PES). Exploratory response analysis (ORR) by BICR and Investigator assessment is provided in Table 5.

Table 4 Distribution of NRG1+ NSCLC Patients Prior Anticancer Therapy (Prior Platinum-Based Chemotherapy or Immunotherapy Treatment) at Baseline (PES, eNRGy Study)

Overall NSCLC (N=75)		**Prior platinum-based chemotherapy**	
		Yes (n=55)	No (n=20)
Prior immunotherapy	Yes (n=41)	36	5
	No (n=34)	19	15 (including 11 treatment naïve)

Table 5 Exploratory Analysis of ORR in NRG1+ NSCLC Patients by Prior Anticancer Therapy at Baseline (PES, eNRGy Study)

	NSCLC (N=75) BICR			**NSCLC (N=75) INV**		
	N	**ORR n (%)**	**95% CI**	**N**	**ORR n (%)**	**95% CI**
Prior anticancer therapy (NSCLC)						
Any prior therapy	64	21 (32.8)	21.6 ; 45.7	63	21 (33.3)	22.0 ; 46.3
Platinum pretreatment	55	18 (32.7)	20.7 ; 46.7	54	18 (33.3)	21.1 ; 47.5
Platinum and IO pretreated	36	11 (30.6)	16.3 ; 48.1	36	10 (27.8)	14.2 ; 45.2
Naive	11	4 (36.4)	10.9 ; 69.2	11	4 (36.4)	10.9 ; 69.2

D. In the BLA submission, provide an analysis of the discrepancy between BICR and investigator's assessment of duration of response in patients with PDAC.

The Kaplan-Meier estimate of median DOR in the 12 PDAC responders was 16.6 months (95% CI: 3.7, not calculable) per BICR and was 7.4 months (95% CI: 5.5, 11.2) in the 13 PDAC responders per investigator.
The Kaplan-Meier estimate of DOR by BICR between 9.1 and 16.6 months was 50.8%, with no DOR events occurring during this period (Figure 1.A). The median by BICR was reached only when the last responder had an event (Figure 1.A), whereas the median DOR by investigator was reached at 7.4 months (Figure 1.B).
Among 29 patients with PDAC in the primary efficacy set, the best overall response met the criteria for partial or complete response per RECIST 1.1 in 12 of them by BICR and in 13 of them by investigator:

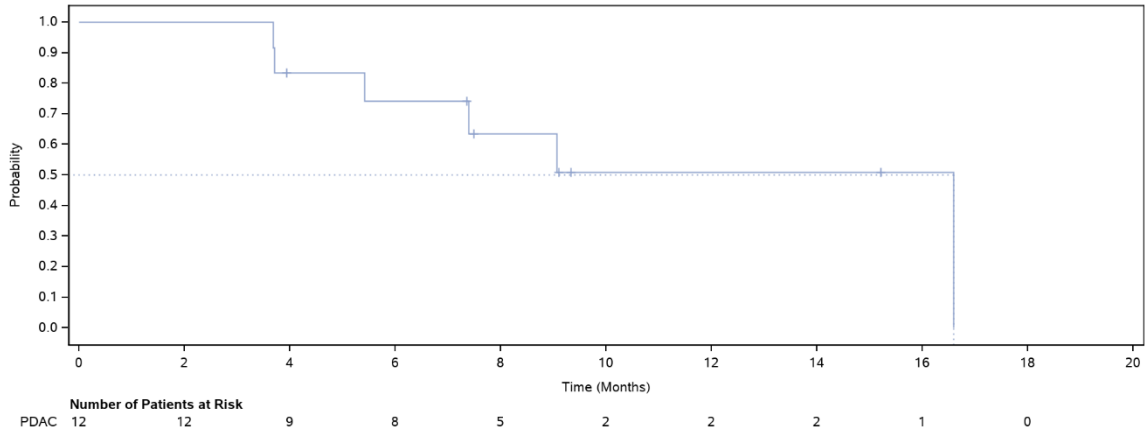
- 11 patients were assessed as CR/PR by BICR and by investigator with onset and end of response differing in few patients
- 1 patient was assessed with BOR of PR by BICR and BOR of SD by investigator
- 2 patients were assessed with BOR of PR by investigator and BOR of SD by BICR

The BLA submission will include a summary accounting for the discrepancy in DOR by BICR and investigator.

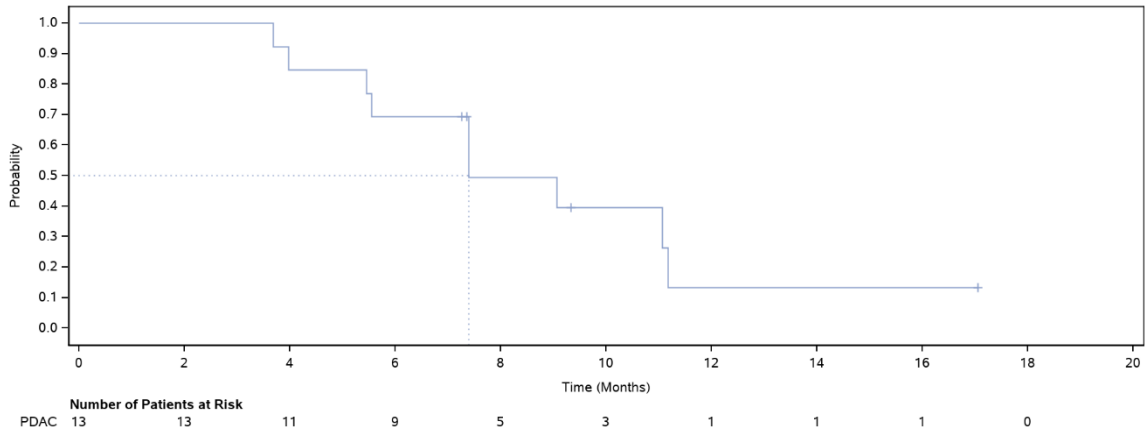
APPEARS THIS WAY ON ORIGINAL

Figure 1 **Kaplan-Meier Plot of Duration of Response per RECIST 1.1 by BIRC (A) and Investigator Assessment (B) – PDAC Primary Efficacy Set.**

A.



B.



Please kindly advise if there are further questions regarding the data provided in this response document.

Discussion During the Meeting: FDA acknowledged Merus' response and additional information provided regarding response rate data, prior therapies, and the observed differential median DoR between INV and BICR assessment in patients with PDAC. Merus noted that these data will be made available in the BLA. FDA also asked Merus to include reasons for censoring for DoR in the BLA submission.

2. REMS - Based on the observed safety profile of zenocutuzumab, does the Agency agree with the proposal to not submit a Medication Guide or a Risk Evaluation and Mitigation Strategy (REMS) for the use of zenocutuzumab in the proposed indications?

FDA Response: It is premature to make a final assessment whether a REMS would be necessary. A final determination will be made during BLA review.

Sponsor's Response: Merus acknowledges FDA's comment. A REMS will not be included in the initial BLA submission as part of the filing review, but Merus understands that the FDA may request a REMS during the BLA review. No further discussion is required at this meeting.

Discussion During the Meeting: No discussion occurred.

3. Proposed BLA Plan and Timing - Does the Agency agree with the proposed submission plan (accelerated approval under Subpart E and rolling submission) and timeline?

   FDA Response: A determination regarding the ability of the proposed BLA to support accelerated approval will be made during BLA review. Your proposed timelines for submission appear reasonable.

   Sponsor's Response: Merus appreciates the FDA's confirmation on our submission plan. No further discussion is required at this meeting.

   Discussion During the Meeting: No discussion occurred.

4. Proposal of Safety Update Report During BLA Review - Does the Agency agree with the scope of the Safety Update and Merus' proposal to submit updated safety and efficacy data in the 90 Day Safety Update Report (SUR) if Priority Request is granted and that the new data would not impact the PDUFA date?

   FDA Response: While it would be acceptable to provide updated efficacy data in the 90-day safety update report, previous assessments of response should not be re-adjudicated. This means that ORR results should not change unless a new response occurred after the original data cut-off date and updated duration of response for responses documented prior to the original cut-off date should be based on date of response used for the initial BLA submission. Additionally, at the time of the 90-day safety update report, please include safety and efficacy data for any additional patients treated with zenocutuzumab for the proposed indications that would meet inclusion criteria for the PES (i.e., enrolled between the July 2023 and January 2024 data cutoffs).

   In general, submission of updated data with the 90 day safety update report alone would not be expected to impact the PDUFA action date, provided there are not substantial changes that would impact assessment of the risk:benefit of zenocutuzumab for the proposed indications.

Sponsor's Response: Merus acknowledges FDA comments. At the time of the 90-day safety update report, Merus will include efficacy data for any additional patients treated with zenocutuzumab for the proposed indications that would meet inclusion criteria for the eNRGy PES (i.e., enrolled up until 16 August 2023, which is 24 weeks prior to 31 January 2024). Safety update will include any patients having received at least one dose of zenocutuzumab as of 31 January 2024.

Discussion During the Meeting: No discussion occurred.

5. Plan for an Application Orientation Meeting - Does the Agency wish to schedule an application orientation meeting with Merus after submission of the BLA to outline the major components of the BLA?

   FDA Response: An Application Orientation Meeting is preferable for new molecular entities such as zenocutuzumab.

   Sponsor's Response: Merus acknowledges FDA's comment and will coordinate with the FDA Project Manager if an AOM is requested by the Review Team during the filing review of the BLA.

   Discussion During the Meeting: No discussion occurred.

Additional FDA comments

Chemistry, Manufacturing, and Controls

6. To facilitate the Agency's assessment of the BLA submission, provide the information in tables as requested below. The requested tables should summarize information from Module 3 and be submitted either in Module 1 or Module 3.2.R. These tables do not replace other sections of Module 3 or impact the nature or amount of information included in those sections of Module 3.

   A. To facilitate the Agency's assessment of the drug substance (DS) and drug product (DP) manufacturing processes for zenocutuzumab, provide the information for each process parameter and in-process control, as applicable, in the following tabular format. Provide a separate table for each unit operation of the zenocutuzumab DS and DP manufacturing processes, as described below.

Process parameter/operating parameters/ In-process control[1]	Proven Acceptable Range/ Control Limits/Targets for commercial manufacturing process[2]	Criticality classification[3]	Characterized range/Control Limits/Targets tested in process development studies[2]	Manufactured Range/ Control Limits/Targets used for clinical batches[2] (mix-max), n=?[4]	Manufactured Range/ Control Limits/Targets used in Process validation [2] (min-max), n=?[4]	Justification of the proposed commercial acceptable range[5]

[1]Terminology should be adapted to the one used by the manufacturing site(s).
[2]As applicable.
[3]For example, critical process parameter, key process parameter, non-critical process parameter, as described in Module 3.
[4]Indicate the total number of batches used for calculating minimum-maximum range for each unit operation and list the batch numbers in the footnote if applicable. If not all batches indicated are included for calculation, provide justification in the footnote or insert a hyperlink to eCTD.
[5]This could be a brief verbal description (e.g., "development range", "validation range", or "platform experience").

B. To facilitate the Agency's assessment of the control strategy for zenocutuzumab, provide information for quality attributes and process- and product-related impurities for DS and DP in the following tabular format. Provide a separate table for the zenocutuzumab DS and DP.

Quality Attributes (including process and product related impurities for DS and DP)	Criticality classification[1]	Impact [2]	Source[3]	Analytical method[4]	Proposed control strategy[5]	Justification of the proposed control strategy[6]

[1]Indicate if it is a CQA or not.
[2]What is the impact of the attribute (e.g., contributes to potency, immunogenicity, safety, efficacy, etc.)?
[3]What is the source of the attribute or impurity (e.g., intrinsic to the molecule, fermentation, purification column, etc.)?
[4]List all methods used to test an attribute in-process, at release, and/or on stability. For example, if two methods are used to test identity, list both methods for that attribute.
[5]List all strategies by which the attribute is controlled (e.g., in-process testing, validated removal, release testing, stability testing, etc.).
[6]This could be a brief verbal description or links to the appropriate section of the eCTD.

C. To facilitate the Agency's assessment of the adequacy of the proposed commercial DS and DP release specifications, provide information for each release specification in the tabular format provided below. Please provide a separate table for zenocutuzumab DS and DP, as described below. In general, include footnotes for each column of grouped results to indicate which lot numbers were used for each calculation of minimum-maximum range, and provide the number of batches or lots used (n=?) in the table as well.

Release Specification for Zenocutuzumab Drug Substance							
Attribute	Analytical Method	Proposed commercial release acceptance criteria	Release results from non-GMP DS batches[1] (n=?) (min-max)	Release results for non-PPQ GMP clinical DS batches using the clinical manufacturing process[2] (n=?) (min-max)	Release results for non-PPQ GMP clinical DS batches using to-be-marketed manufacturing process[3] (n=?) (min-max)	Release results for DS PPQ batches[4] (n=?) (min-max)	Justification of specification (e.g., clinical experience, manufacturing capability, etc.)

[1]List all non-GMP DS batches included in the range calculation.
[2]List all non-PPQ GMP clinical DS batches using the clinical process included in the range calculation.
[3]List all non-PPQ GMP clinical DS batches using the to-be-marketed process included in the range calculation.
[4]List all PPQ DS batches included in the range calculation.

Release Specification for Zenocutuzumab Drug Product							
Attribute	Analytical Method	Proposed Commercial Release acceptance criteria	Release results from developmental and nonclinical DP lots[1] (n=?) (min-max)	Release results for non-PPQ clinical DP lots using clinical formulation[2] (n=?) (min-max)	Release results for non-PPQ clinical DP lots using to-be-marketed formulation[3] (n=?) (min-max)	Release results for DP PPQ lots[4] (n=?) (min-max)	Justification of specification (e.g., clinical experience, manufacturing capability, etc.)

[1]List all non-clinical and developmental DP lots included in the range calculation.
[2]List all non-PPQ clinical DP lots using clinical formulation included in the range calculation.
[3]List all non-PPQ clinical DP lots using to-be-marketed formulation included in the range calculation.
[4]List all PPQ DP lots included in the range calculation.

D. Regarding the immunogenicity testing in the BLA submission, we recommend you provide an Integrated Summary of Immunogenicity (ISI) in eCTD section 2.7.2.4 Special Studies or Section 5.3.5.3 Reports of Analysis of Data from More than One Study. This ISI should include: (1) Immunogenicity Risk Assessment, (2) Tiered Bioanalytical Strategy and Assay Validation Summaries, (3) Clinical Study Design and Detailed Immunogenicity Sampling Plans, and (4) Clinical Immunogenicity Data Analysis. For more information, refer to guidance for industry *Immunogenicity Testing of Therapeutic Protein Products —Developing and Validating Assays for Anti-Drug Antibody Detection* (January 2019).

Sponsor's Response: Merus acknowledges FDA comments and will provide the requested information/format in the initial BLA. No further discussion is required at the meeting.

Discussion During the Meeting: No discussion occurred.

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 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 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.
Meeting 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 the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, to ensure open lines of dialogue before and during their drug development process.

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.

APPEARS THIS WAY ON ORIGINAL

[1] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology
[2] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[3] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[4] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

- 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 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.

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]

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.

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

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

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

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

Corresponding names and titles of onsite contact:

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

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[7] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[8]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions, and the associated conformance guide, Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications, be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested 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.[9]

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:

[7] https://www.fda.gov/media/84223/download
[8] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and
[9] https://www.fda.gov/media/85061/download

- RTOR[10]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- Assessment Aid[11]

NONPROPRIETARY NAME

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

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

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

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

SUBMISSIONS WITH REAL-WORLD EVIDENCE

CDER strongly encourages sponsors to include information in their submission cover letters that identifies uses or proposed uses of real-world evidence (RWE) to support a regulatory decision regarding product safety and/or effectiveness. For recommendations on specific information to include in submission cover letters, see the guidance for industry *Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products.*[12] For questions or clarification, contact cdermedicalpolicy-realworldevidence@fda.hhs.gov.

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[10] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program
[11] https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project
[12] https://www.fda.gov/media/124795/download

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/

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CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	156484
Request Receipt Date	May 5, 2023
Product	Zenocutuzumab
Indication	Treatment of patients with advanced unresectable or metastatic non-small cell lung cancer harboring a neuregulin 1 (NRG1) gene fusion (NRG1+ NSCLC) following progression with prior systemic therapy
Drug Class/Mechanism of Action	HER2/HER3 Bispecific/block NRG1 from binding to HER3 and inhibiting subsequent NRG1-driven PI3K and MAPK signaling pathways
Sponsor	Merus N.V.
ODE/Division	OOD/Division of Oncology 2
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	July 3, 2023

*Note: This document must be uploaded into CDER's electronic document archival system as a **clinical review: REV-CLINICAL-24 (Breakthough Therapy Designation Determination) even if the review is attached to the MPC meeting minutes 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):**

   Zenocutuzumab is indiated for the treatment of patients with advanced unresectable or metastatic non-small cell lung cancer harboring a neuregulin 1 (NRG1) gene fusion (NRG1+ NSCLC) following progression with prior systemic therapy or who have no satisfactory alternative treatment options.

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** ☐YES ☒NO

3. **Was the BTDR submitted to a PIND?** ☐YES ☒NO
   If "Yes" do not review the BTDR. The sponsor must withdraw the BTDR. BTDR's cannot be submitted to a PIND.

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:

4. **Consideration of Breakthrough Therapy Criteria:**

   a. Is the condition serious/life-threatening[1])? ☒YES ☐NO

If 4a is checked "No," please provide the rationale in a brief paragraph below, and send the completed BTDDRT to Miranda Raggio for review so that the BTDR can be denied without MPC review. Once reviewed and cleared by Miranda this BTDR will be removed from the MPC calendar and you can skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

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

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 adequate and sufficiently complete to permit a substantive review?

☒ YES, the BTDR is adequate and sufficiently complete to permit a substantive review
☐ Undetermined
☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore, the request must be denied because (check one or more below):

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) ☐

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

If 4b is checked "No", BTDR can be denied without MPC review. Skip to number 6 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 the division feels MPC review is not required, send the completed BTDDRT to Miranda Raggio for review. Once reviewed, Miranda will notify the MPC Coordinator to remove the BTDR from the MPC calendar. If the BTDR is denied at the Division level without MPC review, the BTD Denial letter still must be cleared by Miranda Raggio, after division director and office director clearance.

If 4b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

6. 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.

7. 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.*

[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

- *Disease mechanism (if known) and natural history (if the disease is uncommon).*

Drug Description

Zenocutuzumab is a bispecific, humanized, full-length, IgG1 antibody which targets HER2 and HER3, preventing HER3 from associating with HER2, blocking NRG1 (or NRG1 fusion protein) from binding to HER3, and inhibiting the subsequent NRG1-driven PI3K and MAPK signaling pathways, thereby inhibiting tumor cell proliferation.

Information regarding NRG1 fusion positive NSCLC and the intended population for the proposed indication

Lung cancer is the second leading cause of cancer and leading cause of cancer-related mortality worldwide[1] and the leading cause of cancer-related deaths in the US[2].

NRG1 fusion positive (NRG1+) NSCLC accounts for less than 1% of NSCLC (<0.5%)[3,4]. These fusions are more common in patients who have adenocarcinoma and are non-smokers. The current natural history and prognostic value of NRG1 positive fusions is unknown.

The drug's relation to existing therapy(ies)

Currently there is no FDA-approved targeted therapy for patients with NRG1+ NSCLC.

Refer to Section 9 below for a summary of conventional systemic therapies that are currently available for NSCLC regardless of NRG1 fusion status.

Relevant regulatory history

On October 2022, a Type B meeting was held with the Sponsor to discuss a BLA submission for a tissue agnostic NRG1+ indication, with the data generated from the Sponsor's ongoing Phase 1 study and early access program. However, 78% of patients from this dataset had NRG1+ NSCLC or pancreatic ductal adenocarcinoma (57/71). The recommendation to the Sponsor was to pursue tumor-specific development. Tissue agnostic approval may be possible if promising activity is observed in additional tumor types and in an adequate number of patients in those tumor types.

8. 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.

Overall response rate (ORR) per RECIST v1.1 and duration of response (DoR) from the zenocutuzumab NRG1 clinical development program (a Phase 1 sponsor conducted study and an early access program) were submitted by the Sponsor to support this breakthrough therapy designation.

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.*

Both overall survival and progression-free survival have been used to support approvals in NSCLC. Additionally, clinically meaningful overall response rate (ORR) with adequate duration of response has been considered a predictor of clinical benefit and has been used to support accelerated approvals. In cases of tumors with low incidence, including NSCLC harboring less common genomic tumor aberrations, ORR of large magnitude associated with durable responses has been accepted to support regular 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

9. 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.*

Currently there are no FDA-approved targeted therapies for patients with NRG1+ NSCLC.

Patients with advanced NSCLC and tumors harboring NRG1 fusions are currently treated with conventional systemic therapies that are available for NRG1 fusion negative tumors, including first-line platinum-containing chemotherapy and/or an anti-PD-(L)1 antibody. Upon progression, subsequent available therapies include: single agent anti-PD-(L)1 antibodies (nivolumab, pembrolizumab, or atezolizumab) and single-agent chemotherapy (docetaxel or pemetrexed), or docetaxel in combination with ramucirumab.

Table 1. Biologics/Drugs Approved for 2nd-line Metastatic NSCLC

	Clinical Trial	Approval Endpoint (with 95% CI)
Single Agent Checkpoint Inhibitor		
Nivolumab	RCT* of nivolumab vs. docetaxel for nonsquamous NSCLC (Checkmate-057) N=582	mOS 12.2 vs. 9.4 mo (HR 0.72 [0.60, 0.89]) mPFS 2.3 vs. 4.2 mo (HR 0.92 [0.77, 1.11]) ORR 19% (15, 24) vs. 12% (9, 17)
Pembrolizumab	RCT of pembrolizumab vs docetaxel for PD-L1 positive metastatic NSCLC (KEYNOTE-010) N=689	Pembrolizumab 10 mg/kg vs. docetaxel mOS 12.7 vs. 8.5 mo (HR 0.61 [0.49, 0.75]) mPFS 4 vs. 4 mo (HR 0.79 [0.66, 0.94]) ORR 19% (15, 23) vs. 9% (7, 13)
Atezolizumab	RCT of atezolizumab vs. docetaxel for metastatic NSCLC (OAK) N=850	mOS 13.8 vs. 9.6 mo (HR 0.74 [0.63, 0.87]) mPFS 2.8 vs. 4.0 mo (HR 0.95 [0.82, 1.10]) ORR 14% (11, 17) vs. 13% (10, 17)
Single Agent Chemotherapy		
Docetaxel	RCT sotorasib vs. docetaxel (Codebreak 200) N=345	mOS 10.6 vs. 11.3 mo (HR 1.01 [0.77, 1.33]) mPFS 5.6 vs. 4.5 mo (HR 0.66 [0.51, 0.86]) ORR 28% (22, 35) vs. 13% (9, 19)
Pemetrexed	RCT pemetrexed vs. docetaxel (study JMEI) N=571	Exploratory OS analysis by histology (non-squamous) mOS 9.3 vs. 8.0 (HR 0.89 [0.71, 1.13])

Combination Therapy		
Docetaxel plus ramucirumab	RCT Ramucirumab/docetaxel vs. placebo/docetaxel (REVEL) N=1253	mOS 10.5 vs. 9.1 mo (HR 0.86 [0.75, 0.98]) mPFS 4.3 vs. 3 mo (HR 0.76 [0.68, 0.86]) ORR 23% (20, 26) vs. 14% (11, 17)

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

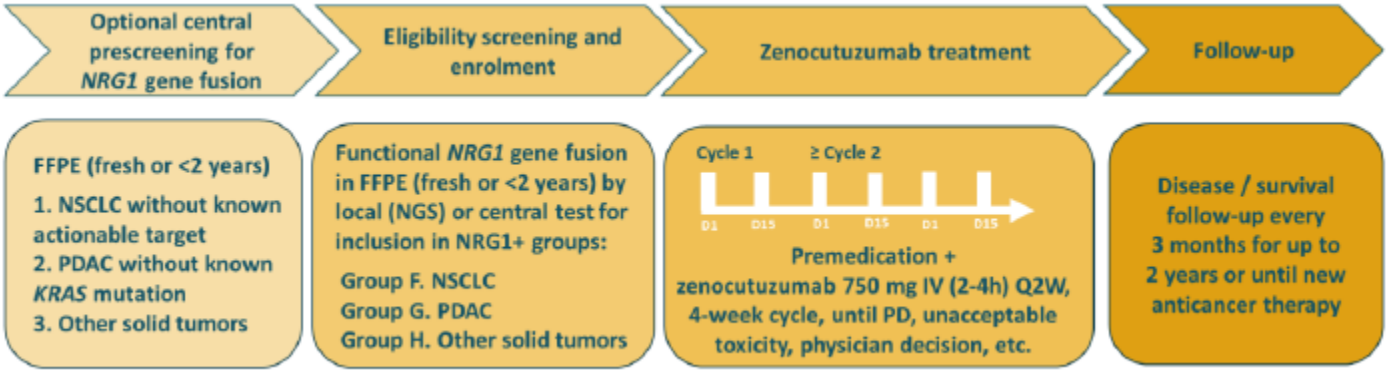
No other drugs have requested breakthrough therapy designation for the same indication or a very similar indication.

11. 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.

Data to support this BTDR are pooled from the ongoing Phase I eNRGy study and the Sponsor's expanded access program (EAP). All patients had NRG1 fusions identified at a central laboratory or in local qualified laboratories. Zenocutuzumab was administered intravenously (IV) every 2 weeks (Q2W) until disease progression, unacceptable toxicity, or withdrawal of consent. At the time of the data cut-off (February 1, 2023), 65 NSCLC patients positive for NRG1 fusions were enrolled (59 in the eNRGy study and 6 in the EAP). Of the 65 patients, 23 had received at least one line of prior therapy, 51 had received prior platinum-based chemotherapy and 36 received both prior platinum-based chemotherapy and immune-checkpoint inhibitor therapy. The subset of patients who received prior platinum chemotherapy is considered the most relevant dataset to support this BTDR.

Figure 1. Current Design of eNRGy Study



At the time of the data cut-off (February 1, 2023) 51 patients with NRG1+ NSCLC who had received prior platinum-based chemotherapy were enrolled and were evaluable for response (Table 2). Of these 51 patients, 17 patients had a confirmed response (ORR 34%, 95% CI 21, 49). Of this group, the percentage of responders with a duration of response lasting over at least 6 months was 59%. The median duration of response was 11.1 months (95% CI 7.4, not calculable). Review of data in the 36 patients with NRG1+ NSCLC who received prior platinum-based chemotherapy and prior

[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.

immune-checkpoint inhibitor therapy showed a similar ORR (33.3% [95% CI 19, 51]) and a duration of response of 7.4 months (95% CI 3.7, not calculable).

Table 2. Clinical Data Supporting BTDR

Studies	Trial Design(s)	No. of Patients	Treatment	Results to support BTD
eNRGy EAP	Single arm studies	51 patients platinum pre-treated (46 from eNRGy and 6 from EAP)	Zenocutuzumab 750 mg Q2W	ORR and mDoR for platinum pre-treated: 34% (95% CI 21, 49) and 11.1 (7.4, NC)

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

Safety data were provided for 156 NRG1+ patients treated with zenotucuzumab at a dose of 750 mg IV Q2W. Eighty-eight percent of patients experienced treatment-emergent adverse events (TEAEs) and 35% experienced Grade ≥3 TEAEs. Eleven percent experienced TEAEs resulting in treatment discontinuation and 3.8% experienced TEAEs resulting in death.

The most common TEAEs (all grade ≥15%) were diarrhea (28%), nausea (19%), fatigue (16%), and anemia (15%). The The most common ≥grade 3 TEAEs were anemia (3.8%), abdominal pain, AST increased, blood alkaline phosphatase increased, diarrhea, and fatigue (2.6% each). Infusion related reactions (IRRs) occurred in 14% of patients; all were grade 1-2 with none leading to treatment discontinuation.

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

☒ GRANT:

Provide brief summary of rationale for granting:

The Division notes that currently there is no FDA-approved targeted therapy for patients with NRG1+ NSCLC. The Division considers the ORR of 34% (95% CI 21, 49) with 59% of responses lasting at least 6 months observed with zenocutumab to be preliminary clinical evidence of a substantial improvement over the currently available therapies.

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:

13. 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):

The Division supports the Sponsor's plans to work toward BLA submission for the NSCLC and anticipates further meetings with the Sponsor to provide advice on this submission.

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:

14. List references, if any:

1. WHO, GLOBOCAN 2018: Estimated Cancer, Incidence, Mortality and Prevalence Worldwide in 2020. http://gco.iarc.fr/today/home
2. NCI, Surveillance, Epidemiology, and End Results Program: Cancer Stat Facts, 2019 https://seer.cancer.gov/statfacts/html/lungb.html
3. Jonna S, Feldman RA, Swensen J, Gatalica Z, Korn WM, Borghaei H, Ma PC, Nieva JJ, Spira AI, Vanderwalde AM, Wozniak AJ, Kim ES, Liu SV. Detection of NRG1 Gene Fusions in Solid Tumors. Clin Cancer Res. 2019
4. Liu S, Feldman R, Borghaei H, Gadgeel S, Ma P, Nieva JJ, Spira AI, Vanderwalde AM, Wozniak AJ, Jonna S, Kim ES. Incidence of Neuregulin1 (NRG1) gene fusions across tumor types. JCO 2018

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

16. 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 10/13/20 /M. Raggio

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/

YUFAN LIU
06/23/2023 11:21:04 AM

GAUTAM U MEHTA
06/30/2023 01:16:32 PM

BONNIE HARPREET MOORE
06/30/2023 01:18:07 PM

IND 156484

MEETING MINUTES

Merus N.V.
Attention: Penny Ng, DRSc, MBA, RAC
Executive Director, Global Regulatory Affairs
139 Main Street, Suite 302
Cambridge, MA 02142

Dear Penny Ng:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for zenocutuzumab (MCLA-128).

We also refer to the video conference between representatives of your firm and the FDA on October 21, 2022. The purpose of the meeting was to obtain the Agency's feedback on the clinical efficacy and safety data of NRG1+ patients from Study eNRGy and Early Access Program (EAP).

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

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

If you have any questions, email me at maritsa.stephenson@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Maritsa Stephenson, PharmD, BCPS
Regulatory Health Project Manager
Office of Regulatory Operations
Division of Regulatory Operations – Oncologic Diseases for DO2
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-BLA

Meeting Date and Time: October 21, 2022; 1:00—2:00pm, EST
Meeting Location: Teleconference

Application Number: 156484
Product Name: zenocutuzumab (MCLA-128)
Indication: NRG1+ Solid Tumors
Sponsor Name: Merus N.V.
Regulatory Pathway: 351(a) of the Public Health Service Act

FDA ATTENDEES (tentative)

Erin Larkins, MD, Supervisory Associate Director
Nicole Drezner, MD, Cross-Disciplinary Team Lead
Oladimeji Akinboro, MD, Clinical Reviewer
Claudia Miller, PhD, Nonclinical Team Lead
Kelie Reece, PhD, Nonclinical Reviewer
Jeanne Fourie-Zirkelbach, PhD, Clinical Pharmacology Team Lead
Sriram Subramaniam, PhD, Clinical Pharmacology Reviewer
Amatya Anup, PhD, Biometrics Team Lead
Michelle Marcovitz, PhD, Biometrics Reviewer
Maritsa Stephenson, PharmD, BCPS, Regulatory Health Program Manager

SPONSOR ATTENDEES

Lex Bakker, PhD, EVP and Chief Development Officer
Noémie Braekeveldt, PhD, Senior Manager Regulatory Affairs
Jim Ford, Executive Director, Clinical Trials
Lokesh Jain, PhD, VP Clinical and Bioanalytical Sciences, Clinical Development
Andrew Joe, MD, SVP Clinical Development and Chief Medical Officer
Bill Lundberg, MD, President and CEO
Penny Ng, DRSc, MBA, RAC, Executive Director Regulatory Affairs
Ashley Pereira, PharmD, SVP Regulatory Affairs
Viktoriya Stalbovskaya, PhD, VP Biometrics
Ernesto Wasserman, MD, SVP Clinical Development

FDA sent Preliminary Comments to Merus N.V. on October 28, 2022.

BACKGROUND

Regulatory History

On November 18, 2016, Merus N.V. (Merus) opened IND 131752 for the evaluation of zenocutuzumab in patients with HER2-amplified/expressing solid tumors of epithelial origin under the Division of Oncology Products 1 (DOP1).

In July 2020, FDA granted orphan drug designation to zenocuzutumab for the treatment of patients with pancreatic cancer. On December 18, 2020, FDA granted fast-track designation for zenocutuzumab for the treatment of patients with solid tumors harboring neuregulin 1 (*NRG1*) gene fusion that have progressed on standard of care therapy.

On May 10, 2021, IND 156484 was opened as an administrative split of IND 131752 to evaluate zenocutuzumab in cohorts of patients with *NRG1*-fusion positive tumors ("Study eNRGy") under the Division of Oncology 2.

On September 8, 2021, FDA and Merus held a Type B pre-BLA teleconference meeting to discuss a potential BLA submission for zenocutuzumab for a proposed tissue agnostic indication based on the pooled objective response rates (ORRs) from Study eNRGy and an expanded access protocol (EAP) for zenocutuzumab. FDA agreed that ORR, per central review, could support a marketing application in the context of the overall risk: benefit assessment of zenocutuzumab for the proposed indication. However, FDA did not agree with Merus' proposal to pool the efficacy results of Study eNRGy and the EAP and stated that Merus would have to provide justification for such pooling.

On, September 7, 2022, FDA received a Type B pre-BLA meeting request from Merus to discuss the development program of zenocutuzumab, specifically to obtain FDA's feedback on the clinical efficacy and safety data from Study MCLA-128-CL01 and Early Access Program (EAP) intended to support an initial BLA submission for the treatment of patients with advanced unresectable or metastatic *NRG1* fusion-positive cancer that has progressed following prior treatment (b) (4)

Clinical

NRG1 fusion-positive cancers are extremely rare with a pan-cancer incidence estimated at approximately 0.2% based on data from a single, multicenter, molecular survey of over 27 types of solid tumors in 21,858 patients in the U.S. (Jonna, 2019), with tumor-specific incidence ≤ 0.5% across all tumor types examined. There is scant data regarding the prognoses of patients with *NRG1* fusion-positive cancers, in general, and the clinical benefit they derive from treatment with tumor-appropriate standard-of-care systemic therapies.

Zenocutuzumab is a bispecific humanized IgG1 monoclonal antibody directed against the transmembrane receptor tyrosine kinases HER2 and HER3 and prevents the

heterodimerization of HER2 and HER3. Merus hypothesizes that the binding of zenocutuzumab to HER2 and HER3 blocks the binding of NRG1 and NRG1 fusion protein, thereby inhibiting the subsequent NRG1-mediated signaling through the PI3K and MAPK signaling pathways.

Merus proposes to submit a biologics license application (BLA) for zenocutuzumab for the treatment of patients with advanced unresectable or metastatic NRG1 fusion-positive cancer that has progressed following prior treatment (b) (4) The primary efficacy and safety data supporting the proposed BLA are derived from patients enrolled on Study eNRGy and the EAP and who were treated with zenocutuzumab 750 mg intravenously (IV) every 2 weeks (Q2W) in 4-week treatment cycles.

Study eNRGy is the dose-expansion phase of the first-in-human (FIH) dose-escalation and dose-expansion study for zenocutuzumab, Study MCLA-128-CL01. Study eNRGy includes the following dose-expansion cohorts:

- Group F: Patients with documented *NRG1* fusion-positive non-small cell lung cancer (NSCLC)
- Group G: Patients with documented *NRG1* fusion-positive pancreatic adenocarcinoma (PDAC)
- Group H: Patients with other documented *NRG1* fusion-positive solid tumors

The EAP for zenocutuzumab includes patients with *NRG1* fusion-positive cancers who are unable to participate in Study eNRGy due to one of the following reasons: inability to travel to the study site due to COVID-19 restrictions, other logistic constraints, or health concerns; or the treating physician's decision not to refer the patient to the study site.

To be eligible for enrollment in either Study eNRGy or the EAP, patients are required to have *NRG1* fusion-positive tumors as detected by next-generation-based sequencing (NGS) methods of DNA or RNA at a CLIA or other similarly certified laboratories. Patients in both studies are required to undergo tumor imaging every 8 weeks.

The primary endpoint of Study eNRGy is ORR per investigator assessment; its key secondary endpoint is duration of response (DoR) per investigator assessment. Other secondary endpoints include ORR and DoR per independent central review, progression-free survival (PFS) and overall survival (OS).

The key baseline patient demographic and disease-related characteristics are summarized in Table 1. The majority of patients in the pooled efficacy population had either NSCLC (57%) or PDAC (24%).

Table 1: Baseline patient characteristics in Study eNRGy and the EAP for zenocutuzumab.

	Study eNRGy FAS *N*=71	EAP analysis Set *N*=12	Pooled analysis population *N*=83
Age, years			
Median (range)	60 (22-86)	54 (34-81)	59 (22-86)
≥ 65, % (*n*)	31 (22)	33 (4)	31 (26)
Gender, % (*n*)			
Female	63 (45)	58 (7)	63 (52)
Race, %			
White	52 (37)	75 (9)	55 (46)
Asian	38 (27)	NA	33 (27)
Black/African-American	1.4 (1)	0	1.2 (1)
Other/Not reported	8.5 (6)	25 (3)	11 (9)
ECOG performance status, % (*n*)			
0	41 (29)	33 (4)	41 (33)
1	59 (42)	42 (5)	58 (47)
≥ 2	0	8.3 (1)	1.2 (1)
Primary tumor type, % (*n*)			
NSCLC	58 (41)	50 (6)	57 (47)
Pancreatic adenocarcinoma	23 (16)	33 (4)	24 (20)
Breast cancer	8.5 (6)	8.3 (1)	8.4 (7)
Cholangiocarcinoma	4.2 (3)	0	3.6 (3)
Colorectal cancer	4.2 (3)	0	3.6 (3)
Other solid tumors	2.8 (2) [a]	8.3 (1) [b]	3.6 (3) [c]
Stage at study entry, % (*n*)			
Stage IIIB	2.8 (2)	NA	NA
Stage IV	97 (69)	NA	NA
Prior lines of systemic therapy			
Median (range)	2 (0-9)	2 (0-5)	2 (0-9)
No prior systemic therapy, % (*n*)	9.9 (7)	NA	9.6 (8)

Abbreviations: EAP=expanded access protocol; ECOG=Eastern Cooperative Oncology Group; FAS=full analysis set; *N*=number; NA=not available; NSCLC=non-small-cell lung cancer.
[a] Other solid tumors were endometrial sarcoma and renal cell carcinoma (*n*=1 each).
[b] Other solid tumor was cancer of unknown primary (*n*=1).
[c] Other solid tumors were cancer of unknown primary, endometrial sarcoma, and renal cell carcinoma (*n*=1 each).

The ORR and DoR per central review in patients with measurable disease at baseline (by central review), presented by tumor type and fusion partners, in Study eNRGy, the EAP, and the pooled efficacy population are summarized in Table 2.

Table 2: ORR by major tumor types, per central review, in the pooled efficacy population of Study eNRGy and the expanded access program for zenocutuzumab (DCO: June 30, 2022)

	Study eNRGy (*N*=65)	EAP (*N*=7)	Pooled population (*N*=72)
ORR, % (95% CI)	31 (20, 43)	57 (18, 90)	33 (23, 45)
CR, %	1.5	0	1.4
PR, %	29	57	32
ORR By tumor type, % (95% CI)			
NSCLC	32 (18, 50)	50 (6.8, 93)	35 (21, 52)
PDAC	47 (21, 73)	50 (1.3, 99)	47 (23, 72)
Other solid tumors	7.1 (0.2, 34) [a]	100 (2.5, 100)	13 (1.7, 41)
ORR by fusion partner, % (95% CI)			
CD74 (*n*=26)	-	-	31 (14, 52)
SLC3A2 (*n*=10)	-	-	50 (19, 81)
ATP1B1 (*n*=8)	-	-	63 (25, 92)
SDC4 (*n*=5)	-	-	20 (0.5, 72)
Other fusion partners (*n*=23)	-	-	22 (7.5, 44) [b]
Median DoR, months (95% CI)	9.1 (4.0, NC)	NR (3.7, NC)	9.1 (4.0, 16.6)
Responses ≥ 6 months, % (95% CI)	64 (37, 82)	50 (5.8, 85)	61 (37, 79)
NSCLC	55 (23, 78)	50 (0.6, 91)	54 (25, 76)
PDAC	86 (33, 98)	0 (NC, NC)	70 (22, 92)

Abbreviations: CI=confidence interval; CR=complete response; CRC=colorectal cancer; DCO=data cut-off date; DoR=duration of response; EAP=expanded access protocol; *n*/*N*=number; NC=not calculable; NR=not reached; NSCLC=non-small-cell lung cancer; ORR=objective response rate; PDAC=pancreatic ductal adenocarcinoma; PR=partial response.
[a] In Study eNRGy, partial response, per central review, was documented for 1 patient with colorectal cancer.
[b] Partial responses, per central review, were documented for 1 patient each with the following fusion partners: *SLC4A4*, *APP*, *ASPH*, *VAMP2*, and *AGRN*.

For the pooled population (n=72) in Table 2, 40 were in the NSCLC group, 17 were in the PDAC group, and 15 were in the other solid tumors group. Based on a footnote on Table 30 in the meeting background package, it appears one patient assigned to the other solid tumors group (and included in the other solid tumors group in the data presented in the above table) had a diagnosis of NSCLC.

The key exposure and safety/tolerability data for the overall primary safety population, which includes patients in Study eNRGy and the EAP who received zenocutuzumab 750 mg IV Q2W, are summarized in Table 3.

Table 3: Summary of safety/tolerability for patients in the pooled primary safety population (DCO: June 30, 2022).

	N=121
Exposure	
Median, months (minimum – maximum)	4.4 (0.1 – 23.6)
≥ 6 months, % (*n*)	43 (52)
≥ 12 months, % (*n*)	15 (18)
Safety	
Any Grade TEAEs,[a] % (*n*)	88 (106)
Grade 3-4 TEAEs,[b] % (*n*)	36 (44)
SAEs,[c] % (*n*)	25 (30)
TEAEs resulting in death,[d] % (*n*)	4.1 (5)
Tolerability	
TEAEs resulting in treatment discontinuation,[e] % (*n*)	6.6 (8)
TEAEs resulting in treatment delay, % (*n*)	0.8 (1)
TEAEs resulting in treatment interruption, % (*n*)	26 (31)
AESIs, % (*n*)	43 (52)
IRRs,[f] % (*n*)	15 (18)
Diarrhea,[g] % (*n*)	32 (39)
Decreased cardiac ejection fraction,[h] % (*n*)	2.5 (3)

Abbreviations: AESIs=adverse events of special interest; DCO=data cut-off date; IRRs=infusion-related reactions; *n*/*N*=number; SAEs=serious adverse events; TEAEs=treatment-emergent adverse events.
[a] The most frequent any grade TEAEs (≥15%) were diarrhea (32%); nausea (21%); dyspnea (16%); and, fatigue (15%).
[b] The most frequent Grade 3-4 TEAEs (≥2%) were fatigue (3.3%); diarrhea (2.5%); nausea (2.5%); aspartate aminotransferase increased (2.5%); blood alkaline phosphatase increased (2.5%); and anemia (2.5%).
[c] The most frequent SAEs (≥2%) were dyspnea (2.5%) and nausea (2.5%).
[d] TEAEs resulting in death were cardiac failure (*n*=1); respiratory failure (*n*=1); lung disorder (*n*=1); NSCLC (*n*=1); and vaginal hemorrhage (*n*=1).
[e] TEAEs resulting in treatment discontinuation were cardiac failure (*n*=1); respiratory failure (*n*=1); dyspnea (*n*=1); ataxia (*n*=1); muscular weakness (*n*=1); back pain (*n*=1); general physical health deterioration (*n*=1); and cerebrovascular accident, intracranial hemorrhage, and myocardial infarction (all occurred in the same patient).
[f] No patient experienced Grade 3-4 IRRs.
[g] Three patients (2.5%) experienced Grade 3-4 diarrhea.
[h] One patient (0.8%) experienced Grade 3 decreased ejection fraction.

Contents of the proposed BLA

- The proposed primary efficacy population is comprised of 83 patients with NRG1 fusion-positive solid tumors who received zenocutuzumab 750 mg Q2W on either Study eNRGy or the EAP, of whom 72 had measurable disease by central review at baseline.
- The proposed primary safety population is comprised of 121 patients with NRG1 fusion-positive solid tumors who received at least one infusion of zenocutuzumab 750 mg Q2W on either Study eNRGy or the EAP. Supportive safety data will be provided from 248 patients enrolled in the expansion portion of Study MCLA-128-CL01 and in the EAP.
- A single interim Clinical Study Report (CSR) will be provided for the expansion portion of Study MCLA-128-CL01 which includes the eNRGy study cohorts.
- The narrative portions of the Integrated Summary of Safety (ISS) and Integrated Summary of Efficacy (ISE) will be provided in Module 2 with tables and appendices included in Module 5.
- Merus proposed to include a Summary of Clinical Pharmacology, tabular listing of all clinical studies, bioanalytical method validation and bioanalytical study reports, reports for noncompartmental pharmacokinetic (PK), population PK, exposure-response (E-R) and immunogenicity analyses, and associated datasets.

DISCUSSION OF FDA RESPONSES TO SPONSOR QUESTIONS

Clinical

1. Does the Agency agree that the NRG1+ cancer population enrolled in the eNRGy study and EAP represents a population which has no established alternative efficacious therapies available?

   FDA Response: We agree that the subgroup of patients enrolled in the eNRGy study and EAP who had received prior available standard therapies for their respective tumor type comprise a population with no established alternative therapies. For example, the subgroup of patients with NSCLC who received both prior platinum-based chemotherapy and an anti-PD-(L)1 agent would be considered a population for which there are few efficacious alternative therapies. However, there is not sufficient data available to conclude that standard FDA-approved treatment regimens for patients without actionable genomic alterations are not efficacious in patients with NRG1 fusion-positive cancer.

   Sponsor Response: Sponsor accepts FDA comments.

   Discussion During the meeting: No discussion occurred.

2. Does the Agency agree that the available clinical data package provides sufficient clinical evidence to characterize the benefit and risk of zenocutuzumab in adult patients with advanced unresectable or metastatic NRG1+ cancer to support a BLA filing?

   FDA Response: No, we do not agree.

   The efficacy population is primarily comprised of patients with two tumor types (NSCLC and pancreatic adenocarcinoma) and is not reflective of the range of tumor types known to have *NRG1* gene fusions. Together, patients with the two tumor types comprised over 78% of every efficacy and safety analysis population in this submission.

   In addition, although the study enrolled patients with eight tumor types, centrally confirmed responses were observed in only four tumor types: NSCLC, pancreatic adenocarcinoma, breast cancer (one response), and colorectal carcinoma (one response), and the ORR for the subgroup of patients with solid tumors was low. Although we acknowledge the limited number of patients with tumor types other than NSCLC and pancreatic adenocarcinoma, the current results and response pattern are not adequate to support a tissue agnostic indication.

   Regarding the subgroup of patients with NSCLC, which represents the largest single tumor type within the overall efficacy population, the reported ORR of 35%

(95% confidence interval [CI]: 21, 50) may be considered promising in a patient population previously treated with platinum-based chemotherapy with or without anti-PD-L(1) antibody. However, given the heterogeneity of the population with respect to prior therapies received, including patients who were treatment naïve and previously treated patients who had never received combination chemotherapy, we are not able to determine if the observed ORR represents a substantial improvement over currently available therapies. Given differences in available therapy based on previous treatment received, in order for us to provide informed feedback, the ORR results for patients with NSCLC should be presented separately for treatment-naïve patients, previously treated patients who have never received platinum-based chemotherapy, and patients previously treated with platinum-based chemotherapy.

We recommend that you consider the following options for development of zenocutuzumab:

- Pursue separate tumor-specific clinical development programs for zenocutuzumab in the tumor types most represented in Study energy, NSCLC and PDAC. If you wish to discuss development for a PDAC indication, you should request a meeting with the Division of Oncology 3 (DO3), which manages this tumor type.
- Alternatively, or in addition, you may continue to enroll patients with other tumor types harboring *NRG1* fusions on the eNRGy study to potentially demonstrate objective responses in a greater variety of solid tumor types and a higher ORR in the subgroup of patients with solid tumors other than NSCLC and PDAC to support a future marketing application for a tissue agnostic indication.

Given that the currently available data are not considered adequate to support the filing of a BLA, questions regarding the data needed to verify clinical benefit and regarding the content and format of a BLA are premature.

Sponsor Response: Sponsor appreciates FDA's guidance and acknowledges its recommendation to consider tumor-specific clinical development programs or continued development of a tissue-agnostic indication. Respectfully, Sponsor remains committed to pursuit of a tumor-agnostic indication, and therefore, would like to discuss two development options:

- Option 1: Tissue-agnostic development in NRG1+ cancer; and
- Option 2: Tissue-agnostic development in NRG1+ cancer, presently limited to NSCLC and PDAC, (b) (4) (under Additional Question Related to Question 2).

The development program for zenocutuzumab in NRG1+ cancer has been consistent with the previous FDA feedback provided at the informal teleconference with the DO1, DO2, and DO3 teams in April 2021. The development program is also consistent with the EOP discussion in Sept 2021 and with the recently issued FDA draft guidance on "Tissue Agnostic Drug

Development in Oncology (Oct 2022)" (FDA, 2022). The development of zenocutuzumab is appropriate for tissue agnostic drug development in NRG1+ cancer, for three compelling reasons: (i) strong biological rationale; (ii) zenocutuzumab's mechanism of action and non-clinical evidence; and (iii) clinical evidence shown across representative NRG1+ tumor types and molecular alterations (*Per* Draft Guidance at IIIA-B).

Biological rationale: NRG1 is a growth factor, and NRG1+ cancer is dependent on NRG1 for growth and carcinogenesis. Merus has identified this new molecular—biomarker-defined cancer (i.e., NRG1+ cancer), actionable across tumor types driven by the presence of NRG1 fusions.
Zenocutuzumab's mechanism of action: Zenocutuzumab, a Her2xHer3 bispecific, is uniquely suited to address this oncogenesis, blocking NRG1+ from binding Her3, and blocking the subsequent joining of Her2 and Her3 that otherwise causes uncontrolled tumor growth and survival. Indeed, nonclinical evidence has shown zenocutuzumab arrests NRG1+ tumor growth and shrinks NRG1+ cancer in *in vivo* models across multiple NRG1+ cancer types and molecular alterations, including NSCLC, PDAC, breast cancer and ovarian, and six molecular alterations.

Zenocutuzumab's clinical activity: Sponsor's clinical experience has been consistent. Upon enrolling a representative cross section of NRG1+ cancer, patients experienced centrally confirmed responses in lung, pancreatic, breast, and CRC, and responses across nine different NRG1+ molecular alterations. Other clinically meaningful levels of activity (including other locally assessed responses in breast cancer and cholangiocarcinoma) have been observed as discussed further in this document (see Appendix 1)[2].
Importantly, these are all very different tumor types with very different risk factors and ordinarily would have different mechanisms of carcinogenesis – and yet, in NRG1+ cancer they all can respond to zenocutuzumab therapy. This is precisely the kind of molecular alteration and targeted therapy the Draft Guidance envisioned can and should be pursued as a tumor-agnostic development because of the appropriateness in "*extrapolation of efficacy findings across multiple subsets [of patients and cancer types] despite the low frequency or absence of patients in some subsets.*" (FDA, 2022 Section II).
Merus fully acknowledges the Division's feedback and would like to discuss why the totality of strong biological rationale and clinical data supports the filing of a BLA in a molecular targeted therapy of NRG1+ cancer. The following addresses the three concerns raised in the feedback, with rationale: (i) the efficacy population represents an appropriate distribution of the NRG1+ cancer population; (ii) within the efficacy population, the response rates observed both

[2] Sponsor acknowledges that ORR and DOR are the established surrogate endpoints; however, ORR and DOR may not fully capture the clinical benefit and activity of zenocutuzumab, therefore presenting supplemental information on breast cancer, cholangiocarcinoma, and colorectal cancer.

across tumor types and molecular alterations—bolstered by nonclinical and clinical activity in additional cancer types—supports an application; and (iii) the clinical benefit is not compromised in the subset of previously treated NRG1+ cancer, as demonstrated by the consistent ORR among the patients treated.

1. The efficacy population represents an appropriate distribution of the NRG1+ cancer

   The distribution of tumor types in our clinical trial is consistent with those documented in the literature (Jonna, 2019), (b) (4) screening, and (b) (4) dataset. NSCLC and PDAC are the most frequent followed by breast and colorectal.

Table 1. Distribution of NRG1+ cancer in tumor types

	(b) (4) (n=83)	(b) (4) [1] (n=154)	(b) (4) [2] (n=44)	Jonna 2019[3] (n=41)
NSCLC	56.6%	40.9%	50.0%	61.0%
Pancreatic	24.1%	9.1%	15.9%	7.3%
Breast	8.4%	14.3%	20.5%	4.9%
CRC	3.6%	5.8%	2.3%	2.4%
Ovarian	-	9.7%	-	7.3%
RCC	1.2%	-	-	2.4%
Sarcoma	1.2%	-	-	2.4%
Bladder	-	1.9%	-	2.4%
Cholangiocarcinoma	3.6%	3.9%	2.3%	7.3%
Head and Neck	-	-	-	-
Prostate	-	1.9%	2.3%	-
Endometrial	-	1.3%	-	-
CUP	1.2%	3.9%	6.8%	-
Unknown	-	-	-	2.4%
Neuroendocrine	-	0.6%	-	-
Soft Tissue	-	0.6%	-	-
Esophageal	-	1.9%	-	-
Salivary	-	0.6%	-	-
Vaginal	-	1.3%	-	-
Vulvar	-	0.6%	-	-
Small intestine	-	0.6%	-	-
Glioblastoma	-	0.6%	-	-

n (number of NRG1+ cancer patients)

[1]Correspondence between Merus and (b) (4) (Aug 2022), confidential and competitive sensitive information per trade agreement
[2]Correspondence between Merus and (b) (4) pathologist (Oct 2022), confidential and competitive sensitive information per trade agreement
[3]Jonna, 2019: Jonna, S., Feldman, R.A., Swensen, J., Gatalica, Z., Korn, W.M., Borghaei, H., Ma, P.C., Nieva, J.J., Spira, A.I., Vanderwalde, A.M., et al. (2019). Detection of NRG1 Gene Fusions in Solid Tumors. Clin Cancer Res 25, 4966-4972.

2. Response Rates Observed Support a BLA Filing

As noted in the Draft Guidance, Sponsor has demonstrated responses across an appropriate spectrum of tumor types and appropriate spectrum of molecular alterations in nonclinical (Table 2) and clinical settings (Figure 1) (FDA, 2022 Draft Guidance at IV-B). Responses are observed across four tumor types and response rates are consistent, as represented in the efficacy population (Table 2).

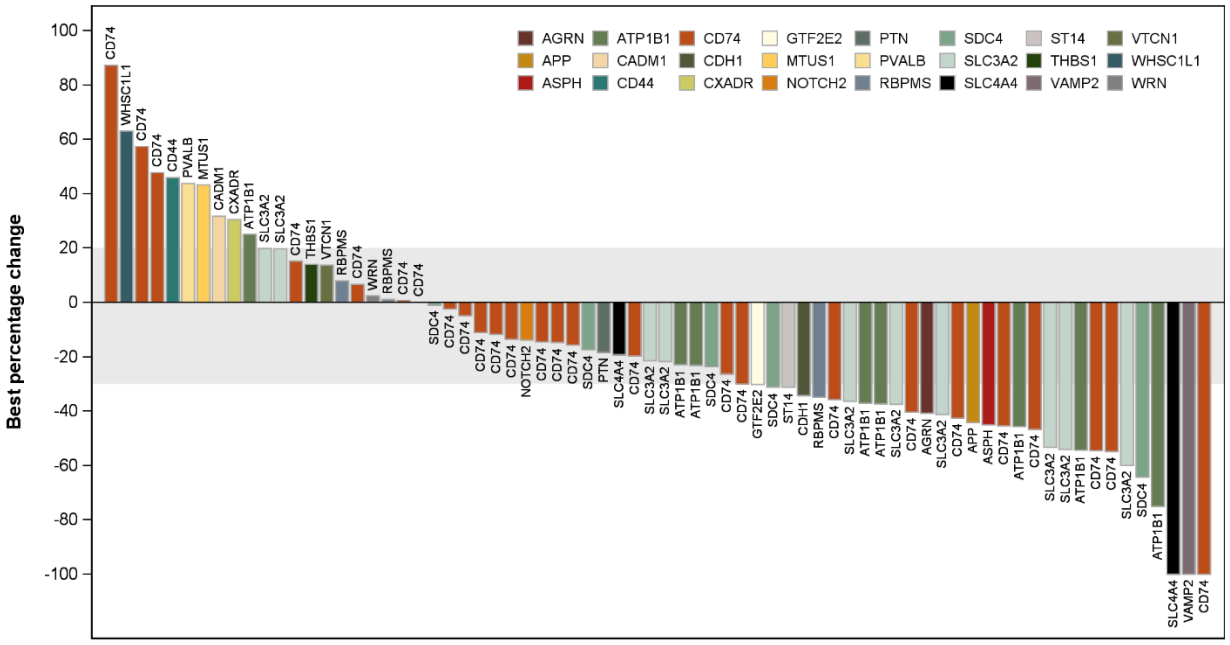
Table 2. Anti-tumor activity of zenocutuzumab

Tumor type	Activity in nonclinical PDX models	Activity in clinical setting			
		ORR Local assessment		ORR Central assessment	
			Mean (95%CI)		Mean (95% CI)
NSCLC	3 PDX models ▪ 2 expressing a CD74-NRG1 fusion ▪ 1 expressing a SLC3A2-NRG1 fusion		39% (25, 55)		34% (20, 51)
PDAC	1 PDX model ▪ expressing APP-NRG1 fusion		45% (23, 69)		47% (23, 72)
Breast Cancer*	1 PDX model ▪ expressing DOC4-NRG1 fusion		40% (5, 85)		17% (0.4, 64)
CRC*	-		0		33% (1, 91)

Cholangiocarcinoma*	-		33% (1, 91)		0
RCC	-		SD (NA)		SD (NA)
CUP	-		SD (NA)		-
Endometrial sarcoma	-		PD (NA)		PD (NA)
Ovarian Cancer*	2 PDX models ▪ 1 expressing CLU-NRG1 fusion ▪ 1 expressing TNFRSF10B-NRG1 fusion		-		-

PDX = patient-derived xenograft; SD = stable disease; PD = progressive disease; NA = not applicable
*Additional clinical activities in these tumor types are described in Appendix 1.

In addition, we have demonstrated clinically confirmed responses across nine different molecular alterations (see Table 31 in the Pre-BLA Meeting Package). Given the clinically meaningful activity in multiple tumor types as well as across multiple molecular alterations (see Figure 1), efficacy of zenocutuzumab can be generalized across NRG1+ cancer.
Figure 1. Best percentage change by fusion partner



Indeed, this is consistent with the Draft Guidance as zenocutuzumab's development as a NRG1+ tissue agnostic program, which can be generalizable to other rare, infrequent NRG1+ tumor types.
The overall ORR of 33% (95% CI, 23, 45) by central radiology review is consistent with the EOP discussion (Sep 2021) that a targeted ORR of 31.1% (95% CI, 18.2, 46.4) in the context of durability of responses, safety profile, and consistent efficacy (ORRs with overlapping 95% CI) across four tumor types in a total sample size of 55 patients may be reasonable for the overall risk/benefit assessment for the therapy in the tissue-agnostic indication setting.

3. The Clinical Benefit is Consistent

   With respect to prior therapies received by NSCLC patients, the majority of patients (72.5%) were exposed to platinum-based chemotherapy combinations and the observed ORRs are consistent with and without the inclusion of the platinum-naïve patients (see Table 3).

4. Overall Conclusion

   The current dataset provides evidence of a favorable risk benefit of zenocutuzumab in NRG1+ cancer to support an application under Subpart E for this extremely rare and serious cancer type.
   Based on the frequency of NRG1+ cancer observed to date, evidence from additional tumor types would take years to acquire, and in the interim, zenocutuzumab would not be available to those patients with NRG1+ cancer who may benefit. Moreover, physicians would not be screening patients for this actionable molecular alteration. Today there

exists sufficient evidence to support zenocutuzumab for the treatment of NRG1+ cancer.
Merus acknowledges the requirement to confirm benefit under accelerated approval and Merus is committed to continuing to acquire additional efficacy and safety data from zenocutuzumab treated NRG1+ cancer patients in the ongoing eNRGy study and EAP.
The tumor agnostic development approach was developed in alignment with the FDA at the EOP meeting in 2021. At that time the frequency was understood then as it is today that the population is comprised primarily of lung, pancreatic, breast and CRC patients. At that time, Sponsor's efficacy population was comprised of essentially the same ratio of these cancer types, and the ORR and durability today exceeds what was previously presented upon FDA's recommendation to seek a tumor agnostic approval.

- Does the Agency agree with the tumor agnostic indication, based on the additional rationale provided above, and that the available clinical data provides sufficient information to support a BLA filing?

Discussion During the Meeting: FDA acknowledged Merus' response. Merus stated that the patient enrollment is reflective of the distribution of patients with NRG1 fusion positive tumors, with the majority having lung, breast, pancreatic, and colon cancers. FDA stated that the magnitude of responses differs across tumor types (e.g., an ORR of 17% in patients with breast cancer and of 33% in 3 patients with colon cancer) and that given this data and the small number of tumor types in which responses were observed, the current data are not adequate to support a tissue agnostic indication.

Additional Question Related to Question 2 – Clinical Package for BLA Filing for Specific Tumor Type(s)

Sponsor strongly prefers continued development in a tissue-agnostic rather than a tumor-specific program, because Sponsor recognizes that the biomarker-defined disease (NRG1+ cancer) is more appropriate than individual tumor-specific development. Sponsor has defined a new disease NRG1+ cancer that is actionable and for which zenocutuzumab has efficacy in multiple tumor types. Therefore, would the Agency agree on continued tissue-agnostic development with an initial registration application of NRG1+ cancer focused on NSCLC and PDAC histologies. Reasons for this include:

- The available data of a total of 58 patients with NRG1+ NSCLC and PDAC in the efficacy population is adequate to support the filing of the initial BLA with ORR 37.9% (95% CI; 25.5, 51.6).

- Strong biological rationale, mechanism of action, preclinical and clinical data supporting a tissue-agnostic approach (as described above).

- The efficacy population is primarily comprised of patients with NRG1+ NSCLC and PDAC with consistent safety and efficacy across tumor types.

- Consistent with our EOP interaction, we have agreement that durable ORR is an adequate endpoint for assessing clinical benefit in NRG1+ cancer, whereas ORR would not be accepted as a standalone endpoint for an indication in PDAC. A randomized study with a time to event endpoint would not be viable with NRG1+ PDAC in this setting given the rarity of the disease. The zenocutuzumab-treated PDAC patients are deriving significant clinical benefit with an ORR of 47% (95%; 23, 72) and DOR of 9.1 months.

Therefore, the Sponsor proposes the following indication for the initial BLA based on the available clinical data as described in the preliminary Pre-BLA meeting package:

Treatment of patients with advanced unresectable or metastatic neuregulin 1 (NRG1) gene fusion-positive (NRG1+ cancer) in the tumor types of NSCLC and PDAC that have progressed following prior treatment (b) (4)

- **Does the Division agree that with this alternative registrational proposal for NRG1+ cancer?**

Discussion During the Meeting: Merus inquired whether FDA would consider an initial application(s) for two tumor types (NSCLC and PDAC) followed by a tissue agnostic marketing application. FDA stated that two separate BLAs could potentially be submitted in the future for NSCLC and PDAC indications after further discussion with DO2 for NSCLC and DO3 for PDAC regarding what data would be needed to support such applications. Tissue agnostic development to potentially support a future marketing application for a tissue agnostic indication could continue in the eNRGy study.

FDA stated that, based on the currently available data, Merus would likely need to evaluate activity in additional previously treated patients with NSCLC and whether the data would be adequate to potentially support a marketing application would be dependent on the magnitude and durability of responses and the overall risk:benefit assessment.

Additional follow-up to FDA feedback on responses of NSCLC patients

ORR results for patients with NSCLC are presented separately for treatment-naïve patients, previously treated patients who have never received platinum-

based chemotherapy, and patients previously treated with platinum-based chemotherapy in Table 3 below. This demonstrates ORR of 34.5% in 29 patients previously treated with platinum-based chemotherapy have clinical benefits from zenocutuzumab monotherapy treatment.

Table 3. ORR by Prior Therapies (Naïve vs. Platinum-Based Prior Treatment)

	No prior systemic therapy	Pretreated with chemo, no platinum	Pretreated with platinum-based combinations	Total
# of patients with measurable disease	6	5	29	40
Responders (n), ORR (%)	3 (50.0)	1 (20.0)	10 (34.5)	14 (35.0)

Discussion During the meeting:

3. For the proposed NRG1+ cancer indication, does the Agency agree that the results demonstrate a positive benefit-risk assessment to support an accelerated approval in the proposed indication and that conversion to traditional approval may be based on 1) durable ORR from enrolling additional patients with a follow-up of a minimum of 6 months and 2) additional follow-up efficacy and safety data of the ongoing patients in the initial BLA?

FDA Response: See FDA response to Question 2.

Sponsor Response: Sponsor accepts FDA comments.

Discussion During the meeting: No discussion occurred.

4. Based on the observed safety profile of zenocutuzumab, does the Agency agree with the proposal to not submit a Medication Guide or a Risk Evaluation and Mitigation Strategy (REMS) for the use of zenocutuzumab in the proposed indication of NRG1+ cancer?

FDA Response: See FDA response to Question 2.

Sponsor Response: Sponsor accepts FDA comments.

Discussion During the meeting: No discussion occurred.

Regulatory

5. Does the Agency agree with the scope of the Safety Update and Merus' proposal to submit updated safety and efficacy data in the 90 Day Safety Update Report (SUR) if Priority Request is granted and that the new data would not impact the PDUFA date?

   FDA Response: See FDA response to Question 2.

   Sponsor Response: Sponsor accepts FDA comments.

   Discussion During the meeting: No discussion occurred.

6. Based on the feedback from the FDA on the comment noted in the Request for Proprietary Name Review of BIZENGRI ("Conditionally Acceptable" Letter dated 21 July 2022), Merus intends to update the labelled vial strength to 375 mg to avoid confusion. Does the Agency concur?

   FDA Response: We acknowledge your response. The label claim of strength will be a review issue based on the product quality attributes and strength proposed in a BLA.

   Sponsor Response: Sponsor accepts FDA comments.

   Discussion During the meeting: No discussion occurred.

7. Does the Agency agree with the layout of the proposed BLA Table of Contents and the follow-up proposal for data presentation of the non-NRG1+/HER3+ patients in the EAP to support review of the BLA?

   FDA Response: See FDA response to Question 2.
   Sponsor Response: Sponsor accepts FDA comments.

   Discussion During the meeting: No discussion occurred.

8. Does the Agency agree with the proposed list of items that may be provided during the BLA filing review period?

   FDA Response: See FDA response to Question 2.

   Sponsor Response: Sponsor accepts FDA comments.

   Discussion During the meeting: No discussion occurred.

9. Does the Agency wish to schedule an application orientation meeting with Merus after submission of the BLA to outline the major components of the BLA?

FDA Response: See FDA response to Question 2.

Sponsor Response: Sponsor accepts FDA comments.

Discussion During the meeting: No discussion occurred.

ADDITIONAL COMMENTS

Clinical Pharmacology

The content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support a marketing application should be consistent with FDA Guidance for Industry, "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format". 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. We have the following advice regarding any future original BLA submission.

10. Address the following questions in the Summary of Clinical Pharmacology:
    a. 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.
    b. What are the exposure-response relationships for efficacy, safety and biomarkers?
    c. 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?
    d. 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:

11. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.
12. 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.
13. 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.
    a. 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.

b. Identify individual subjects with dosage modifications; the time to the first dose reduction, interruption or discontinuation; the reasons for dosage modifications in the datasets.

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

    Refer to the pharmacometric data and models submission guidelines.

15. Submit the following information and data to support the population pharmacokinetic analysis:
    a. SAS transport files (*.xpt) for all datasets used for model development and validation
    b. 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
    c. 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)
16. Submit a study report describing exploratory exposure-response (measures of effectiveness, biomarkers and safety) relationships in the targeted patient population.
17. Refer to Guidance for Industry for population PK, exposure-response relationships, and pharmacometric data and models submission guidelines. Use the laboratory analysis dataset (adlb.xpt) for the laboratory-based adverse reactions and the adverse event analysis dataset (adae.xpt) for the non-laboratory-based adverse reactions (individual and pooled terms as appropriate) to evaluate the exposure-response relationship for safety and the effect of intrinsic and extrinsic factors on safety based on the maximum toxicity grade compared to baseline.
18. Include a variable that identifies the maximum toxicity grade compared to baseline for laboratory-based adverse reactions in laboratory analysis dataset (adlb.xpt) and for non-laboratory-based adverse reactions (individual or pooled where applicable) in adverse event analysis dataset (adae.xpt) to support these analyses. A description of the pooled non-laboratory-based adverse reactions should be provided in the reviewer guide and consistent with common pooled terms used to inform labeling if applicable.

References

1. Jonna S, Feldman RA, Swensen J, Gatalica Z, Korn WM, Borghaei H, et al. Detection of NRG1 gene fusions in solid tumors. *Clin Cancer Res.* 2019;25(16):4966-72.
2. Drilon A, Duruisseaux M, Han JY, Ito M, Falcon C, Yang SR, et al. Clinicopathologic features and response to NRG1 fusion-driven lung cancers: the eNRGy1 global multicenter registry. *J Clin Oncol.* 2021;39(25):2791-802.

Sponsor Response: Sponsor accepts FDA comments.

Discussion During the meeting: No discussion occurred.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our September 9, 2022, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VII. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at FDA.gov.[3]

[3] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm

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.[4]

FDARA REQUIREMENTS

Sponsors 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.
Meeting 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 the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, to ensure open lines of dialogue before and during their drug development process.

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.[5]

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[6] and Pregnancy and Lactation Labeling Final Rule[7] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for

[4] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology
[5] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[6] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[7] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

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 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.

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.[8]

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.[9]

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).

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested 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*

[8] http://www.fda.gov/ectd
[9] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

Specifications.[10]

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

- Assessment Aid[12]

NONPROPRIETARY NAME

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

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

[10] https://www.fda.gov/media/85061/download
[11] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program
[12] https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project

collection of information.

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

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

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/

MARITSA T STEPHENSON
11/15/2022 02:44:26 PM

IND 156484

MEETING MINUTES

Merus N.V.
Attention: Noémie Braekeveldt Ph.D.
Manager, Regulatory Affairs
Merus US, 139 Main Street, Suite 302
Cambridge, MA 02142

Dear Dr. Braekeveldt:[1]

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

We also refer to the teleconference between representatives of your firm and the FDA on September 8, 2021. The purpose of the meeting was to discuss the proposed data package to support a BLA for the use of zenocutuzumab as treatment for patients with *neuregulin 1* (*NRG1*) gene fusion-positive advanced unresectable or metastatic cancers that have progressed following prior treatment (b) (4)

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

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

If you have any questions, call me at maritsa.stephenson@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Maritsa Stephenson, PharmD, BCPS
Regulatory Health Project Manager
Office of Regulatory Operations
Division of Regulatory Operations – Oncologic Diseases for DO2
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes
- Sponsor's Presentation Slides

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	End of Phase
Meeting Date and Time:	September 8, 2021; 4:00pm – 5:00pm, EST.
Meeting Location:	Teleconference
Application Number:	156484
Product Name:	MCLA-128 (zenocutuzumab)
Indication:	Treatment of patients with *neuregulin 1* (*NRG1*) gene fusion-positive advanced unresectable or metastatic cancers who have progressed following prior treatment (b) (4)
Sponsor/Applicant Name:	Merus N.V.
Regulatory Pathway:	351(a)of the Public Health Service Act
Meeting Chair:	Nicole Drezner, MD
Meeting Recorder:	Maritsa Stephenson

FDA ATTENDEES

Harpreet Singh, MD, Director DO2
Nicole Drezner, MD, Cross Disciplinary Team Lead
Erick Nakajima, MD, Clinical Reviewer
Emily Wearne, PhD, Non-Clinical Team Lead
Kelie Reece, PhD, Non-Clinical Reviewer
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Andrew Joe, MD, SVP Clinical Development and Chief Medical Officer
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BACKGROUND

Regulatory

The original MCLA-128-CL01 (zenocutuzumab) IND for the treatment of solid tumors was opened with the Division of Oncology 1 (DO1) in 2016 (IND 131752). To increase patient enrollment targets and initiate drug development discussions with the Review Division regarding the NRG1+ tissue-agnostic indication, the Sponsor requests that the MCLA-128-CL01 protocol be administratively split under the new IND 156484 with DO2.

Nonclinical

Merus describes zenocutuzumab as a bispecific, humanized, IgG1 antibody with enhanced antibody-dependent cell-mediated cytotoxic (ADCC) activity that targets HER2 and HER3, blocking ligand (e.g., NRG1)-mediated PI3K/AKT/mTOR signaling. Merus has conducted in vitro and in vivo pharmacology studies, including proof-of-concept studies; safety pharmacology studies; pharmacokinetic assessments; in vitro cytokine release assays using human whole blood and human peripheral blood mononuclear cells; a GLP-compliant 1-month repeat-dose toxicology study in cynomolgus monkeys; and a tissue cross-reactivity study. Merus does not plan to conduct a 13-week repeat-dose toxicology study or reproductive toxicity studies.

Clinical Pharmacology

Per Merus, MCLA-128 exposure increased approximately dose-proportionally at dose levels 240 mg or higher in patients with solid tumors. Merus developed a PopPK model to explore relevant patient covariates across the patient population. Immunogenicity of zenocutuzumab was assessed using a semi-homogenous bridging ELISA assay. A cytokine panel was collected during the Phase 1 dose escalation study. ECGs were collected in all clinical studies. Merus stated that no formal trials will be conducted to evaluate the effect of hepatic or renal impairment on the PK of zenocutuzumab.

Clinical

Background
NRG1 gene fusions occur in approximately 30% of cases of invasive mucinous adenocarcinoma (IMA), a rare subtype of lung adenocarcinoma (2-10% of all lung adenocarcinoma). NRG1 gene fusions have been reported at an incidence of 0.2% across a wide range of tumor types including pancreatic adenocarcinoma, gallbladder cancer, renal cell cancer (RCC), ovarian cancer, non-small cell lung cancer (NSCLC), breast cancer, sarcoma, bladder cancer, and colorectal cancer (CRC).

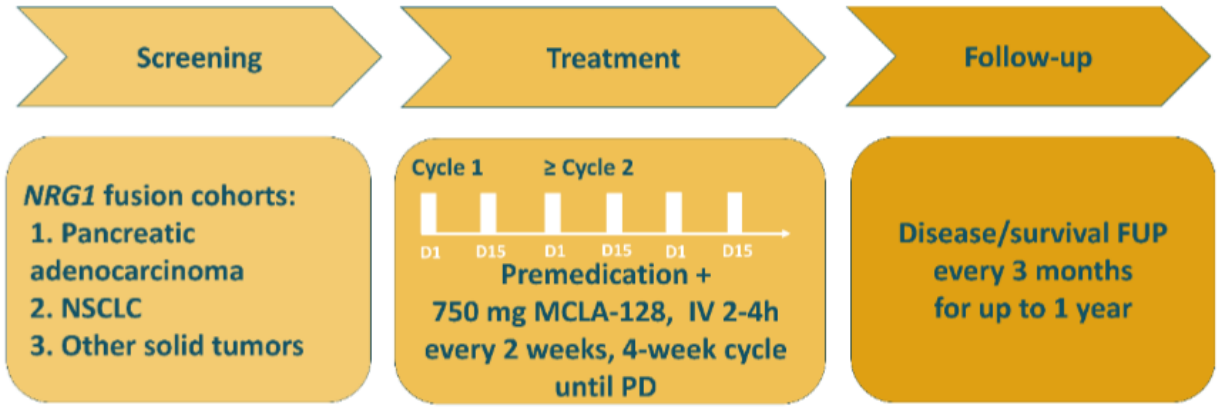
Merus NV intends to submit a marketing application for zenoctuzumab for the treatment of patients with neuregulin 1 gene fusion-positive (NRG1+) advanced unresectable or metastatic cancers who have progressed following prior treatment (b) (4) based on the results of Study MCLA-128-CL01 and their expanded access program (EAP), described below. The companion diagnostic for identifying NRG1 fusion mutations will be the (b) (4) next generation sequencing (NGS) test.

Study MCLA-128-CL01/eNRGy
Study MCLA-128-CL01 (eNRGy) is an ongoing, open-label, global, dose escalation (Phase 1) and dose expansion (Phase 2) study to assess the safety, tolerability, PK, PD, immunogenicity and anti-tumor activity of zenocutuzumab (MCLA-128) in patients with NRG1+ solid tumors.

The dose expansion portion was modified in June 2019 to include all NSCLC patients (IMA or otherwise) with a documented NRG1 gene fusion (Cohort F). Two new cohorts were added: Group G (NRG1+ pancreatic adenocarcinoma, 1.26% prevalence in the US) and Group H (other NRG1+ solid tumors with a documented NRG1 fusion). These are the only cohorts currently recruiting patients.

The primary endpoint of the dose expansion portion of eNRGy is overall response rate (ORR) per RECIST v1.1 as determined by local investigator. Key secondary endpoints include ORR and duration of response (DOR) per central independent radiologist review, progression free survival (PFS), overall survival (OS), and safety.

Key eligibility criteria for eNRGy include patients with locally advanced, unresectable, or metastatic solid tumor malignancy with a documented NRG1 gene fusion identified through molecular assays such as NGS-based assays performed at CLIA or similarly-certified laboratories. Patients must have received prior standard therapy for their malignancy, be unable to tolerate benefit from standard therapy, or have no alternative treatment options. A study schema is provided below.



Meeting package, p. 27

Enrollment in Group F (NSCLC) will be limited to 100 patients, Group G (pancreatic adenocarcinoma) will be limited to 50 patients, and enrollment in Group H (basket *NRG1* fusion) will be limited to 100 patients across various tumor types with documented *NRG1* gene fusions. The primary endpoint of ORR will be summarized separately for Groups F, G and H. If there are at least 7 patients with the same tumor type in Group H, these tumor types may be tabulated separately. If a consistent level of activity is seen across several tumor types, the ORR will be assessed in the overall population of patients with confirmed *NRG1* fusion. A random effect meta-analysis may be used to estimate the ORR across patients with NSCLC, pancreatic adenocarcinoma, and other tumor types with documented *NRG1* fusion if the level of activity across tumor types is heterogeneous.

Early Access Program
An EAP was established for zenoctuzumab in March 2019 for patients with NRG1+ solid tumors who are unable to participate in the eNRGy study. In order to be eligible for the EAP, patients with an advanced solid tumor with a documented NRG1 gene fusion who have progressed on or ineligible for standard therapy must meet one of the following criteria: cannot travel to the study site due to COVID restrictions, cannot travel to the study site due to other logistic constraints or health concerns, or the treating physician and/or patient prefer not to refer the patient to the study site. Tumor assessments are conducted every 8 weeks with imaging scans submitted for central independent radiologist review at the same facility that is used for the eNRGy study.

Proposed pivotal population/statistical analysis plan
Merus intends for the first 55 patients treated in the three ongoing eNRGy expansion cohorts or the EAP to provide the pivotal data in support of a marketing application for zenocutuzumab if the lower limit of the 95% confidence interval for ORR exceeds 15%. This dataset will include an analysis of 4 tumor types: pancreatic adenocarcinoma, NSCLC, ER+ breast cancer, and cholangiocarcinoma. The primary analysis for ORR and DOR will be conducted when the first 55 patients have a minimum follow-up duration of 6 months from the onset of response.

Preliminary efficacy data
As of the data cutoff date of April 13, 2021, a total of 61 patients with NRG1+ cancer had been enrolled across the eNRGy study (n=47) and the EAP (n=14). Of these, 45 had measurable disease and had at least one tumor assessment after initiating treatment. Efficacy results are provided in the table below; including patients with NSCLC (n=24), pancreatic adenocarcinoma (n=12), and a basket group (n=9), including breast cancer, unknown primary, cholangiocarcinoma, CRC, endometrial cancer, RCC, and pancreatic neuroendocrine tumor.

Table 1. ORR with zenoctuzumab (RECIST 1.1 per investigator assessment)

	Total N=45	NSCLC N=24	Pancreatic adenocarcinoma N=12	Basket N=9
ORR, n (%) (95% CI)	14 (31%) (18, 47)	7 (29%) (13, 51)	5 (42%) (15, 72)	2 (22%) (2.8, 60)

Preliminary safety data
The primary safety population will include approximately 150 patients with NGR1+ cancers or HER2-amplified cancers who have received zenocutuzumab according to 3 different regimens in the eNRGy trial: 101 patients treated with 750 mg every 3 weeks; 26 patients treated with 750 mg every week; and more than 35 patients treated with 750 mg every 2 weeks.

According to Merus, the most common adverse events that have occurred in the eNRGy clinical trial are infusion related reactions, gastrointestinal tract disturbances, skin rash, and fatigue.

Companion diagnostic
Local testing, including (b) (4), for enrollment to the eNRGy study and the EAP is performed at CLIA certified laboratories. Merus intends to develop an NRG1 gene fusion CDx assay using an RNA-sequencing-based NGS methodology. The *NRG1* gene fusion diagnostic assay will be developed as part of a broader molecular profiling test, the (b) (4) test by (b) (4) This test identifies gene fusions in formalin-fixed paraffin-embedded (FFPE) tumor tissue.

FDA sent Preliminary Comments to Merus N.V. on September 1, 2021.

DISCUSSION OF FDA RESPONSES TO SPONSOR QUESTIONS

Nonclinical

1. Does the Agency agree that the non-clinical safety package, as prepared by the Sponsor, is sufficient to support a marketing authorization for the proposed indication?

FDA Response:

We do not have sufficient information to answer this question. Your rationale for not conducting a 13-week toxicology study with zenocutuzumab based on data from approved products in the same class is not acceptable, unless it is a product with the same mechanism of action for which you have the right of reference. It is unclear whether the ADA response observed in your 4-week toxicology study was strong enough to infer that a 13-week toxicology study would not provide useful information. You may provide additional PK data for our review and consideration; however, at this time, a 13-week toxicology study appears warranted to support filing a BLA and should be submitted to the IND prior to initiating a study intended to support a marketing application.

In addition, an integrated summary using a weight-of-evidence (WOE) approach for reproductive risk assessment should be provided with the BLA. We recommend that you submit this assessment to the IND prior to submission of a marketing application for FDA feedback. The WOE approach may not rely on product-specific literature for which you do not have right-to-reference, including product labeling or FDA's Summary Basis of Approval, for products submitted under the 351(a) BLA pathway. See the guidance for industry titled Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations for factors that could be included in a WOE approach https://www.fda.gov/media/124829/download.

We will make a final determination of the adequacy of the nonclinical data during review of the original BLA submission.

Sponsor's Response:

The Sponsor acknowledges FDA's response and agrees to perform a 13-week repeated dose toxicity study with zenocutuzumab to support the BLA. In addition, the Sponsor will provide an integrated summary using a weight-of-evidence (WOE) approach for reproductive risk assessment in the BLA. The assessment will be submitted to the IND prior to submission of a marketing application for FDA feedback.

Does the Agency agree that the non-clinical safety package would be sufficient to support a marketing authorization for the proposed indication with the commitment of the Sponsor to performing the 13-week repeated dose toxicity study and providing an integrated summary for reproductive risk assessment? Of note, the

table below summarizes the non-clinical safety studies that have been performed with zenocutuzumab, in line with the recommendations outlined in the ICH S6 (R1) guideline.

Toxicology studies performed during the development of zenocutuzumab

Type of Study	**Species/cell type, zenocutuzumab concentration, and outcome**
Single Dose Toxicity Study: Study 612347	Cynomolgus monkeys received 10, 30 and 100 mg/kg IV zenocutuzumab. There were no treatment effects on clinical signs, body weight or terminal organ weight/necropsy findings. Systemic exposure to zenocutuzumab was dose-related. Anti-drug antibodies (ADAs) were detected on Days 22 and 43 for all animals at 10 and 30 mg/kg, and on Day 43 only for the male animal at 100 mg/kg.
Repeat Dose Toxicity Study Cynomolgus monkey: Study 612352	Cynomolgus monkeys received 10, 30 and 100 mg/kg IV zenocutuzumab for 5 doses. There were no changes indicative of toxicity of zenocutuzumab. All changes observed were procedural in origin, or related to an immune response to zenocutuzumab in individual monkeys in the treatment groups. There was no evidence of target organ toxicity in the clinical pathology investigations or terminal pathology data. On this basis, 100 mg/kg/week was considered to be the no observable adverse effect level (NOAEL) for this study.
Tissue Cross-Reactivity Study: Study (b)(4) 2405	Human tissues were treated with zenocutuzumab (2 and 10 µg/mL). Widespread specific staining with zenocutuzumab was observed in nearly all tissues (apart from blood cells). Epithelial staining was observed in most tissues, consistent with documented expression of HER2. Overall, the pattern of staining was consistent with known HER2/3 expression, and was similar to that observed with other anti-HER2 antibodies. Staining in the renal glomerular tuft cells and mesothelium was not supported by literature reports of HER2/3 expression, but staining was cytoplasmic and unlikely to be of clinical significance. In conclusion, no unexpected or clinically significant tissue cross reactivity was observed in human tissues.

Type of Study	Species/cell type, zenocutuzumab concentration, and outcome
Pilot Human Whole Blood Cytokine Release Study: Study 13/150-001	Zenocutuzumab (0.1, 1.0, 10 and 100 µg/mL) was incubated (37ºC for 24 hours) with fresh whole human blood, and supernatants harvested to assay released cytokines (IL-1β, IL-2, IL-6, IL-8, IL-10, TNFα, IFNγ). Alemtuzumab (Campath; 10 µg/mL) was included as a positive control, palivizumab (Synagis; (10 µg/mL) as a negative control, and TGN1412 and trastuzumab (Herceptin) (both at 10 µg/mL) as comparators. Zenocutuzumab did not induce cytokine release at concentrations up to 10 µg/mL, with slight release of most cytokines (except IL-8) at 100 µg/mL. trastuzumab (10 µg/mL) and palivizumab did not induce cytokine release, whereas TGN1412 and alemtuzumab both induced significant increases in several cytokines. The human whole blood assay was considered suitable for use as an *in vitro* assessment of cytokine release by zenocutuzumab.
Human Whole Blood Cytokine Release Study: Study (b) (4)-14/150-002	Zenocutuzumab (0.1, 1.0, 10 and 100 µg/mL) was incubated (37ºC, 24 hours) with whole blood from 12 healthy human volunteers, with palivizumab and alemtuzumab (10 µg/mL) as negative and positive controls, and trastuzumab (100 µg/mL) as a comparator antibody. No significant cytokine release was observed for zenocutuzumab, trastuzumab or palivizumab. The positive control antibody, alemtuzumab induced significant increases in most cytokines apart from IL-2.
Evaluation of Effector Functions (Including Cytokine Release): Study 200-8888-002	Cytokine release was assessed as part of ADCC assays conducted with co-incubation of zenocutuzumab (0.004-6000 ng/mL) or trastuzumab with HER2-expressing target cells (SKBR-3 cells) and human peripheral blood mononuclear cells (PBMCs) as effector cells. EC_{20} and EC_{50} values for release of IFNγ, IL-6, IL-8 and TNFα by zenocutuzumab and trastuzumab were calculated. EC_{20} values for cytokine release for zenocutuzumab were 2.2 to 5.0-fold lower than those for trastuzumab, suggesting a slightly greater potential for cytokine release for zenocutuzumab due to enhanced ADCC activity from Fc region engineering of the antibody.
In Vitro Hemocompatibility Study: Study 318757	Zenocutuzumab (1, 2 and 4 mg/mL) was added to human whole blood and human plasma. No detectable haemolytic potential or adverse reaction with plasma were detected at any of the concentrations evaluated.

Type of Study	Species/cell type, zenocutuzumab concentration, and outcome
In silico Immunogenicity Screening: Study R06423	An (b) (4) in silico immunogenicity screening was conducted assessing binding of 10-mer peptides derived from zenocutuzumab to human HLA Class II molecules. Zenocutuzumab showed a similar pattern and strength of binding to HLA Class II molecules compared to a number of approved humanized 'benchmarking' antibodies, indicating no increased risk of immunogenicity compared to these marketed antibodies.
Cardiomyocyte Viability *in Vitro*: Study P1208-R13	Zenocutuzumab (22, 68, 204 nM) was incubated with adult human stem cell derived cardiomyocytes in the presence of doxorubicin and viability was assessed through assay of ATP levels. Zenocutuzumab had no effect on cardiomyocyte viability, whereas incubation with trastuzumab or trastuzumab/pertuzumab (Perjeta) in combination resulted in decreased viability.

With the studies listed in the above table the Sponsor has addressed safety pharmacology, PK/toxicokinetics, immunogenicity, single-dose toxicity, repeated-dose toxicity (1-month duration, 5 weekly IV infusions), and injection-site tolerance in the cynomolgus monkey, a relevant species for zenocutuzumab, in line with the ICH S6 (R1) guideline. In addition, tissue cross-reactivity studies have been performed to characterize the binding of zenocutuzumab to antigenic determinants in human tissues, in line with the ICH S6 (R1) guideline, as well as hemocompatibility in human blood and cytokine release studies. Standard genotoxicity and carcinogenicity studies have not been performed and are not considered appropriate for this class of biological product, in line with the ICH S6 (R1) and ICH S9 guideline.
Taken together, the Sponsor considers the non-clinical safety package for zenocutuzumab, as performed by the Sponsor, and with the commitment to performing a 13-week repeated dose toxicity study and providing an integrated summary for reproductive risk assessment, is sufficient to support further clinical trials with zenocutuzumab as well as marketing authorization for the proposed indication. Does the Agency concur?

Discussion During the Meeting:
FDA acknowledged Merus' response and agreed that the proposed nonclinical safety package, including the newly planned 13-week repeat-dose toxicology study and an integrated summary for reproductive risk assessment using a WOE approach, appears sufficient to support the filing of a BLA for the proposed indication. FDA stated that a final determination of the adequacy of the nonclinical data will be made during review of the original BLA submission.

Clinical

2. Does the Agency agree that the proposed clinical pharmacology program is sufficient to support a BLA in the proposed indication?

FDA Response:
Conduct the proposed exposure-response analysis for both efficacy and safety to support the proposed BLA. The exposure-response analysis for safety should also include all patients treated with MCLA-128 at all dose levels (i.e., 40 – 900 mg) and all dosing schedules (i.e., QW, Q2W, and Q3W).

In the proposed PopPK analysis, also include information on formulation or drug product in the popPK dataset to enable evaluation of the impact of changes in formulation or drug product on MCLA-128 PK, PD, efficacy and safety.

Sponsor's Response:
The Sponsor acknowledges FDA's response, including recommendations for the PopPK analysis, the exposure-response analysis, and the additional Clinical Pharmacology Comments. Does FDA agree with the Sponsor's plan to not conduct a thorough QT study or dedicated studies in elderly patients or patients with renal or liver insufficiency? If so, then will the proposed clinical pharmacology program be sufficient to support a BLA?

Discussion During the Meeting:
FDA agreed with Merus' plan to not conduct a thorough QT study or dedicated studies in elderly patients or patients with renal or liver impairment and stated that the adequacy of the proposed clinical pharmacology package will be assessed during the BLA review.

3. Does the Agency agree with the design of the pivotal eNRGy study, intended to provide substantial evidence of efficacy to support a BLA in the proposed indication, specifically:

a) Does the Agency agree with the eligibility criteria?

FDA Response:
In general, the eligibility criteria are reasonable. We have some concerns about the proposed size of the pancreatic adenocarcinoma cohort relative to the primary efficacy population given that ORR is not generally accepted as an efficacy endpoint to support marketing applications for pancreatic adenocarcinoma due to the difficulty in estimating response. However, given that your proposal is for a tissue agnostic indication, inclusion of patients with pancreatic adenocarcinoma may be acceptable, though a final

determination will be made based on the magnitude of responses observed. All tumor imaging should be assessed by an independent review committee. In addition, see FDA Response to Question 3d.

b) Does the Agency agree with the patient identification methodology?

FDA Response:
Yes, we agree. You should collect all available information about the local tests used to confirm the presence of the NRG1 gene fusion. See FDA Response to Question 8.

c) Does the Agency agree with the dose and dosing regimen?

FDA Response:
The proposed dose and dosing regimen (i.e., 750 mg Q2W) appears acceptable. Also see FDA Response to Question 2 and Additional Clinical Pharmacology Comments.

d) Does the Agency agree with the primary and key secondary endpoints?

FDA Response:
We agree with the primary endpoint of ORR and key secondary endpoint of DOR; however, ORR should be assessed by independent central review.

As described in the FDA Response to Question 3a, ORR is difficult to estimate in patients with locally advanced or unresectable pancreatic adenocarcinoma due to the presence of chronic pancreatitis and/or fibrosis at the site of the primary lesion, and therefore, ORR would not be accepted as a standalone endpoint for an indication in pancreatic adenocarcinoma. Metastatic lesions of pancreatic adenocarcinoma are generally more assessable for response as assessed by RECIST 1.1.; therefore, you may consider only including patients with metastatic pancreatic adenocarcinoma in the primary efficacy population.

e) Does the Agency agree with the statistical analysis plan?

FDA Response:
No, we do not agree with the use of a random effect meta-analysis to estimate the ORR across tumor types and/or subtypes for the eNRGy study.

To support the proposed tissue agnostic marketing application, the efficacy decision will be based on the magnitude of the ORR and DOR in the pooled population as well as each specific disease cohort. In addition, please clarify how many patients were enrolled in Group F prior to Amendment 5 and how these patients will be treated in the analysis plan.

Sponsor's Response:
The Sponsor acknowledges FDA's responses to questions 3b, 3c, and 3e.
The Sponsor will discuss comments regarding the use of ORR as a surrogate efficacy endpoint in pancreatic adenocarcinoma (Questions 3a and 3d).
The fibrotic and infiltrative nature of pancreatic adenocarcinoma and local inflammatory pancreatitis are factors that could lead to an under-evaluation of tumor response, where it may be difficult to distinguish accurately between residual tumor and scarring from tumor regression (Zhang et al., World J Gastroenterol 2021; Wei et al., Pancreatology 2021; Cassinotto et al., Radiology 2014). This could in fact under estimate the high ORR observed with zenocutuzumab in pancreatic adenocarcinoma (ORR 42%). Importantly, tumor responses generally occur concurrently with significant decreases in the CA-19-9 tumor marker and metabolic responses observed with PET-CT scans. Moreover, ORR has been the basis for approval in other tumors with significant fibrosis (Erivedge® PI, 2020; Libtayo® PI, 2021 Refs of approvals with Basal Cell Carcinoma).
In fact pancreatic cancer ORRs have contributed to three tissue-agnostic FDA approvals based on ORR: pembrolizumab (6 pts), larotrectinib (1 pt) and entrectinib (3 pts).

Discussion During the Meeting:
FDA acknowledged Merus' response and stated that the inclusion of pancreatic cancer patients as part of a tissue-agnostic indication is acceptable and that ORR results will be considered in the context of tissue agnostic development.

4. Does the Agency agree that the efficacy data collected through the EAP in patients with NRG1+ cancer can be included in the primary analysis of the pivotal dataset (i.e., pooled analysis) to support the BLA in the proposed indication?

FDA Response:
Due to the potential heterogeneity in this subset of patients, we do not recommend inclusion of these patients in the primary analysis of trial data. Instead, this data may be used as supportive efficacy and safety evidence for the proposed BLA**.**

Sponsor's Response:
The following table demonstrates consistency between patients treated in the eNRGy study and patients treated in the EAP. Patients in the eNRGy study and EAP have similar characteristics in terms of demographics, burden of metastatic disease, and number of previous treatments.

		eNRGy (N=47)	EAP (N=14)	Total (N=61)
Gender	Male	44.7%	42.9%	44.3%
	Female	55.3%	57.1%	55.7%
ECOG	Median (range)	1 (0-1)	1 (0-3)	1 (0-3)
Age	Median (range)	59.0 (22-84)	58.0 (34-81)	59.0 (22-84)
No. lines prior systemic therapy	Median (range)	2.0 (0-6)	2.0 (0-5)	2.0 (0-6)
No. metastatic sites	Median (range)	3.0 (0-8)	2.5 (1-5)	3.0 (0-8)
Sum diameters baseline lesions (mm)	Median (range)	76.0 (10-214)	66.0 (30-351)	70.0 (10-351)
No. baseline target lesions	Median (range)	2.0 (1-5)	2.0 (1-4)	2.0 (1-5)

As described in the BB, the main eligibility criteria for the eNRGy study and EAP are similar. Eligibility for both is checked by the Sponsor using patient eligibility inclusion forms.
It is important to note that 11 centers have treated 14 patients in the EAP. Seven of these centers have also been selected to participate as an eNRGy study site. In addition, the majority of sites that have treated EAP patients are large academic institutions such as Memorial Sloan-Kettering Cancer Center, University of Texas MD Anderson Cancer Center, University of Navarra, etc.. These are clinical trial sites with much experience in conducting clinical trials, including conducting tumor evaluations and assessments per RECIST 1.1. The dosing schedule of zenocutuzumab and frequency of tumor assessments in the EAP are the same as for the study (every 8 weeks). Moreover, CT scans/images of the patients treated in the EAP will be collected and sent to the same central radiology review vendor as for the eNRGy study patients. Finally, the efficacy for the EAP subset ORR is consistent with the total 45-patient dataset (ORR 31%, 95% CI: 18-47%).
In summary, based on the similarity of key relevant demographic and disease factors, study procedures, and efficacy between the eNRGy study and EAP, the 55 subjects may be viewed as 1 relatively homogeneous population of advanced NRG1+ cancer patients.

Discussion During the Meeting:
FDA acknowledged the additional details provided regarding the EAP data and agreed that this data may provide supplementary information in a marketing application. However, FDA disagreed with the use of a pooled efficacy analysis including data from the eNRGy study and the EAP data. Although the design of the EAP is similar to the eNRGy study and initial summaries indicate similar

demographic make-up, the potential for heterogeneity between the two data sources, particularly when considering patient choice to enroll on a clinical trial, cannot be measured or controlled for in the proposed analysis. FDA stated that data submitted from the eNRGy study and from the EAP should be presented separately and that if Merus also chooses to submit pooled data in addition to separate data, FDA will review the submission, but generally does not accept pooling of data between studies and considers the eNRGy study data to be primary. FDA also stated that Merus should provide justification for submitting EAP data as part a pooled efficacy analysis.

Merus acknowledged FDA's response.

5. Does the Agency agree that clinical data from the first 75 patients in the registration dataset (i.e., eNRGy study and EAP) based on ORR and DOR per RECIST 1.1 per investigator assessment in patients with NRG1+ cancer, according to pre-specified success criteria, will constitute substantial evidence of effectiveness in support of an accelerated approval of a BLA in the proposed indication under 21 CFR 601 Subpart E?

FDA Response:
No, we do not agree.

The proposed magnitude of effect (e.g., excluding a lower limit of the 95% confidence interval of 15%) is likely inadequate to support a marketing application for zenocutuzumab for the proposed indication, particularly for the pancreatic adenocarcinoma cohort and the NSCLC cohort, for whom docetaxel with or without ramucirumab is an available treatment option with an observed ORR of approximately 23%. Given that results from the NSCLC cohort may contribute significantly to the overall ORR observed in the tissue agnostic population, the ORR observed for this cohort should be adequate to support a marketing application for patients with NRG1+ NSCLC.

Sponsor's Response:
(Please note, FDA's response refers to details from the Meeting Request, rather than updated details from the Briefing Book. For this Question. Updated details are inserted into the Question above.)

Sponsor's Response regarding the magnitude of effect in pancreatic adenocarcinoma and NSCLC.

The Sponsor will discuss the use of ORR in pancreatic adenocarcinoma in Question 3 below. Liposomal irinotecan (Onivyde®) in combination with 5-FU/ leucovorin (LV) is the only approved treatment for pancreatic adenocarcinoma after first-line chemotherapy. In the approval, the confirmed ORR was 7.7%, which is lower than the Sponsor's proposed historical comparator ORR of 15%.

Regarding FDA's comments for NSCLC, available approved second-line treatment options include docetaxel monotherapy and the docetaxel-ramucirumab combination, the latter of which does not appear to be effective in patients with NRG1+ NSCLC. In the recent and largest retrospective series of NRG1+ NSCLC (110 patients), the efficacy of different cytotoxic chemotherapy, immunotherapy, and targeted therapy regimens was poor, and platinum- and taxane-doublet based chemotherapy regimens resulted in ORRs of 13% and 14%, respectively. Of note is that no responses were observed among the three NRG1+ NSCLC patients treated with docetaxel plus ramucirumab, and disease progression was the best reported outcome (Drilon et al., JCO 2021).
Previous treatments administered to NRG1+ NSCLC patients enrolled in the eNRGy study are consistent with currently approved global standard therapies (i.e., first-line platinum- or taxane-based chemotherapy and immunotherapy), except for the use of docetaxel monotherapy or docetaxel-ramucirumab combination therapy after first-line therapy. Only one patient each received docetaxel with or without ramucirumab in the eNRGy study. Thus, in this dataset, NRG1+ NSCLC patients are more frequently referred for clinical trial participation, rather than be treated with standard docetaxel +/- ramucirumab. Of note, the eNRGy study is being conducted across 47 sites in the USA/Canada, western Europe and Asia, including academic and community institutions.
In addition to its uncommon use, docetaxel-ramucirumab does not appear to be effective in the NRG1+ NSCLC patients, since the best response in the 4 patients (3 patients from Drilon et al., and 1 patient from eNRGy study) described was PD. The Sponsor considered relevant comparators in NSCLC as described in the BB. Based on the low efficacy reported with docetaxel-ramucirumab in this population and the low preference by investigators to use this regimen, the Sponsor does not consider it suitable to include as a comparator in this setting. Therefore, if docetaxel-ramucirumab can be excluded as a historical comparator, is the following dataset sufficient for a tumor-agnostic submission and approval?

- Total sample size – 55
- ORR 31.1% (95% CI, 18.2, 46.6)
- Consistent efficacy (ORRs with overlapping 95% CIs) across 4 tumor types

Discussion During the Meeting:
FDA agreed that Merus' proposal for target ORR is reasonable and stated that the response rate will be considered in the context of the durability of responses, the safety profile, and the overall risk:benefit assessment for the therapy.

6. The Sponsor proposes a safety database that will include all patients with solid tumors treated with single agent zenocutuzumab across 3 different regimens: approximately 200 patients (101 patients with 750 mg q3w; 26 with weekly; > 75 patients with 750 mg q2w). Does the Agency agree that the size of the proposed safety base is appropriate considering the rarity of the disease?

FDA Response:
No, we do not agree. To be included in the primary safety population, patients should have received at least one dose of zenocutuzumab at the proposed registrational dose and treatment schedule. Your proposal to include patients with HER2-amplified cancers in the primary safety population is acceptable. Patients who received alternative doses/schedules should be included as supportive safety populations.

Sponsor's Response:
(Please note, FDA's response refers to details from the Meeting Request, rather than updated details from the Briefing Book. For this Question. Updated details are inserted into the Question above.)

The Sponsor acknowledges FDA's response. Would FDA please clarify that the following datasets are sufficient:

- Primary safety dataset – 67 patients treated at 750 mg q2w
- Supportive safety dataset >136 patients treated at 750 mg q3w or weekly regimen

Discussion During the Meeting:
FDA agreed with Merus' proposal.

7. The Sponsor plans to prepare 2 clinical study reports (CSRs) for the eNRGy study. The first CSR will present data from the dose escalation part of the study as well as the initial expansion cohorts that did not enroll NRG1+ patients. These patients will contribute to the safety population. The second CSR will present data from the three groups of NRG1+ patients intended to provide evidence of zenocutuzumab effectiveness in the treatment of NRG1+ cancer. Dose the Agency agree with this approach?

FDA Response:
This approach appears acceptable.

8. In a partnership with a diagnostic company, the Sponsor is in the process of developing a Companion Diagnostic (CDx) test to identify patients with NRG1+ cancer who are most likely to benefit from zenocutuzumab. The intention is to complete the CDx development in time to submit a CDx application contemporaneously with the BLA. In the event the CDx development is still underway at the time of the zenocutuzumab BLA approval, does the Agency agree that the labeled patient population could be defined by local testing with the development of the CDx as a post-marketing commitment (PMC)?

FDA Response: If a CDx is required for the safe and effective use of the drug in the biomarker-selected population, it will be expected that a CDx be approved at the same time as drug approval. We have the following comments regarding CDx development.

1. You propose to use multiple local tests for enrollment. The performance of the different local tests may not be comparable due to differences in the assays, technologies, cut-offs, and platforms. Also, the different assays may not be adequately validated to detect NRG1 fusions. As such, the use of different local tests to enroll patients may not identify the same intent to treat (ITT) populations. In addition to ensuring that alterations are annotated consistently, we encourage you to enroll patients based on limited number of local tests or test methods/technology platforms. If the proposed study is intended to support a marketing application, then we recommend that you use FDA approved/cleared tests with tumor profiling claims that may detect NRG1 fusions for patient eligibility in the trial. If you decide to move forward with the proposed plan of enrolling patients based on multiple local tests, we recommend that you:

    a. Provide the minimum analytical validation requirements (i.e., minimum acceptable performance characteristics for LoD, precision, analytical accuracy, etc.) to all enrollment sites and enroll patients from sites that meet the acceptance criteria.
    b. Ensure all clinical sites should follow the same protocol for specimen collection, banking, and processing.
    c. Prespecify variant classification rules (e.g., biomarker rules to establish positivity for NRG1-fusions) and ensure the rules are locked down and clinically and scientifically justified prior to enrollment of patients in the trial. The same biomarker rules should also be applied at all enrollment sites. You should prespecify the fusion breakpoints and cutoffs that will be considered a biomarker positive result.
    d. Ensure each CTA is fully specified, and cutoffs are established and locked down prior to registrational study.
    e. Provide information on CTAs including test methodology/name, test cut-off, specimen type used, quality metrics across the sample level, biomarker level and flow cell level for NGS-based assays, and brief analytical validation data (including but not limited to test precision & reproducibility, analytical accuracy, limit of detection, limit of blank, minimum tumor content, assay robustness, and interference studies, stability of the samples, reagents, intermediate products, minimum nucleic acid input, reagent lot interchangeability, carry over/cross contamination, in silico cross reactivity, testing with a standard set of reference materials, etc.) should be available to evaluate if test results are comparable and are identifying the same group of patients that are receiving the drug.

2. You indicated that you will enroll patients by both tissue- and plasma-based assays. You further indicate that you will only market a tissue-based CDx. If you plan to develop both tissue- and plasma-based CDx tests, we strongly recommend that you bank all specimens, i.e., both tissue and plasma from each patient, that were screened (biomarker positives and a random subset of negatives) to conduct a bridging study with the test intended for marketing. We also recommend that you work to obtain a high sample ascertainment rate to complete a successful bridging study to demonstrate the safety and effectiveness of the CDx assay.

   Since enrollment is based on the results of tissue- and plasma-based tests, then it is possible that multiple populations are being selected, e.g., ctDNA positive/tissue negative patients, ctDNA positive/tissue positive patients, ctDNA negative/tissue positive patients will be enrolled in this trial. Therefore, the drug efficacy in these subgroups should also be analyzed. Additionally, you should evaluate the concordance between the tissue and plasma test results to inform the device labeling.

   Refer to the summary of safety and effectiveness for P170019/S011 for consideration of study design and analyses:
   https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019S011B.pdf

3. You have not provided details about biomarker rules for enrollment of patients harboring NRG1 fusions. You will need to prespecify and justify the specific NRG1 fusions and ensure these rules are aligned with those of the final CDx.

4. The analytical validation of the device should be demonstrated utilizing intended use clinical specimens as much as possible (including all tissue types that were represented in the trial) for the key analytical studies such as analytical accuracy, limit of detection, precision, nucleic acid input, and other studies. All tissue types that are represented in the trial should also be used in the analytical studies to support the robust detection of NRG1 fusions across multiple tissue types. Non-clinical samples whose performance is demonstrated to be functionally equivalent to clinical samples may be used to supplement sample numbers in studies that are not adequately represented by clinical samples.

Sponsor's Response:

The Sponsor acknowledges FDA's responses to Question 8, in addition FDA's responses 1 a-e, 2, 3 and 4. The Sponsor will pursue additional discussion with its CDx partner and CDRH, including discussion of analytical and clinical validations and bridging studies as needed.

Discussion During the Meeting:
No discussion occurred.

9. Does the Agency agree with the Sponsor's proposed indication for zenocutuzumab as follows: "Treatment of patients with neuregulin 1 (NRG1) gene fusion-positive advanced unresectable or metastatic cancers who have progressed following prior treatment [redacted] (b) (4)

FDA Response:
The proposed indication is acceptable; however, see FDA responses to Questions 3, 4, 5, and 6.

10. The Sponsor intends to submit an initial Pediatric Study Plan (iPSP) that will include a proposal for a waiver for pediatric studies. Does the Agency agree with this approach?

FDA Response:
Yes, we agree that the request for a full waiver is reasonable.

Additional Clinical Pharmacology Comments

The content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support this application should be consistent with FDA Guidance for Industry, "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format". 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.

Address the following questions in the Summary of Clinical Pharmacology:

11. What is the basis for selecting the doses and dosing regimen used in the registration trials to support your marketing application? Include the rationale for the selection of these dosages along with the following information, as appropriate:

a) Summary of nonclinical pharmacology and toxicology data and clinical PK, PD (e.g., target engagement), activity and safety data to support an optimum biological dosage selection strategy.
b) Integrated dose- and exposure-response analyses using the preliminary and emerging efficacy and safety data.
c) Detailed tabular summaries of the following from completed and ongoing clinical trials:
   - Pharmacokinetic and pharmacodynamic data, analyzed by dose cohort

- Safety data, including dose intensity, dosage modifications (i.e., time course and prevalence of interruptions, reductions and discontinuations), dose-limiting toxicities, fatal events, all grade and grade 3 - 4 adverse events, analyzed by dose cohort.
- Preliminary efficacy data from relevant indications, analyzed by dose cohort.

12. 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.

13. What are the exposure-response relationships for efficacy, safety and biomarkers?

14. 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?

15. 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:

16. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.

17. 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.

18. 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 dosage modifications; the time to the first dose reduction, interruption or discontinuation; the reasons for dosage modifications in the datasets.

19. 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 pharmacometric data and models submission guidelines.

20. Submit the following information and data to support the population pharmacokinetic analysis:
    - SAS transport files (*.xpt) for all datasets used for model development and validation
    - 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
    - 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)

21. Submit a study report describing exploratory exposure-response (measures of effectiveness, biomarkers and safety) relationships in the targeted patient population. Refer to Guidance for Industry for population PK, exposure-response relationships, and pharmacometric data and models submission guidelines.

22. In Module 5 of your submission, incorporate race and ethnicity, in addition to other covariates, in the population pharmacokinetic (PPK) and exposure-response (for safety and effectiveness) analyses. Include an assessment to determine if the data are of sufficient quantity and quality to permit an analysis to detect a clinically meaningful difference. Provide complete datasets, model codes or control streams, output listings, and final study reports used to support these analyses.

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.[2]

FDARA REQUIREMENTS

Sponsors 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/

[2] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology

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.
Meeting 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 the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, to ensure open lines of dialogue before and during their drug development process.

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.[3]

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.[4]

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format - Standardized Study Data.* This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, *Study Data Technical Conformance Guide*, 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 are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page[5] that provides specifications for sponsors regarding

[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[4] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm
[5] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

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.

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov. For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

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

Additional information can be found at FDA.gov.[6]

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[7] and the CDER/CBER Position on Use of SI Units for Lab Tests website.[8]

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).

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims.*

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[6] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber
[7] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[8] https://www.fda.gov/media/109533/download

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.

UNITED STATES PATIENT POPULATION

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the guidance for industry *Collection*

of Race and Ethnicity Data in Clinical Trials for more information.

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

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

- Assessment Aid[10]

ISSUES REQUIRING FURTHER DISCUSSION
None.

ACTION ITEMS
None.

ATTACHMENTS AND HANDOUTS
None.

[9] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program
[10] https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project

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

/s/

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