CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761210Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 135405

REVISED MEETING MINUTES

Janssen Research and Development LLC
Attention: Julie Brennan
Associate Director, Global Regulatory Affairs
920 Route 202 South
Raritan, NJ 08869

Dear Ms. Brennan:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for amivantamab (JNJ-61186372).

We also refer to the teleconference between representatives of your firm and the FDA on November 4, 2020. The purpose of the teleconference was to discuss the topline results from Study 61186372EDI1001 to support a proposed BLA to be submitted under the provisions of 21 CFR 610.41 for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with Exon 20 insertion mutation, whose disease has progressed on or after platinum-based chemotherapy.

We also refer to the minutes of that teleconference issued on November 6, 2020, and to your November 18, 2020, request for revisions. We agree to all of your proposed revisions and have revised the minutes accordingly. In addition, we have added an Addendum of CDRH's revised response to Question 3 originally communicated to you via email on November 17, 2020.

A copy of the official minutes of the teleconference is enclosed for your information.

If you have any questions, please call me at 301-796-2320 or email sharon.sickafuse@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Sharon Sickafuse, M.S.
Senior Regulatory Health Project Manager
Division of Regulatory Operations – Oncologic Diseases for DO2
Office of Regulatory Operations
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:

- Revised Teleconference Minutes

MEMORANDUM OF TELECONFERENCE MINUTES

Meeting Type:	Type B
Meeting Category:	pre-BLA
Teleconference Date:	November 4, 2020
Application Number:	IND 135405
Product Name:	amivantamab (JNJ-61186372)
Indication:	Treatment of patients with metastatic non-small cell lung cancer (NSCLC) with Exon 20 insertion mutation, whose disease has progressed on or after platinum-based chemotherapy.
Sponsor Name:	Janssen Research and Development LLC
Regulatory Pathway:	351(a) of the Public Health Service Act
Meeting Chair:	Nicole Drezner
Meeting Recorder:	Sharon Sickafuse

FDA ATTENDEES

Office of Oncologic Diseases

Vishal Bhatnagar, M.D., Associate Director for Patient Outcomes

Division of Oncology 2
Nicole Drezner, M.D.
Abigail Koch, M.D.
Erin Larkins, M.D.
Harpreet Singh, M.D.

Division of Hematology Oncology Toxicology
Whitney Helms, Ph.D.

Office of Biostatistics

Division V
Pallavi Mishra-Kalyani, Ph.D.
Pourab Roy, Ph.D.

Office of Drug Evaluation Science

Division of Clinical Outcome Assessment
Selena Daniels, PharmD., M.S.

Office of Pharmaceutical Quality
Office of Biological Products
Division of Biotechnology Review and Research IV
Andrea Franco, Ph.D.
Leslie Rivera Rosado, Ph.D.

Office of Regulatory Operations
Division of Regulatory Operations – Oncologic Diseases for DO2
Sharon Sickafuse, M.S

CDRH
Office of Product Evaluation and Quality
Office of In Vitro Diagnostics and Radiological Health
Division of Molecular Genetics and Pathology
Rama Kamesh Bikkavilli, Ph.D.

SPONSOR ATTENDEES
Kiran Patel, M.D., VP, Clinical Research & Development
Amy Roshak, Compound Development Team Lead
Roland Knoblauch, M.D., Ph.D., Clinical Lead
Meena Thayu, M.D., Study Physician
Pamela Thorpe, M.D., Medical Safety Lead
Sudhakar Rao, Ph.D., Head, Oncology Biostatistics
John Xie, Ph.D., Biostatistics Lead
Renee Pierson, M.B.A., Patient Reported Outcomes
Leon Freytor, M.S., Global Regulatory Lead
Jayaprakash Karkera, Ph.D., Diagnostics Lead
Sarah Parsons, M.S., Diagnostics Regulatory Lead
Debra Rasmussen, M.B.A., Head, Diagnostics Regulatory
Julie Brennan, M.S., North America Regulatory Lead
Aaron Seto, Ph.D., North America Regulatory Scientist
Par Mahadevia, Global Medical Affairs Lead

BACKGROUND
On September 8, 2020, Janssen submitted a meeting request (SDN 144) to discuss the topline results from Study 61186372EDI1001 entitled, “A Phase 1, First-in-Human, Open-Label, Dose Escalation Study of JNJ-61186372, a Human Bispecific EGFR and cMet Antibody, in Subjects with Advanced Non-Small Cell Lung Cancer,” to support a proposed BLA to be submitted under the provisions of 21 CFR 610.41 for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with Exon 20 insertion mutation, whose disease has progressed on or after platinum-based chemotherapy.

The meeting package was submitted on October 5, 2020, as SDN 148.

Regulatory

On March 9, 2020, amivantamab was granted Breakthrough Therapy designation (BTD) for the treatment of patients with metastatic NSCLC with EGFR Exon 20 insertion mutation, whose disease has progressed on or after platinum-based chemotherapy, based on the objective response rate (ORR 41.4%, 95% CI 23.5, 61.1) results from 29 patients enrolled in Parts 1 or 2 of Study 61186372EDI1001. Among the 12 patients who had a partial remission, 4 patients (33%) had a duration of response of ≥6 months at the time of the data cut-off.

A teleconference to obtain FDA feedback on the overall development program following the granting of BTD was held on May 6, 2020. During that teleconference, the adequacy of efficacy and safety data from Study 61186372EDI1001 to support a BLA for accelerated approval and the design of a confirmatory study (Study 61186372NSC3001) was discussed. In addition, FDA provided advice on the clinical pharmacology section of the proposed BLA. FDA also advised Janssen to submit their proposed assessment for reproductive toxicity/embryo-fetal development (EFD) toxicity for feedback with sufficient time so that if FDA determines that any EFD studies are necessary, then conducting such studies would not impact the developmental timeline.

FDA issued an Agreed iPSP letter on June 10, 2020.

A teleconference was held on July 22, 2020, to discuss the content and format of the proposed BLA. During that teleconference, FDA advised Janssen that in order to allow an adequate assessment of durability of response, all responders should have follow-up of 6 months past onset of response.

FDA issued a Type B WRO letter on August 3, 2020, regarding Janssen's proposed assessment for reproductive toxicity/embryo-fetal development toxicity

Janssen canceled a pre-BLA CMC meeting scheduled for August 6, 2020, after receiving FDA's preliminary comments.

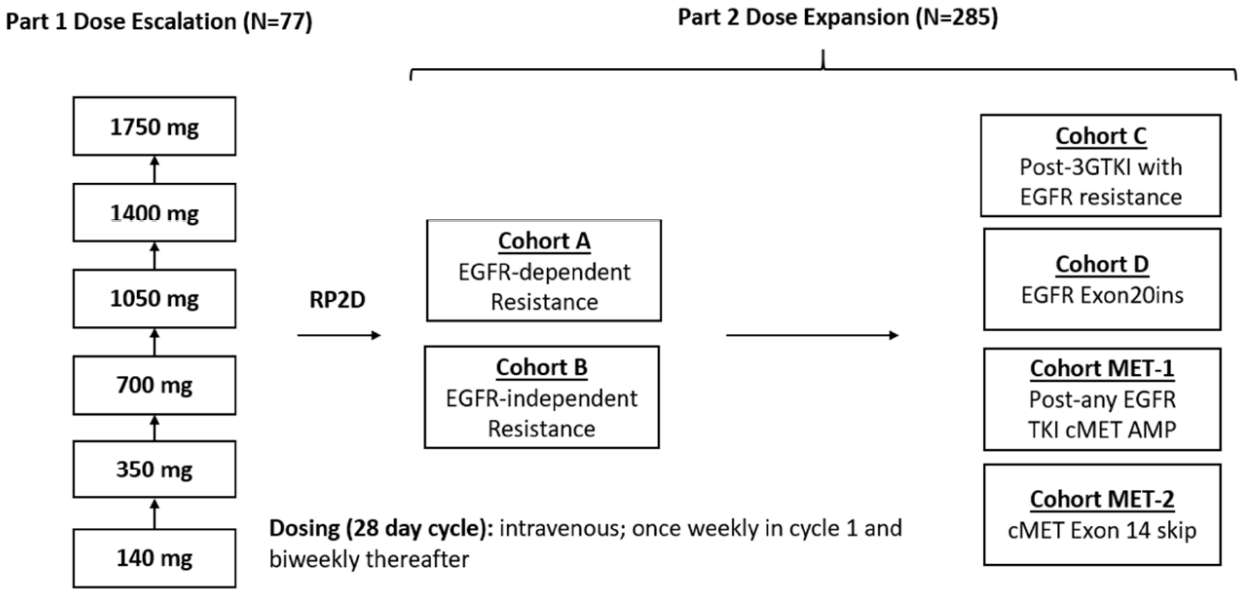
On October 5, 2020, Janssen submitted a request for a rolling BLA.

Clinical

Janssen intends to submit an original BLA for amivantamab, a bispecific antibody directed against the epidermal growth factor (EGF) and mesenchymal epidermal transition (MET) receptors, for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with Exon 20 insertion mutation, whose disease has progressed on or after platinum-based chemotherapy based on the results from the ongoing Study 61186372EDI1001.

Study Design
Study 61186372EDI1001 is an ongoing first-in-human, open label, single-arm, multi-cohort dose escalation (Part 1) and dose expansion (Part 2) study to evaluate the safety, tolerability, and preliminary antitumor activity of amivantamab as a single agent and in combination with other agents in patients with NSCLC with EGFR or MET mutations. The primary endpoint of the dose escalation portion of the study is to establish the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of amivantamab and the primary endpoint of the dose expansion portion of the study is overall response rate (ORR) as assessed by the investigator per RECIST v1.1.

The primary efficacy population supporting the original BLA will include patients with EGFR Exon20ins mutant NSCLC treated at the RP2D of 1050 mg for patients with baseline weight < 80 kg and 1400 mg for patients with baseline weight ≥ 80 kg (administered intravenously every week for the first 4 weeks and every 2 weeks thereafter) who have progressed on prior platinum-based chemotherapy from Parts 1 and 2 of the study. The study schema is provided below.



EGFR=epidermal growth factor receptor; Exon 20 ins=Exon 20 insertion mutation; TKI=tyrosine kinase inhibitor
Cohorts A and B in Part 2 were closed to enrollment upon opening of subsequent cohorts. Note that a weight-based RP2D was added after the initial RP2D determination.

Meeting package, p.10

Efficacy Summary
As of a clinical cutoff date of June 8, 2020, a total of 362 patients received at least one dose of amivantamab. Of these, 258 patients were treated at the RP2D and of these, 114 patients had Exon 20ins NSCLC and had received treatment with prior chemotherapy. A total of 81 patients had undergone at least 3 scheduled post-baseline

disease assessments or had discontinued the study for any reason. For these patients, the median duration of follow up was 6.5 months (range 1.1-29.3). In the BLA submission, Janssen intends to include supportive efficacy data from the 24 patients with Exon 20ins who received treatment with amivantamab at the RP2D but had not received prior chemotherapy. A summary of the efficacy results is provided in the table below.

Efficacy parameter	Exon20ins w/ prior chemo at RP2D N=81	Exon20ins w/o prior chemo at RP2D N=24
ORR by BICR, n(%) 95% CI	32 (40%) (29, 51)	38% (19, 59)
DOR, months 95% CI	8.2 (5.1, NE)	9.4 (5.4, NE)
% with response ≥ 6 mos	31%*	11%**

*Of 22 responders with DOR < 6 months, response is ongoing for 16 patients
**Of 7 responders with DOR < 6 months, response is ongoing for 6 patients

Safety Summary
The primary safety population includes all patients with NSCLC with Exon20ins mutation treated with amivantamab at the RP2D after platinum-based chemotherapy (N=114). Supportive safety populations that will be analyzed include all patients treated at the RP2D (N=258) and all patients who received at least one dose of amivatamab (N=362).

The median duration of follow-up for the primary safety population was 5.1 months (range: 0.2-29.3). Within this population, a total of 8 patients (7%) experienced an adverse event (AE) resulting in death (infections [3 events], dyspnea [2 events], respiratory failure, sudden death, and cardio-respiratory distress [1 event each]). Thirty percent of patients experienced a serious adverse event of which back pain and pulmonary embolism were the most common (3 events each). A total of 10%, 13%, and 35% of patients had an AE that led to discontinuation, dose reduction, or interruption of study therapy, respectively. Infusion related reaction was the most commonly reported treatment emergent adverse events (TEAE) (66%). Other common TEAEs (>20%) were dermatitis acneiform (46%), paronychia (45%), rash (37%), hypoalbuminemia (27%), constipation (24%), and stomatitis (21%). Major TEAEs were similar between patients in each safety population.

Overall Summary of the Submission
Janssen proposes a rolling review and submission of an assessment aid with the BLA submitted in two parts on November 5 and 24, 2020.

Janssen intends to include the following additional information in the BLA submission:

- Results from Study 61186372NSC1002RWE, a retrospective cohort study of data from 181 patients with EGFR Exon20 ins mutant NSCLC and 2833 patients with NSCLC with common EGFR mutations from the Flatiron Health Advanced NSCLC database to describe the differences in prognosis, outcomes, and treatment patterns in EGFR exon 20 insertion mutations vs. EGFR exon 19 deletions and L858R mutations.

(b) (4)

FDA preliminary comments were emailed to Janssen on November 2, 2020. On November 3, 2020, Janssen emailed a response document stating that they wish to discuss items 1, 4, and 8.

SPONSOR QUESTIONS AND FDA RESPONSES

1. *The Sponsor believes that the Study 61186372EDI1001 topline results are supportive of a BLA submission for amivantamab for the treatment of patients with metastatic NSCLC with Exon 20 insertion mutation, whose disease has progressed on or after platinum-based chemotherapy. Does the Agency agree?*

   FDA Response:
   FDA does not agree. An original BLA for amivantamab should not be submitted until a majority of these patients (e.g. 80-90%) have had follow-up of at least 6 months post onset of response; it remains unclear how many responders of the 32 patients with a response assessed by BICR have had such follow-up. Based on the meeting package, it appears that 22/32 patients with a BICR-assessed response have not had post-response follow-up of 6 months ("Of the 22 responders with a duration of response <6 months, response was ongoing for 16 subjects" p.18).

   As requested during the July 22, 2020, teleconference, provide the following information:

   - Percentage of the 32 responders (by BICR assessment) who have at least 6 months of follow-up from onset of response
   - The actual proportion of responders with a DOR ≥ 6 months.

Janssen response received November 3, 2020:
The primary efficacy population is comprised of 81 consecutively treated subjects who had initiated therapy by February 5, 2020, and had undergone at least 3 post-baseline disease assessments or discontinued therapy at the time of the clinical cutoff of June 8, 2020. As discussed at the July 22, 2020 teleconference, the updated preliminary efficacy data including durability of responses by BICR and by investigator assessment is described below.

As of the October 8, 2020, clinical cut-off, all 32 (100%) BICR-assessed responders had at least 6 months of follow-up from onset of response or had discontinued treatment. The overall response rate remains consistent at 39.5% (95% CI: 28.8%, 51.0%) with an associated median duration of response (mDOR) of 11.14 months (95% CI: 6.90, 21.65). Twenty of the 32 responders (62.5%) have a DOR of at least 6 months. A summary of efficacy updates by investigator and BICR assessments is provided in **Table 1**.

Table 1. Summary of Selected Efficacy Endpoints as of October 8, 2020

	Investigator	BICR
N	81	81
Overall response rate, 95% CI (%)	35.8% (25.4%, 47.2%)	39.5% (28.8%, 51.0%)
Responders; total, ongoing (n)	29, 12	32, 17
Duration of response, median (95% CI), months	11.20 (6.34, 13.14)	11.14 (6.90, 21.65)
Duration of response >=6 months (n,%)	19 (65.5%)	20 (62.5%)
Median progression free survival, months	8.25 (5.49, 10.61)	8.28 (6.51, 10.87)

Summary data on 32 BICR-assessed responders

- 20/32 (62.5%) subjects with DOR ≥ 6 months
    - 13/20 with ongoing responses
- 12/32 subjects with DOR < 6 months
    - 4 subjects have ongoing response by BICR but have discontinued treatment based on investigator assessment, and no new data is forthcoming
    - None of the remaining 8 subjects have ongoing responses
        - 6 subjects have discontinued due to investigator assessed progressive disease

- 1 subject died
- 1 subject has continued on treatment based on investigator assessment

Summary data on 29 investigator-assessed responders

- 19/29 (65.5%) subjects with DOR ≥ 6 months
  - 10/19 subjects with ongoing responses
- 10/29 subjects with DOR < 6 months
  - 2/10 with ongoing response (DOR 4.17 and 5.55 months)
  - The remaining 8 subjects have discontinued study treatment due to progressive disease

These preliminary updated efficacy results from the October 8, 2020 clinical cut-off represent a median follow-up of 9.7 months for the 81 subject efficacy population, and a median follow-up of 11.6 months for the 32 BICR-assessed responders. These data will be provided as a stand-alone report with the BLA submission. The associated updated efficacy datasets will be provided with the 120-day safety update, planned for submission the week of February 22, 2021.

The Sponsor believes the updated efficacy data demonstrate that amivantamab provides robust and durable clinical benefit, and the results are supportive of a BLA submission in subjects with metastatic NSCLC with Exon 20 insertion mutation whose disease has progressed on or after platinum-based chemotherapy.

Discussion during the teleconference:
FDA stated that the original BLA submission must have 6 months of follow-up data from onset of response for all 32 BICR responders in the primary efficacy population of 81 subjects. Without this data, FDA is unable to accept the submission.

After discussion, Janssen and FDA agreed to the following:

- Janssen will submit a BLA containing efficacy data from the primary efficacy population (N=81) with an October 2020 cut-off and safety data with a June 2020 cut-off.
- The BLA will be a rolling submission of 2 parts with the final part submitted by November 24, 2020.
- The 120 day safety update will contain safety data with an October 2020 cut-off.
- By December 31, 2020, Janssen will submit an updated efficacy dataset with an October 2020 cut-off, an Assessment Aid, an addendum to the clinical study report, an addendum to the Summary of Clinical Efficacy, an addendum to the clinical overview, and an updated proposed USPI, all

based on efficacy data from the primary efficacy population (N=81) with an October 2020 cut-off.

2. *The Sponsor plans to request Priority Review at the time of the initial BLA submission. Does the Agency agree with the Sponsor rationale for requesting Priority Review?*

FDA Response:
FDA agrees; however, whether priority review is granted will be determined at the time of BLA submission.

Janssen response received November 3, 2020:
The Sponsor acknowledges FDA's response, no further discussion is required.

Discussion during the teleconference:
None.

3. *Does the Agency agree with the proposed strategy to submit the Guardant Health Inc plasma test (Guardant360 CDx [P200010]) as companion diagnostics for amivantamab?*

FDA Response:
You mention that Guardant Health (for plasma diagnostic test) is partnering with Janssen to bridge the test performance from the Study 61186372EDI1001 local testing result to the market-ready CDx assay and is planning to submit the Guardant360 CDx (P200010) PMA supplement (sPMA) concurrently with the amivantamab BLA submission. CDRH has no objection to your plans. However, CDRH highly recommends Guardant Health follow the feedback that was offered as a part of pre-submission meeting (Q200694 and Q200694/A001) regarding their analytical and clinical validation strategies. Please also ensure that the sample ascertainment rate for the proposed bridging study is high to demonstrate robust clinical performance of the Guardant 360 CDx test for the proposed indication. Furthermore, CDRH recommends Guardant Health submit the Guardant360 CDx sPMA within 30 days of the BLA submission to CDER for a contemporaneous approval with amivantamab. Of note, when the Guardant Health sPMA is submitted to CDRH concurrently with the BLA submission to CDER, the Guardant360 CDx test can be cross-referenced with the proposed BLA for amivantamab. However, Janssen should provide an authorization letter for this purpose.

In addition to the analytical and clinical validation data submitted in sPMA in support of the device indications for use, any additional data that the diagnostic sponsor plans to leverage from the amivantamab clinical trial to establish the safety and effectiveness of the Guardant360 CDx test should also be submitted

in the Guardant Health sPMA. If Guardant Health is unable to provide certain information under the Guardant360 CDx test sPMA due to confidentiality reasons, Janssen can provide a letter of authorization to CDRH to cross-reference the BLA. Please note that the letter should clearly indicate the attachment/appendix number and the section of the BLA to locate the specific information along with the date of submission of the information to CDER. Alternatively, any confidential clinical validation information in support of device performance can be submitted under the device master file to CDRH by Janssen.

Janssen response received November 3, 2020:
The Sponsor acknowledges FDA's response, no further discussion is required.

Discussion during the teleconference:
None.

4. (b) (4)

ADDITIONAL FDA COMMENTS

Clinical

5. Clarify what therapy, if any, the 24 patients in the primary efficacy population who did not receive prior chemotherapy prior to amivantamab.

Janssen response received November 3, 2020:
Of the 24 subjects who did not receive prior chemotherapy in the metastatic setting, the majority of subjects (16/24; 67%) were treatment naïve. The remaining 8 subjects had received prior treatment summarized below:

- 2 subjects received platinum-based chemotherapy in the adjuvant setting (> 12 months prior to the diagnosis of metastatic disease) without further treatment in the metastatic setting
- 4 subjects received a single line of a first or second generation GFR TKI

- 1 subject received afatanib followed by vinorelbine
- 1 subject received a single line of uftoral (tegafur)

Discussion during the teleconference:
None.

6. Clarify whether enrollment has begun for Study 61186372NSC3001 and, if so, how many patients have been enrolled to date.

Janssen response received November 3, 2020:
Study 61186372NSC3001 is currently underway with 2 sites open in Spain and 2 additional sites (one in US, one in Spain) to be opened by the end of this week. Enrollment is on track to begin this month.

Discussion during the teleconference:
None.

7. Provide a breakdown of the results for rwPFS and rwOS for the 111 patients who received platinum-based chemotherapy regimens as their first line treatment by those who received platinum-based chemotherapy plus immunotherapy and those who received platinum-based chemotherapy alone.

Janssen response received November 3, 2020:

		Median (month)	95% CI
Platinum-based doublet chemotherapy (n=50)*	rwOS	18.3	(11, 28.6)
	rwPFS	6.6	(3.4, 10.9)
Platinum-based chemotherapy + immunotherapy (n=32)	rwOS	11	(5.7, 23.3)
	rwPFS	4.8	(2, 5.7)

*Since original analysis (n=48), 2 patients originally classified as receiving single-agent platinum were reclassified as having received platinum doublet (cisplatin and etoposide)

Discussion during the teleconference:
None.

8. Provide any real world data available on ORR in the subgroups included in the meeting package and described in Comment #7.

Janssen response received November 3, 2020:
This Flatiron dataset did not contain real-world tumor response data. The Sponsor is currently evaluating an expanded Flatiron dataset that is curated to assess real-world tumor response. This dataset will not be available at the time of BLA submission. The Sponsor would like to further understand the usefulness of this data in the context of the BLA review.

Discussion during the teleconference:
FDA clarified that Janssen will need to demonstrate that patients with EGFR Ex20 ins mutations do not benefit from first-line immunotherapy (b) (4) (b) (4) (b) (4). Data on the effectiveness of immunotherapy in this patient population will be a review issue for the confirmatory study.

Clinical Outcome Assessments

9. Anchor-based methods are the primary methods we use to interpret meaningful within-patient score changes in COA endpoints. You should plan to incorporate these methods for the proposed COAs in your protocol and analyses. Anchor-based methods should be supplemented with anchor-based empirical cumulative distribution function and probability density function curves. Other methods may be explored to complement the anchor-based methods or when anchor-based methods are not feasible (i.e., when no adequate anchor measure(s) are available, small sample size). For example, patients can be queried via cognitive interviews, exit interviews, or surveys to help inform the improvement threshold.

Janssen response received November 3, 2020:
The Sponsor acknowledges FDA's response, no further discussion is required.

Discussion during the teleconference:
None.

10. External anchor scales should have the following properties:

a. Selected anchor scales should be associated with the target COA endpoint in a way that addresses the question of clinical meaningfulness of the target COA endpoint. For example, for an endpoint measuring a specific aspect of the disease, an anchor scale measuring the global status of the disease may not be helpful.

b. The anchor scale should be easier to interpret than the COA endpoint itself and meaningful to patients. The anchor scale's response categories should be distinct and non-overlapping and should represent meaningful

differences among adjacent response categories. For example, an anchor scale that uses a 0-10 numeric rating scale would not be easy to interpret and would not be an appropriate anchor scale in most contexts. An example of a commonly used response scale for rating severity is none, mild, moderate, or severe.

c. The anchor scale's recall period should be consistent with the assessment time period of the prespecified endpoint to the extent possible. Additionally, the selected anchors should be assessed at comparable time points as the target COA endpoint but completed by the respondent after the target COA in the order of assessments.

d. The anchor scale should be plainly understood by respondents in the context of use; you should consider testing the draft anchor item(s) including their response categories in cognitive interviews.

Multiple anchors should be explored to provide an accumulation of evidence to help interpret a clinically meaningful within-patient score change (can also be a range) in the clinical outcome endpoint score. At a minimum, we recommend a current state (non-comparative) global impression rating scale, when appropriate, as an anchor scale as these scales are less likely to be subject to recall error than global impression of change scales; it also is a more reliable measure for change from baseline data. We recommend submitting exact copies of your anchor scales for Agency review and concurrence prior to implementing them in your clinical trial(s).

Janssen response received November 3, 2020:
The Sponsor acknowledges FDA's response, no further discussion is required.

Discussion during the teleconference:
None.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. See discussion and agreements for Question 1.

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion was held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan and it was concluded that FDA does not foresee the need for a REMS at this point.

In addition, FDA notes that Janssen cancelled the chemistry pre-submission meeting scheduled for August 6, 2020, after receiving FDA's preliminary comments of July 28, 2020.

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[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, which include:

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

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

[1] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[2] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

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.

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[3] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[4]. 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*.[5]

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the

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

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

- Assessment Aid[7]

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.

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

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.

ADDENDUM
The following revised FDA response to Question 3 was emailed to Janssen on November 17, 2020:

FDA's response to Janssen's Question 3 in the meeting minutes issued on November 6, 2020, was based on the assumption that (b) (4) (b) (4) Guardant's plasma-based test discussed under pre-submission Q200694) would be submitted concurrently for CDRH review along with the submission of a BLA to CDER for the review of amivantamab. However, CDRH subsequently realized that your intent is to submit the BLA concurrently with the Guardant plasma test PMA application only.

Based on this, FDA has the following additional comments:
CDRH would like to reiterate that (1) patient enrollment to Study 61186372EDI1001 was primarily based on tissue-based testing, (2) the tissue to plasma concordance is not known for exon 20 insertions in the proposed indication, and (3) tissue to plasma concordance results can lead to inclusion of a reflex testing requirement for the negative results from plasma-based tests. Therefore, it is critical that the tissue CDx test is also submitted concurrently with the plasma-based CDx test along with the submission of a BLA to CDER for the review of amivantamab, such that the tissue- and plasma-based tests can be concurrently reviewed by CDRH when the BLA application is being reviewed by CDER.

Janssen submitted a response to this issue on November 18, 2020.

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/

SHARON K SICKAFUSE
11/20/2020 06:50:16 PM

IND 135405

MEETING MINUTES

Janssen Research and Development LLC
Attention: Julie Brennan
Associate Director, Global Regulatory Affairs
920 Route 202 South
Raritan, NJ 08869

Dear Ms. Brennan:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for amivantamab (JNJ-61186372).

We also refer to the teleconference between representatives of your firm and the FDA on November 4, 2020. The purpose of the teleconference was to to discuss the topline results from Study 61186372EDI1001 to support a proposed BLA to be submitted under the provisions of 21 CFR 610.41 for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with Exon 20 insertion mutation, whose disease has progressed on or after platinum-based chemotherapy.

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 teleconference outcomes.

If you have any questions, please call me at 301-796-2320 or email sharon.sickafuse@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Sharon Sickafuse, M.S.
Senior Regulatory Health Project Manager
Division of Regulatory Operations – Oncologic Diseases for DO2
Office of Regulatory Operations
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:

- Teleconference Minutes

MEMORANDUM OF TELECONFERENCE MINUTES

Meeting Type:	Type B
Meeting Category:	pre-BLA
Teleconference Date:	November 4, 2020
Application Number:	IND 135405
Product Name:	amivantamab (JNJ-61186372)
Indication:	Treatment of patients with metastatic non-small cell lung cancer (NSCLC) with Exon 20 insertion mutation, whose disease has progressed on or after platinum-based chemotherapy.
Sponsor Name:	Janssen Research and Development LLC
Regulatory Pathway:	351(a) of the Public Health Service Act
Meeting Chair:	Nicole Drezner
Meeting Recorder:	Sharon Sickafuse

FDA ATTENDEES

Office of Oncologic Diseases

Vishal Bhatnagar, M.D., Associate Director for Patient Outcomes

Division of Oncology 2
Nicole Drezner, M.D.
Abigail Koch, M.D.
Erin Larkins, M.D.
Harpreet Singh, M.D.

Division of Hematology Oncology Toxicology
Whitney Helms, Ph.D.

Office of Biostatistics

Division V
Pallavi Mishra-Kalyani, Ph.D.
Pourab Roy, Ph.D.

Office of Drug Evaluation Science

Division of Clinical Outcome Assessment
Selena Daniels, PharmD., M.S.

Office of Pharmaceutical Quality
Office of Biological Products
Division of Biotechnology Review and Research IV
Andrea Franco, Ph.D.
Leslie Rivera Rosado, Ph.D.

Office of Regulatory Operations
Division of Regulatory Operations – Oncologic Diseases for DO2
Sharon Sickafuse, M.S

CDRH
Office of Product Evaluation and Quality
Office of In Vitro Diagnostics and Radiological Health
Division of Molecular Genetics and Pathology
Rama Kamesh Bikkavilli, Ph.D.

SPONSOR ATTENDEES
Kiran Patel, M.D., VP, Clinical Research & Development
Amy Roshak,Compound Development Team Lead
Roland Knoblauch, M.D., Ph.D., Clinical Lead
Meena Thayu, M.D., Study Physician
Pamela Thorpe, M.D., Medical Safety Lead
Sudhakar Rao, Ph.D., Head, Oncology Biostatistics
John Xie, Ph.D., Biostatistics Lead
Renee Pierson, M.B.A., Patient Reported Outcomes
Leon Freytor, M.S., Global Regulatory Lead
Jayaprakash Karkera, Ph.D., Diagnostics Lead
Sarah Parsons, M.S., Diagnostics Regulatory Lead
Debra Rasmussen, M.B.A., Head, Diagnostics Regulatory
Julie Brennan, M.S., North America Regulatory Lead
Aaron Seto, Ph.D., North America Regulatory Scientist
Par Mahadevia, Global Medical Affairs Lead

BACKGROUND
On September 8, 2020, Janssen submitted a meeting request (SDN 144) to discuss the topline results from Study 61186372EDI1001 entitled, “A Phase 1, First-in-Human, Open-Label, Dose Escalation Study of JNJ-61186372, a Human Bispecific EGFR and cMet Antibody, in Subjects with Advanced Non-Small Cell Lung Cancer,” to support a proposed BLA to be submitted under the provisions of 21 CFR 610.41 for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with Exon 20 insertion mutation, whose disease has progressed on or after platinum-based chemotherapy.

The meeting package was submitted on October 5, 2020, as SDN 148.

Regulatory

On March 9, 2020, amivantamab was granted Breakthrough Therapy designation (BTD) for the treatment of patients with metastatic NSCLC with EGFR Exon 20 insertion mutation, whose disease has progressed on or after platinum-based chemotherapy, based on the objective response rate (ORR 41.4%, 95% CI 23.5, 61.1) results from 29 patients enrolled in Cohort D of Study 61186372EDI1001. Among the 12 patients who had a partial remission, 4 patients (33%) had a duration of response of ≥6 months at the time of the data cut-off.

A teleconference to obtain FDA feedback on the overall development program following the granting of BTD was held on May 6, 2020. During that teleconference, the adequacy of efficacy and safety data from Study 61186372EDI1001 to support a BLA for accelerated approval and the design of a confirmatory study (Study 61186372NSC3001) was discussed. In addition, FDA provided advice on the clinical pharmacology section of the proposed sBLA. FDA also advised Janssen to submit their proposed assessment for reproductive toxicity/embryo-fetal development (EFD) toxicity for feedback with sufficient time so that if FDA determines that any EFD studies are necessary, then conducting such studies would not impact the developmental timeline.

FDA issued an Agreed iPSP letter on June 10, 2020.

A teleconference was held on July 22, 2020, to discuss the content and format of the proposed BLA. During that teleconference, FDA advised Janssen that in order to allow an adequate assessment of durability of response, all responders should have follow-up of 6 months past onset of response.

FDA issued a Type B WRO letter on August 3, 2020, regarding Janssen's proposed assessment for reproductive toxicity/embryo-fetal development toxicity

Janssen canceled a pre-BLA CMC meeting scheduled for August 6, 2020, after receiving FDA's preliminary comments.

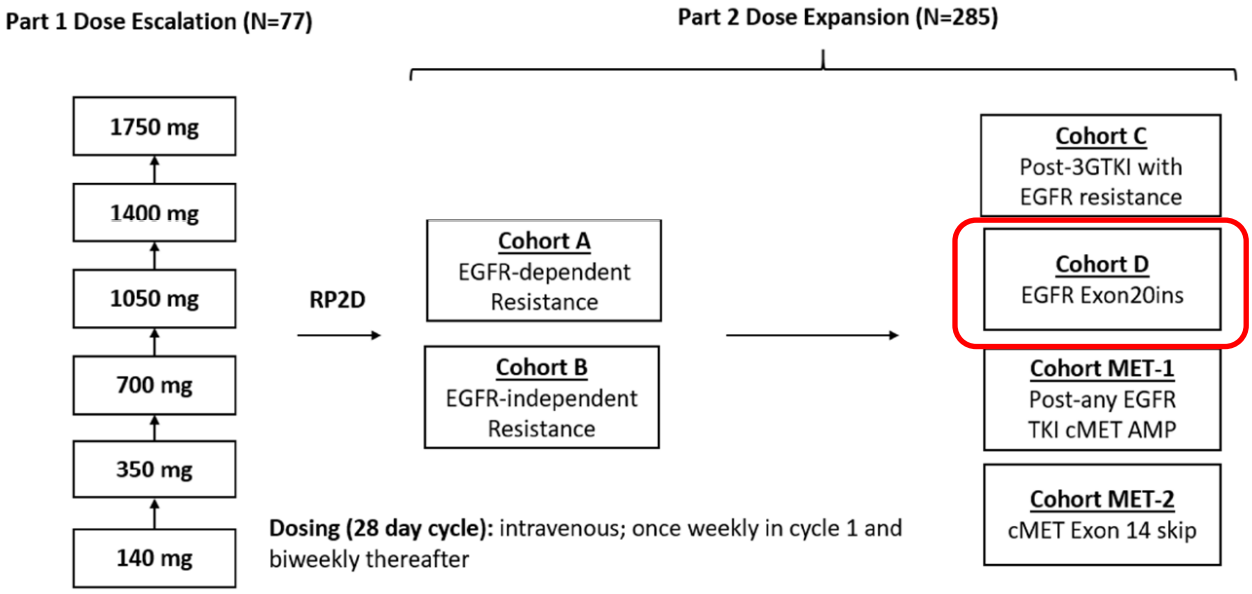
On October 5, 2020, Janssen submitted a request for a rolling BLA.

Clinical

Janssen intends to submit an original BLA for amivantamab, a bispecific antibody directed against the epidermal growth factor (EGF) and mesenchymal epidermal transition (MET) receptors, for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with Exon 20 insertion mutation, whose disease has progressed on or after platinum-based chemotherapy based on the results from the ongoing Study 61186372EDI1001.

Study Design
Study 61186372EDI1001 is an ongoing first-in-human, open label, single-arm, multi-cohort dose escalation (Part 1) and dose expansion (Part 2) study to evaluate the safety, tolerability, and preliminary antitumor activity of amivantamab as a single agent and in combination with other agents in patients with NSCLC with EGFR or MET mutations. The primary endpoint of the dose escalation portion of the study is to establish the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of amivantamab and the primary endpoint of the dose expansion portion of the study is overall response rate (ORR) as assessed by the investigator per RECIST v1.1.

The primary efficacy population supporting the original BLA will include patients with EGFR Exon20ins mutant NSCLC treated at the RP2D of 1050 mg for patients with baseline weight < 80 kg and 1400 mg for patients with baseline weight ≥ 80 kg (administered intravenously every week for the first 4 weeks and every 2 weeks thereafter) who have progressed on prior platinum-based chemotherapy from Cohort D of the dose expansion portion of the study. The study schema is provided below.



EGFR=epidermal growth factor receptor; Exon 20 ins=Exon 20 insertion mutation; TKI=tyrosine kinase inhibitor
Cohorts A and B in Part 2 were closed to enrollment upon opening of subsequent cohorts. Note that a weight-based RP2D was added after the initial RP2D determination.

Meeting package, p.10

Efficacy Summary
As of a clinical cutoff date of June 8, 2020, a total of 362 patients received at least one dose of amivantamab. Of these, 258 patients were treated at the RP2D and of these, 114 patients had Exon 20ins NSCLC and had received treatment with prior chemotherapy. A total of 81 patients had undergone at least 3 scheduled post-baseline

disease assessments or had discontinued the study for any reason. For these patients, the median duration of follow up was 6.5 months (range 1.1-29.3). In the BLA submission, Janssen intends to include supportive efficacy data from the 24 patients with Exon 20ins who received treatment with amivantamab at the RP2D but had not received prior chemotherapy. A summary of the efficacy results is provided in the table below.

Efficacy parameter	Exon20ins w/ prior chemo at RP2D N=81	Exon20ins w/o prior chemo at RP2D N=24
ORR by BICR, n(%) 95% CI	32 (40%) (29, 51)	38% (19, 59)
DOR, months 95% CI	8.2 (5.1, NE)	9.4 (5.4, NE)
% with response ≥ 6 mos	31%*	11%**

*Of 22 responders with DOR < 6 months, response is ongoing for 16 patients
**Of 7 responders with DOR < 6 months, response is ongoing for 6 patients

Safety Summary
The primary safety population includes all patients with NSCLC with Exon20ins mutation treated with amivantamab at the RP2D after platinum-based chemotherapy (N=114). Supportive safety populations that will be analyzed include all patients treated at the RP2D (N=258) and all patients who received at least one dose of amivatamab (N=362).

The median duration of follow-up for the primary safety population was 5.1 months (range: 0.2-29.3). Within this population, a total of 8 patients (7%) experienced an adverse event (AE) resulting in death (infections [3 events], dyspnea [2 events], respiratory failure, sudden death, and cardio-respiratory distress [1 event each]). Thirty percent of patients experienced a serious adverse event of which back pain and pulmonary embolism were the most common (3 events each). A total of 10%, 13%, and 35% of patients had an AE that led to discontinuation, dose reduction, or interruption of study therapy, respectively. Infusion related reaction was the most commonly reported treatment emergent adverse events (TEAE) (66%). Other common TEAEs (>20%) were dermatitis acneiform (46%), paronychia (45%), rash (37%), hypoalbuminemia (27%), constipation (24%), and stomatitis (21%). Major TEAEs were similar between patients in each safety population.

Overall Summary of the Submission
Janssen proposes a rolling review and submission of an assessment aid with the BLA submitted in two parts on November 5 and 24, 2020.

Janssen intends to include the following additional information in the BLA submission:

- Results from Study 61186372NSC1002RWE, a retrospective cohort study of data from 181 patients with EGFR Exon20 ins mutant NSCLC and 2833 patients with NSCLC with common EGFR mutations from the Flatiron Health Advanced NSCLC database to describe the differences in prognosis, outcomes, and treatment patterns in EGFR exon 20 insertion mutations vs. EGFR exon 19 deletions and L858R mutations.

(b) (4)

FDA preliminary comments were emailed to Janssen on November 2, 2020. On November 3, 2020, Janssen emailed a response document stating that they wish to discuss items 1, 4, and 8.

SPONSOR QUESTIONS AND FDA RESPONSES

1. *The Sponsor believes that the Study 61186372EDI1001 topline results are supportive of a BLA submission for amivantamab for the treatment of patients with metastatic NSCLC with Exon 20 insertion mutation, whose disease has progressed on or after platinum-based chemotherapy. Does the Agency agree?*

   FDA Response:
   FDA does not agree. An original BLA for amivantamab should not be submitted until a majority of these patients (e.g. 80-90%) have had follow-up of at least 6 months post onset of response; it remains unclear how many responders of the 32 patients with a response assessed by BICR have had such follow-up. Based on the meeting package, it appears that 22/32 patients with a BICR-assessed response have not had post-response follow-up of 6 months ("Of the 22 responders with a duration of response <6 months, response was ongoing for 16 subjects" p.18).

   As requested during the July 22, 2020, teleconference, provide the following information:

   - Percentage of the 32 responders (by BICR assessment) who have at least 6 months of follow-up from onset of response
   - The actual proportion of responders with a DOR ≥ 6 months.

Janssen response received November 3, 2020:
The primary efficacy population is comprised of 81 consecutively treated subjects who had initiated therapy by February 5, 2020, and had undergone at least 3 post-baseline disease assessments or discontinued therapy at the time of the clinical cutoff of June 8, 2020. As discussed at the July 22, 2020 teleconference, the updated preliminary efficacy data including durability of responses by BICR and by investigator assessment is described below.

As of the October 8, 2020, clinical cut-off, all 32 (100%) BICR-assessed responders had at least 6 months of follow-up from onset of response or had discontinued treatment. The overall response rate remains consistent at 39.5% (95% CI: 28.8%, 51.0%) with an associated median duration of response (mDOR) of 11.14 months (95% CI: 6.90, 21.65). Twenty of the 32 responders (62.5%) have a DOR of at least 6 months. A summary of efficacy updates by investigator and BICR assessments is provided in **Table 1**.

Table 1. Summary of Selected Efficacy Endpoints as of October 8, 2020

	Investigator	BICR
N	81	81
Overall response rate, 95% CI (%)	35.8% (25.4%, 47.2%)	39.5% (28.8%, 51.0%)
Responders; total, ongoing (n)	29, 12	32, 17
Duration of response, median (95% CI), months	11.20 (6.34, 13.14)	11.14 (6.90, 21.65)
Duration of response >=6 months (n,%)	19 (65.5%)	20 (62.5%)
Median progression free survival, months	8.25 (5.49, 10.61)	8.28 (6.51, 10.87)

Summary data on 32 BICR-assessed responders

- 20/32 (62.5%) subjects with DOR ≥ 6 months
    - 13/20 with ongoing responses
- 12/32 subjects with DOR < 6 months
    - 4 subjects have ongoing response by BICR but have discontinued treatment based on investigator assessment, and no new data is forthcoming
    - None of the remaining 8 subjects have ongoing responses
        - 6 subjects have discontinued due to investigator assessed progressive disease

- 1 subject died
- 1 subject has continued on treatment based on investigator assessment

Summary data on 29 investigator-assessed responders

- 19/29 (65.5%) subjects with DOR ≥ 6 months
  - 10/19 subjects with ongoing responses
- 10/29 subjects with DOR < 6 months
  - 2/10 with ongoing response (DOR 4.17 and 5.55 months)
  - The remaining 8 subjects have discontinued study treatment due to progressive disease

These preliminary updated efficacy results from the October 8, 2020 clinical cut-off represent a median follow-up of 9.7 months for the 81 subject efficacy population, and a median follow-up of 11.6 months for the 32 BICR-assessed responders. These data will be provided as a stand-alone report with the BLA submission. The associated updated efficacy datasets will be provided with the 120-day safety update, planned for submission the week of February 22, 2021.

The Sponsor believes the updated efficacy data demonstrate that amivantamab provides robust and durable clinical benefit, and the results are supportive of a BLA submission in subjects with metastatic NSCLC with Exon 20 insertion mutation whose disease has progressed on or after platinum-based chemotherapy.

Discussion during the teleconference:
FDA stated that the original BLA submission must have 6 months of follow-up data for all responders. Without this data, FDA is unable to accept the submission.

After discussion, Janssen and FDA agreed to the following:

- Janssen will submit a BLA containing efficacy data with an October 2020 cut-off and safety data with a June 2020 cut-off.
- The BLA will be a rolling submission of 2 parts with the final part submitted by November 24, 2020.
- The 120 day safety update will contain safety data with an October 2020 cut-off.
- By December 31, 2020, Janssen will submit an updated efficacy dataset with an October 2020 cut-off, an Assessment Aid with an October 2020 data cut-off, an addendum to the clinical study report, an addendum to the Summary of Clinical Efficacy, and an addendum to the clinical overview.

2. *The Sponsor plans to request Priority Review at the time of the initial BLA submission. Does the Agency agree with the Sponsor rationale for requesting Priority Review?*

FDA Response:
FDA agrees; however, whether priority review is granted will be determined at the time of BLA submission.

Janssen response received November 3, 2020:
The Sponsor acknowledges FDA's response, no further discussion is required.

Discussion during the teleconference:
None.

3. *Does the Agency agree with the proposed strategy to submit the Guardant Health Inc plasma test (Guardant360 CDx [P200010]) as companion diagnostics for amivantamab?*

FDA Response:
You mention that Guardant Health (for plasma diagnostic test) is partnering with Janssen to bridge the test performance from the Study 61186372EDI1001 local testing result to the market-ready CDx assay and is planning to submit the Guardant360 CDx (P200010) PMA supplement (sPMA) concurrently with the amivantamab BLA submission. CDRH has no objection to your plans. However, CDRH highly recommends Guardant Health follow the feedback that was offered as a part of pre-submission meeting (Q200694 and Q200694/A001) regarding their analytical and clinical validation strategies. Please also ensure that the sample ascertainment rate for the proposed bridging study is high to demonstrate robust clinical performance of the Guardant 360 CDx test for the proposed indication. Furthermore, CDRH recommends Guardant Health submit the Guardant360 CDx sPMA within 30 days of the BLA submission to CDER for a contemporaneous approval with amivantamab. Of note, when the Guardant Health sPMA is submitted to CDRH concurrently with the BLA submission to CDER, the Guardant360 CDx test can be cross-referenced with the proposed BLA for amivantamab. However, Janssen should provide an authorization letter for this purpose.

In addition to the analytical and clinical validation data submitted in sPMA in support of the device indications for use, any additional data that the diagnostic sponsor plans to leverage from the amivantamab clinical trial to establish the safety and effectiveness of the Guardant360 CDx test should also be submitted in the Guardant Health sPMA. If Guardant Health is unable to provide certain information under the Guardant360 CDx test sPMA due to confidentiality reasons, Janssen can provide a letter of authorization to CDRH to cross-

reference the BLA. Please note that the letter should clearly indicate the attachment/appendix number and the section of the BLA to locate the specific information along with the date of submission of the information to CDER. Alternatively, any confidential clinical validation information in support of device performance can be submitted under the device master file to CDRH by Janssen.

Janssen response received November 3, 2020:
The Sponsor acknowledges FDA's response, no further discussion is required.

Discussion during the teleconference:
None.

4. (b) (4)

ADDITIONAL FDA COMMENTS

Clinical

5. Clarify what therapy, if any, the 24 patients in the primary efficacy population who did not receive prior chemotherapy prior to amivantamab.

Janssen response received November 3, 2020:
Of the 24 subjects who did not receive prior chemotherapy in the metastatic setting, the majority of subjects (16/24; 67%) were treatment naïve. The remaining 8 subjects had received prior treatment summarized below:

- 2 subjects received platinum-based chemotherapy in the adjuvant setting (> 12 months prior to the diagnosis of metastatic disease) without further treatment in the metastatic setting
- 4 subjects received a single line of a first or second generation GFR TKI

- 1 subject received afatanib followed by vinorelbine
- 1 subject received a single line of uftoral (tegafur)

Discussion during the teleconference:
None.

6. Clarify whether enrollment has begun for Study 61186372NSC3001 and, if so, how many patients have been enrolled to date.

Janssen response received November 3, 2020:
Study 61186372NSC3001 is currently underway with 2 sites open in Spain and 2 additional sites (one in US, one in Spain) to be opened by the end of this week. Enrollment is on track to begin this month.

Discussion during the teleconference:
None.

7. Provide a breakdown of the results for rwPFS and rwOS for the 111 patients who received platinum-based chemotherapy regimens as their first line treatment by those who received platinum-based chemotherapy plus immunotherapy and those who received platinum-based chemotherapy alone.

Janssen response received November 3, 2020:

		Median (month)	95% CI
Platinum-based doublet chemotherapy (n=50)*	rwOS	18.3	(11, 28.6)
	rwPFS	6.6	(3.4, 10.9)
Platinum-based chemotherapy + immunotherapy (n=32)	rwOS	11	(5.7, 23.3)
	rwPFS	4.8	(2, 5.7)

*Since original analysis (n=48), 2 patients originally classified as receiving single-agent platinum were reclassified as having received platinum doublet (cisplatin and etoposide)

Discussion during the teleconference:
None.

8. Provide any real world data available on ORR in the subgroups included in the meeting package and described in Comment #7.

Janssen response received November 3, 2020:
This Flatiron dataset did not contain real-world tumor response data. The Sponsor is currently evaluating an expanded Flatiron dataset that is curated to assess real-world tumor response. This dataset will not be available at the time of BLA submission. The Sponsor would like to further understand the usefulness of this data in the context of the BLA review.

Discussion during the teleconference:
FDA clarified that Janssen will need to demonstrate that patients with EGFR Ex20 ins mutations do not benefit from first-line immunotherapy (b) (4) (b) (4) (b) (4). Data on the effectiveness of immunotherapy in this patient population will be a review issue for the confirmatory study.

Clinical Outcome Assessments

9. Anchor-based methods are the primary methods we use to interpret meaningful within-patient score changes in COA endpoints. You should plan to incorporate these methods for the proposed COAs in your protocol and analyses. Anchor-based methods should be supplemented with anchor-based empirical cumulative distribution function and probability density function curves. Other methods may be explored to complement the anchor-based methods or when anchor-based methods are not feasible (i.e., when no adequate anchor measure(s) are available, small sample size). For example, patients can be queried via cognitive interviews, exit interviews, or surveys to help inform the improvement threshold.

Janssen response received November 3, 2020:
The Sponsor acknowledges FDA's response, no further discussion is required.

Discussion during the teleconference:
None.

10. External anchor scales should have the following properties:

a. Selected anchor scales should be associated with the target COA endpoint in a way that addresses the question of clinical meaningfulness of the target COA endpoint. For example, for an endpoint measuring a specific aspect of the disease, an anchor scale measuring the global status of the disease may not be helpful.

b. The anchor scale should be easier to interpret than the COA endpoint itself and meaningful to patients. The anchor scale's response categories should be distinct and non-overlapping and should represent meaningful

differences among adjacent response categories. For example, an anchor scale that uses a 0-10 numeric rating scale would not be easy to interpret and would not be an appropriate anchor scale in most contexts. An example of a commonly used response scale for rating severity is none, mild, moderate, or severe.

c. The anchor scale's recall period should be consistent with the assessment time period of the prespecified endpoint to the extent possible. Additionally, the selected anchors should be assessed at comparable time points as the target COA endpoint but completed by the respondent after the target COA in the order of assessments.

d. The anchor scale should be plainly understood by respondents in the context of use; you should consider testing the draft anchor item(s) including their response categories in cognitive interviews.

Multiple anchors should be explored to provide an accumulation of evidence to help interpret a clinically meaningful within-patient score change (can also be a range) in the clinical outcome endpoint score. At a minimum, we recommend a current state (non-comparative) global impression rating scale, when appropriate, as an anchor scale as these scales are less likely to be subject to recall error than global impression of change scales; it also is a more reliable measure for change from baseline data. We recommend submitting exact copies of your anchor scales for Agency review and concurrence prior to implementing them in your clinical trial(s).

Janssen response received November 3, 2020:
The Sponsor acknowledges FDA's response, no further discussion is required.

Discussion during the teleconference:
None.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. See discussion and agreements for Question 1.

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion was held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan and it was concluded that FDA does not foresee the need for a REMS at this point.

In addition, FDA notes that Janssen cancelled the chemistry pre-submission meeting scheduled for August 6, 2020, after receiving FDA's preliminary comments of July 28, 2020.

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[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, which include:

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

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

[1] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[2] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

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.

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[3] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[4]. 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*.[5]

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the

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

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

- Assessment Aid[7]

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.

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

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/

SHARON K SICKAFUSE
11/06/2020 12:15:57 PM

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	135405
Request Receipt Date	January 9, 2020
Product	JNJ-61186372
Indication	For the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with EGFR exon 20 insertion mutation, whose disease has progressed on or after platinum-based chemotherapy
Drug Class/Mechanism of Action	Humanized monoclonal antibody targeting the extracellular domain of EGFR and cMET tyrosine kinase receptor
Sponsor	Janssen Research and Development LLC
ODE/Division	OOD/Division of Oncology 2
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	March 9, 2020

*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):**

   JNJ-61186372 is indicated for the treatment of patients with metastatic NSCLC with EGFR exon 20 insertion mutation, whose disease has progressed on or after platinum-based chemotherapy.

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," the BTDR can be denied without MPC review. 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.*
- *Disease mechanism (if known) and natural history (if the disease is uncommon).*

[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

Drug description

JNJ-61186372 is a fully-human, bispecific antibody targeting the extracellular domain of both the EGFR and cMET tyrosine kinase receptors. According to the Sponsor, preclinical data suggest three potential mechanisms of action: inhibition of ligand-dependent signaling, downregulation of EGFR and cMET expression levels, and inhibition of antibody-dependent cellular cytotoxicity (ADCC). Janssen is currently developing JNJ-61186372 for treatment of patients with NSCLC with EGFR exon 20 insertion or with MET amplification or mutation.

Information regarding the disease and intended population for the proposed indication

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

EGFR exon 20 mutations occur in approximately 1.7%[5] – 4 %[6] of all EGFR mutations in NSCLC and consist of in-frame insertions in exon 20, leading to activation of the downstream AKT and MEK pathways. These mutations induce a pattern of *in vitro* and *in vivo* resistance to EGFR-TKIs and are reported to increase the affinity of EGFR for adenosine triphosphate (ATP), thus decreasing the efficacy of TKI inhibition (Yasuda et al, Lancet Oncol 2012). *EGFR* exon 20 insertion mutations occur in the same group of patients and tumors with classic EGFR mutations (i.e., women, non-smokers, adenocarcinoma histology) are resistant to clinically achievable doses of EGFR inhibitors approved to date, including gefinitib, erlotinib, neratinib, afatinib, and dacomitinib.

The drug's relation to existing therapy(ies)

Currently there is no FDA-approved targeted therapy for patients with EGFR exon 20 insertion mutation-positive tumors.

Refer to Section 9 below for a summary of conventional systemic therapies that are currently available for EGFR wild-type tumors.

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.

Objective response rate (ORR) per RECIST v.1.1 and duration of response in a single arm study were submitted by the Sponsor to support this breakthrough therapy designation request.

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, objective response rate (ORR) with duration of response has been considered clinically meaningful and supportive of 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.

b. 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 is no FDA-approved target therapy for patients with EGFR exon 20 insertion mutation-positive tumors.

Patients with advanced NSCLC and tumors harbouring EGFR exon 20 insertion mutations are treated with conventional systemic therapies that are available for EGFR wild-type 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 antibody (nivolumab, pembrolizumab or atezolizumab) and single agent chemotherapy (docetaxel, pemetrexed) or docetaxel in combination with ramucirumab. A summary of the trial and approval endpoints are shown in the following table.

Of note, docetaxel with ramucirumab is used infrequently in favor of single agent immunotherapy or chemotherapy. This is due to the additive toxicity of the combination regimen and largely due to the rapid uptake of immunotherapy in clinical practice post 2015. In addition, many ongoing trials utilize single agent docetaxel as a control arm in the second line metastatic NSCLC setting. DO2 considers this acceptable given the additive toxicity and marginal OS benefit of docetaxel plus ramucirumab.

Table 1. Biologic/Drug Approved for 2nd-line metastatic NSCLC

	Clinical Trial	Approval Endpoint
Single Agent checkpoint inhibitor		
Nivolumab	RCT* of nivolumab vs. docetaxel for nonsquamous NSCLC (Checkmate-057)	median OS 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% (95% CI 15, 24) vs. 12% (95% CI 9, 17)**
Pembrolizumab	RCT of pembrolizumab vs. docetaxel for PD-L1 positive metastatic NSCLC (KEYNOTE-010)	Pembrolizumab 10 mg/kg vs. docetaxel mOS 12.7 vs. 8.5mo [HR 0.61 (95% CI 0.49, 0.75)] mPFS 4.0 vs. 4.0 mo [HR 0.79 (0.66, 0.94)] **ORR 19% (95% CI 15, 23) vs. 9% (95% CI 7, 13)**
Atezolizumab	RCT of atezolimab vs. docetaxel for metastatic NSCLC (OAK)	mOS 13.8 vs. 9.6 mo [HR 0.74 (95% CI 0.63, 0.87)] mPFS 2.8 vs. 4.0 mo (HR 0.95 (0.82, 1.10) **ORR 14% (95% CI 11, 17) vs. 13% (95% CI 10, 17)**
Single Agent Chemotherapy		
Docetaxel	RCT docetaxel vs. vinorelbine/Ifosfamide (TAX320 trial)	mOS 5.7 vs. 5.6 mo (Risk Ratio, Mortality 0.82 (95% CI 0.63, 1.06) mTTP 8.3 vs. 7.6 weeks **ORR 5.7% (95% CI 2.3, 11.3) vs. 0.8% vs. (95% CI 0.0, 4.5)**
Pemetrexed	RCT pemetrexed vs. docetaxel (study JMEI)	Exploratory OS analysis by histology (non-squamous) mOS 9.3 vs. 8.0 [HR 0.89 (95% CI 0.71-1.13)]
Combination Therapy		
Docetaxel plus ramucirumab	RCT ramucirumab/docetaxel vs. placebo/docetaxel (REVEL study)	N=1253 mOS 10.5 vs. 9.1 m (HR 0.86 (95% CI 0.75, 0.98) PFS 4.5 v.s 3.0 months [HR 0.76 (0.68, 0.86) **ORR 23% (95% CI 20, 26) vs. 14% (95% CI 11, 17)**

*RCT, randomized, controlled trial

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

NON-RESPONSIVE

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

11. Information related to the preliminary clinical evidence:

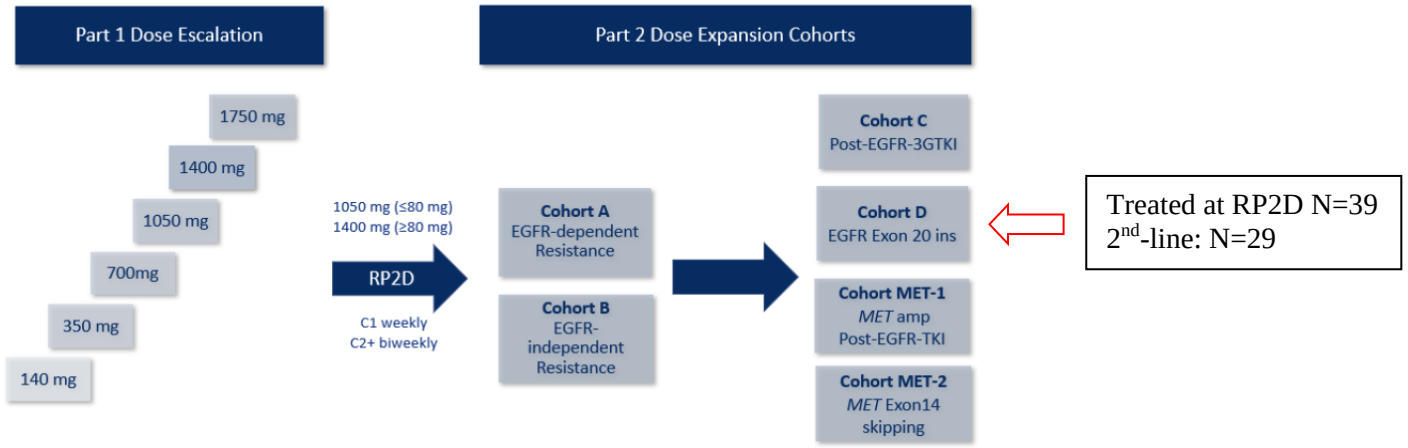
a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design[4], trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio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

Table 2. Clinical Trial Supporting the BTDR

Study ID	Trial Design	No. of Patients	Treatment Group	Results to support BTD
61186372EDI1001	Single arm, dose- finding, activity estimating	Total enrolled: 252 Cohort D: N=39 at RP2D N=29 2nd-line	Part 1: dose escalation Part 2: dose expansion phase, cohorts A, B, C, **D**, MET-1 and MET-2	**Cohort D:** EGFR exon 20 insertion, 2nd-line population N=29 ORR 41.4% (95% CI 23.5, 61.1) DoR 6.8 months (range 1.1+-16.1)*

*4 responders had DOR ≥6 months; 4 had ongoing response but were <6 months from onset of response at the time of the data cut-off; 4 had progressed with a DOR of <6 months

Figure 1. Current Study Design of Study 61186372EDI1001: Monotherapy Cohorts



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.*

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

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

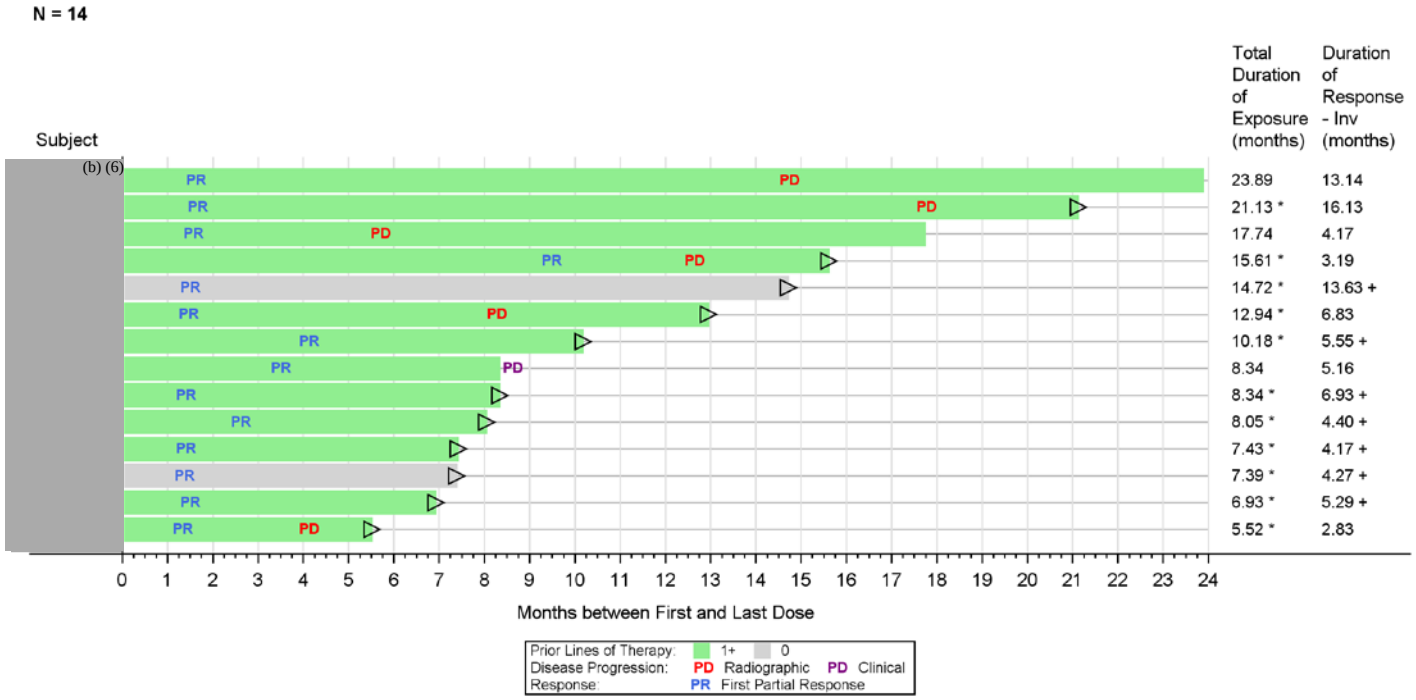
Data to support the BTDR is derived from Cohort D of EDI1001 study, an ongoing, dose-finding, multi-cohort study to evaluate the safety, tolerability and preliminary activity of JNJ-61186372 in patients with EGFR or MET mutations (Figure 1). JNJ-61186372 is administered intravenously, weekly for first 28 day cycle (Cycle 1), and then biweekly until disease progression, unacceptable toxicity or withdrawal of consent.

A the time of the data cut-off (October 30, 2019) 39 patients with EGFR exon 20 insertion mutation NSCLCwere enrolled in Cohort D were evaluable for response. Of the 39 patients, 29 patients had received at least one line of prior therapy, including platinum-based chemotherapy in the metastatic setting. Objective response rate was observed in 12 of 29 patients (ORR 41.4%, 95% CI 23.5, 61.1).

During the review of BTD request, the Sponsor provided at the Division's request additional follow-up data for the duration of response for the patients who had a tumor response. Among the 12 patients who had a partial remission, 4 patients (33%) had a duration of response of ≥6 months and 4 patients had ongoing response but were <6 months from onset of response at the time of the data cut-off. Four responders had progressed with a duration of response of <6 months (data cut off date February 17, 2020). With median duration follow-up time of 9.4 months, the median duration of response was 6.8 months (95% CI: 3.19, 16.1), and the median duration of treatment was 9.2 months.

In addition, the Sponsor stated that as off February 17 data cut-off, one additional patient among the 29 patients with one prior line of therapy demonstrated a confirmed response, which was ongoing, with a duration of response of 1.4 months. The duration of response is summarized in the following figure. Note that 2 patients who had not received prior platinum therapy were included in the figure.

Figure 1. Swim Plot of Treatment Duration for Responders



Safety data were provided for 252 patients enrolled in the EDI1001 study. The most common adverse events (all grades) (≥ 25%) were infusion related reaction (63%), rash (32%), dermatitis acneiform (29%), and paronychia (28%). The most common grade ≥3 adverse events were infusion-related reaction (1.6%), dermatitis acneiform (1.2%), diarreha and rash (0.8% each). Infusion-related reaction (IRR) was the most common adverse event. The majority of IRR were grade 1- 2 and were managed with decrease in infusion rate, anti-histamines and corticosteroids. Other than IRR, the safety profile of JNJ-61186372 is, in general, consistent with the drugs of anti-EGFR class. Infusion-related reaction, the most common adverse reaction, appears to be manageable and tolerable with the risk mitigation strategies in place.

The division notes that currently there is no FDA-approved targeted therapy for patients with EGFR exon 20 insertion mutation-positive tumors. The division considers the ORR (41.4%, 95% CI 23.5, 61.1) observed with JNJ-61186372 as preliminary clinical evidence of a substantial improvement over the currently available therapies. , The division further notes that based on recent data provided by the Sponsor, docetaxel plus ramucirumab is used in less than 4% of the patients receiving second-line therapy for metastatic NSCLC, with anti-PD(L)1 antibodies (nivolumab, pembrolizumab and atezolizumab) the preferred treatment choice. ORRs for the approved anti-PD(L)1 antibodies in second-line treatment of NSCLC has been reported as 14 to 19%.

As stated above, docetaxel with ramucirumab is used infrequently in favor of single agent immunotherapy or chemotherapy. This is due to the additive toxicity of the combination regimen and largely due to the rapid uptake of immunotherapy in clinical practice post 2015. In addition, many ongoing trials utilize single agent docetaxel as a control arm in the second line metastatic NSCLC setting. DO2 considers this acceptable given the additive toxicity and marginal OS benefit of docetaxel plus ramucirumab.

The Division believes that the preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies.

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

☒ GRANT:

Provide brief summary of rationale for granting: The division considers the ORR (41.4%, 95% CI 23.5, 61.1) observed with JNJ-61186372 as 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):

A Type C meeting was held in October 2019 to discuss the Sponsor's plan to introduce manufacturing changes in preparation for the phase 3/commercial launch of the product. FDA provided advice and comments in a WRO letter.

The Division will advise the Sponsor to contact CDRH to discuss issues related to development of a companion diagnostic test to be used in patient selection.

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 2018. 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. Rosell R, Moran T et al.: Screening for Epidermal Growth Factor Receptor Mutations in Lung Cancer. N Engl J Med 2009 Sep 3; 361 (10):958-67

4. NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung cancer https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf

5. Zhang Yue-Lun, Yuan J-Q at al. The Prevalence of EGFR Mutation in Patients with Non-Small Cell Lung Cancer: a Systematic Review and Meta-Analysis. Oncotarget, Vol.7, No. 48, October 12, 2016

6. Yasuda H, Kobayashi Sand Costa DB: EGFR exon 20 insertion mutations in non-small-cell lung cancer: Preclinical data and clinical implications. Lancet Oncol 13: e23-e31, 2012.

7. Noronha V, Choughule A, Patil VM, Joshi A, Kumar R, Susan Joy Philip D, et al. Epidermal growth factor receptor exon 20 mutation in lung cancer: types, incidence, clinical features and impact on treatment. OncoTargets and therapy. 2017;10:2903-8.

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 3/18/19/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/

LEE HONG PAI SCHERF
02/24/2020 09:29:50 PM

ERIN A LARKINS
02/25/2020 09:40:26 AM

B HARPREET SINGH
02/26/2020 07:51:22 PM