CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761291Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	IND 131272
Request Receipt Date	April 8, 2021
Product	Teclistamab (JNJ-64007957)
Indication	Treatment of adult patients with relapsed or refractory multiple myeloma, who have received at least (b) (4) prior therapies, including a proteasome inhibitor (PI), an immunomodulatory agent (IMiD), and an anti-CD38 monoclonal antibody.
Drug Class/Mechanism of Action	Biologic/Teclistamab is a humanized IgG-4 bispecific antibody directed against the B cell maturation antigen (BCMA) and CD3 receptors with proline, alanine, alanine (PAA) (b) (4)
Sponsor	Janssen Research & Development, LLC
ODE/Division	DHM2
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	June 7, 2021

*Note: This document must be uploaded into CDER's electronic document archival system as a **clinical review: REV-CLINICAL-24 (Breakthrough 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):**

   Proposed Indication: For the treatment of adult patients with relapsed or refractory multiple myeloma, who have received at least (b) (4) prior therapies, including a proteasome inhibitor (PI), an immunomodulatory agent (IMiD), and an anti-CD38 monoclonal antibody.

   Revised Indication: For the treatment of adult patients with relapsed or refractory multiple myeloma, who have received at least (b) (4) prior lines of therapy (b) (4) a proteasome inhibitor (PI), an immunomodulatory agent (IMiD), and an anti-CD38 monoclonal antibody.

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

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

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

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

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

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

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}

[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
[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

<u>Section II:</u> 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.

Multiple myeloma (MM) is a hematologic malignancy characterized by clonal expansion of malignant plasma cells in the bone marrow and overproduction of monoclonal immunoglobulins, leading to impaired hematopoiesis and immunity, bone destruction, and kidney injury. MM accounts for 1.8% of all cancers and 2% of all cancer deaths. In 2021, it is estimated that there will be 34, 920 new cases and 12,410 deaths due to MM in the U.S. The median age at diagnosis is 69 (SEER 2014-2018) and the 5-year relative survival is 55.6% (SEER 2011-2017).

Despite the availability of multiple approved therapies for newly diagnosed and relapsed/refractory MM (RRMM), including agents within the three major classes of anti-myeloma therapies – proteasome inhibitors (PIs), immunomodulatory agents (IMiDs), and anti-CD38 monoclonal antibodies (mAb) – and the option of autologous stem cell transplantation (ASCT) for patients who are eligible, MM remains incurable. Prognosis is poor for patients whose MM becomes refractory to available therapies, and patients who are triple-class refractory (i.e., refractory to a PI, an IMiD, and an anti-CD38 mAb) represent a population with unmet medical need.

Teclistamab (JNJ-64007957) is a bispecific monoclonal antibody (mAb) directed against B cell maturation antigen (BCMA) on B cells and cluster of differentiation 3 (CD3) on T cells. BCMA is an attractive target for MM as it is a B-lineage marker that is expressed on normal plasma cells and MM cells. Binding of teclistamab to BCMA on MM cells and CD3 on T cells leads to T cell-mediated cytotoxicity directed against the MM cells.

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.

In the trial being used to support BTD in patients with RRMM, MMY1001, the primary efficacy endpoint for the registrational phase 2 portion of the trial is the overall response rate (ORR), defined as the rate of partial response (PR) or better by the International Myeloma Working Group (IMWG) response criteria, as assessed by an independent review committee (IRC). Key secondary efficacy endpoints include duration of response (DOR), progression-free survival (PFS), overall survival (OS), and minimal residual disease (MRD)-negativity.

The clinical development plan for teclistamab also includes a proposed a phase 3 confirmatory trial, MMY3001, evaluating the efficacy of teclistamab in combination with daratumumab-SC vs. investigator's choice of the DPd or DVd regimen with a primary endpoint of PFS.

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

ORR, supported by DOR data, is an intermediate endpoint that has been used to support accelerated approval for MM. The Division considers PFS an acceptable endpoint for confirmatory trials in patients with MM.

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

MRD-negativity is not a currently accepted endpoint to support approval, but in the future, may be deemed likely to predict clinical benefit in patients with MM.

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.

The table below includes anti-myeloma therapies approved since 2003. Therapies that are relevant to the current BTDR are highlighted in yellow.

Drug	Approval	Indication	Endpoint	Trial Design/Results
Velcade (bortezomib)	Accelerated (2003)	MM, at least 2 prior lines	ORR	Single-arm trial: ORR 28%
Velcade	Regular (2005)	MM, 1-3 prior lines	TTP/OS	RCT: V vs. dex TTP: 6.2 months vs. 3.5 months (HR=0.55) OS: HR=0.57
Doxil Liposomal (doxorubicin HCl)	Regular (2007)	MM, at least 1 prior line	TTP	RCT: Doxil + V vs. V TTP: 9.3 vs. 6.5 months (HR=0.55)
Revlimid (lenalidomide) with dex	Regular (2005)	MM, at least 1 prior line	TTP	RCT: Rd vs. dex Study 1: TTP: 13.9 vs. 4.7 months (HR=0.285) Study 2: TTP: 12.1 vs. 4.7 months (HR=0.32)
Kyprolis (carfilzomib)	Accelerated (2012)	MM, at least 1 prior line	ORR	Single-arm trial: ORR 23%
Kyprolis with Rd	Regular (2015)	MM, 1-3 prior lines	PFS	RCT: KRd vs. Rd PFS: 26.3 vs. 17.6 months (HR= 0.69)
Kyprolis with dex	Regular (2016)	MM, 1-3 prior lines	PFS	RCT: Kd vs. Vd PFS: 18.7 vs. 9.4 months
Pomalyst (pomalidomide)	Accelerated (2013)	MM, at least 2 prior lines, including len and bortez	ORR	RCT: P vs Pd ORR: 7.4% vs. 29.2%
Pomalyst with dex	Regular (2015)	MM, at least 2 prior lines, including len and PI	PFS/OS	RCT: Pd vs. dex PFS: 3.6 vs. 1.8 months (HR=0.45) OS: 12.4 vs. 8.0 months (HR=0.70)
Farydak (panobinostat) with Vd	Accelerated (2015)	MM, at least 2 prior lines, including bortez and IMiD	PFS	RCT: PVd vs. Vd PFS: 10.6 vs. 5.8 months (HR=0.52)
Ninlaro (ixazomib) with Rd	Regular (2015)	MM, at least 1 prior line	PFS	RCT: Ixaz + Rd vs. placebo + Rd PFS: 20.6 vs. 14.7 months
Darzalex (daratumumab)	Accelerated (2015)	MM, at least 3 prior lines, including PI and IMiD	ORR	Single-arm trial ORR: 29% (median 5 prior lines)
Darzalex with Rd	Regular (2016)	MM, at least 1 prior line	PFS	RCT: DRd vs. Rd PFS: 45 vs. 17.5 months (HR=0.37) ORR: 91.3%
Darzalex with Vd *	Regular (2016)	MM, at least 1 prior line	PFS	RCT: DVd vs. Vd PFS: NE vs. 7.2 months (HR=0.39) ORR: 79.3% (median 2 prior lines)
Darzalex with Pd	Regular (2017)	MM, at least 2 prior lines, including len and PI	ORR	Single-arm trial ORR: 59.2% (median 4 prior lines)
Empliciti (elotuzumab) with Rd	Regular (2015)	MM, 1-3 prior lines	PFS	RCT: ERd vs. Rd PFS: 19.4 vs. 14.9 months (HR=0.70)
Empliciti (elotuzumab) with Pd	Regular (2018)	MM, at least 2 prior lines, including len and PI	PFS	RCT: EPd vs. Pd PFS: 10.3 vs. 4.7 months (HR= 0.54)

Xpovio (selinexor) with dex	Accelerated (2019)	MM, at least 4 prior lines, refractory to 2 PIs, 2 IMiDs, and anti-CD38 mAb	ORR	Single-arm trial ORR: 25.4% mDOR 3.8 months (median 7 prior lines)
Xpovio with Vd	Regular (2020)	MM, at least 1 prior line	PFS	RCT: SVd vs. Vd PFS: 13.9 vs. 9.5 months (HR=0.70)
Darzalex with VMP	Regular (2018)	MM, newly diagnosed, transplant-ineligible	PFS	RCT D-VMP vs. VMP PFS: 36.4 vs. 19.3 months (HR=0.50) OS: NR vs. NR (HR=0.60)
Darzalex with Rd*	Regular (2019)	MM, newly diagnosed, transplant-ineligible	PFS	RCT DRd vs. Rd PFS: NR vs. 31.9 months (HR=0.56)
Darzalex with Kd	Regular (2020)	MM, 1-3 prior lines	PFS	RCT: DKd vs. Kd PFS: NR vs. 15.8 months (HR=0.63)
Darzalex with VTd*	Regular (2019)	MM, newly diagnosed, transplant-eligible	PFS, sCR/CR (Day +100)	RCT: D-VTd vs. VTd sCR 28.9% vs. 20.3% CR 9.9% vs. 5.7% PFS: NR vs. NR (HR=0.47)
Darzalex Faspro (daratumumab and hyaluronidase)	Regular (2020)	MM, at least 3 prior lines, including PI and IMiD or PI/IMiD double-refractory	ORR, Max C_{trough}	Non-inferiority trial: SC vs. IV ORR: 41% vs. 37%
Darzalex Faspro with VMP	Regular (2020)	MM, newly diagnosed, transplant-ineligible	ORR	Single-arm trial ORR: 88%
Darzalex Faspro with Rd	Regular (2020)	MM, at least 1 prior line	ORR	Single-arm trial ORR: 91%
Blenrep (belantamab mafodotin)	Accelerated (2020)	MM, 4 prior lines, including anti-CD38 mAb, PI, IMiD	ORR	Single-arm trial ORR: 31% mDOR NR (median 7 prior lines)
Sarclisa (isatuximab) with Pd	Regular (2020)	MM, at least 2 prior therapies, including Len and PI	PFS	RCT: Isa-Pd vs. Pd PFS: 11.5 vs. 6.5 months (HR=0.59)
Sarclisa with Kd	Regular (2021)	MM, 1-3 prior lines	PFS	RCT: Isa-Kd vs. Kd PFS: NR vs. 20.3 months (HR=0.55)
Pepaxto (melphalan flufenamide)	Accelerated (2021)	MM, at least 4 prior lines, refractory to PI, IMiD, anti-CD38 mAb	ORR	Single-arm trial ORR: 23.7% mDOR 4.2 months (median 6 prior lines)
Abecma (idecabtagene vicleucel)	Regular (2021)	MM, at least 4 prior lines, including anti-CD38 mAb, PI, and IMiD	ORR, CR	Single-arm trial ORR: 72%, sCR: 28% mDOR 11 months (median 6 prior lines)

*Indication also approved for Darzalex Faspro

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

There are currently no other drugs being studied for the same or very similar indication in patients with RRMM that have requested BTD. Belantamab mafodotin was granted accelerated approval and received BTD for a similar indication (b) (4)

[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:

Trial	Study Design	Population	Treatment	Endpoint	Results
MMY1001 (MajesTEC-1)	Phase 1/2, first-in-human, open-label dose escalation and dose expansion trial	Phase 1 (Parts 1 and 2, N=157): RRMM refractory or intolerant to therapies with established clinical benefit, prior PI, IMiD and anti-CD38 mAb Phase 2 (Part 3): • Cohort A (N=100): ≥3 prior lines, triple-class exposed • Cohort B (N=90) ≥4 prior lines, penta-refractory • Cohort C (N=38) ≥3 prior lines, triple-class/anti-BCMA exposed	Teclistamab IV or SC RP2D: teclistamab 1500 mcg/kg SC QW preceded by 60 and 300 mcg/kg step-up doses	ORR	Phase 1 (ongoing)* • RP2D (N=40) ORR 65% [95% CI: 48.3, 79.4] ≥CR 40% [95% CI: 24.9, 56.7] • Triple-class refractory (N=33) ORR 60.6% [95% CI: 41.1, 77.1] ≥CR 33.3% [95% CI: 18, 51.8] Phase 2 (ongoing)

*Median follow-up of 6.1 months and 6.7 months for RP2D cohort and triple-class refractory subset, respectively

The request for BTD is based on preliminary results from the ongoing phase 1, first-in-human dose escalation and dose expansion trial, MajesTEC-1. The trial was amended to include a phase 2 registrational portion, which will further evaluate the recommended phase 2 dosing regimen (RP2D) of teclistamab 1500 mcg/kg SC weekly, preceded by two step-up doses of 60 and 300 mcg/kg SC as monotherapy in 3 parallel cohorts that differ based on prior therapies.

The data supporting the BTDR comes from 157 patients that have received teclistamab IV or SC, including 40 patients treated at the RP2D in phase 1. In this subgroup (N=40), the median age was 62.5, patients received a median of 5 prior lines of therapy, and 75% had 4 or more prior lines, 100% were triple-class exposed (prior PI, IMiD, and anti-CD38 mAb), 82.5% were triple-class refractory (TCR, N=33), and 37.5% were penta-refractory (refractory to 2 PIs, 2 IMiDs, and an anti-CD38 mAb).

Efficacy data was provided for the 40 patients who received teclistamab SC at the RP2D and for the subset of 33 patients with TCR-MM treated at the RP2D. In the RP2D cohort, with a median follow-up of 6.1 months, the ORR was 65% [95% CI: 48.3, 79.4], and the ≥ complete response (≥CR) rate was 40% [95% CI: 24.9, 56.7]. Of the 26 responders, 4 patients discontinued treatment (3 due to progressive disease, and 1 due to physician decision based on laboratory evidence of progression not meeting the consensus criteria for progression). The other 22 patients remain on treatment, median DOR has not been reached (range 0.7+ to 10.8+ months), and 12 patients have an ongoing response with a duration of at least 6 months. In the TCR subset, with a median follow-up of 6.7 months, the ORR was 60.6% [95% CI: 41.1, 77.1] and the ≥CR rate was 33.3% [95% CI: 18, 51.8]. Of the 20 responders in this subset, 16 patients remain on treatment, the median DOR is 7.2 months (range 0.7+ to 10.4+ months), and 10 patients have an ongoing response with a duration of at least 6 months.

b. Include any additional relevant information:

A comparison of teclistamab to approved therapies for similar populations of patients with RRMM is summarized in the table below.

Drug	Population	Efficacy	Median DOR
Teclistamab	RRMM, triple-class exposed (N=40)/TCR (N=33)	Triple-class exposed: ORR 65% [95% CI: 48.3, 79.4] ≥CR 40% [95% CI: 24.9, 56.7] TCR: ORR 60.6% [95% CI: 41.1, 77.1] ≥CR 33.3% [95% CI: 18, 51.8]	Triple-class exposed: NR TCR: 7.2 months
Selinexor + dexamethasone (Regular Approval)	RRMM, TCR (N=122)/penta-refractory (N=83)	TCR: ORR 25.4%, ≥CR 1.6% Penta-refractory: ORR 25.3%, ≥CR 1.2%	TCR: 4.4 months Penta-refractory: 3.8 months
Belantamab mafodotin (Accelerated Approval)	RRMM, PI/IMiD-refractory, anti-CD38 mAb-exposed (N=97)	ORR 31%, ≥CR 3.1%	NR
Melphalan flufenamide (Accelerated Approval)	RRMM, TCR (N=97)	ORR 23.7%, ≥CR 0%	4.2 months
Idecabtagene vicleucel (Regular Approval)	RRMM, triple-class exposed (N=100) [85% TCR]	ORR 72%, ≥CR 28%	11 months

Although included in the above table comparing approved therapies for similar patient populations, belantamab mafodotin and melphalan flufenamide are not considered available therapy because both are approved under accelerated approval regulations. In addition, although the CAR T-cell product, idecabtagene vicleucel has regular approval, CAR T-cell products may not be appropriate for consideration as available therapy for patients with MM due to the requirement for patient-specific manufacturing and the toxicity profile of this product, which may preclude some patients from being eligible to receive this product. Therefore, selinexor in combination with dexamethasone is the only currently relevant regimen for comparison with teclistamab.

Experience with the safety of teclistamab includes 157 patients who have received teclistamab IV at doses up to 720 mcg/kg or teclistamab SC at doses up to 3000 mcg/kg. Teclistamab SC is the planned route of administration for further clinical development. At the RP2D (N=40), all patients had at least one treatment-emergent adverse event (TEAE), 43% had at least one Grade 3 TEAE, 38% had at least one Grade 4 TEAE, 43% had at least one serious TEAE, and there were no Grade 5 TEAEs. The most common TEAEs (in ≥20% of patients) were: cytokine release syndrome (CRS, 70%), neutropenia (65%), anemia (50%), thrombocytopenia (45%), fatigue (38%), leukopenia, injection site erythema, nausea (33%), diarrhea (23%), vomiting and headache (20%). Although CRS occurred in 70% of patients, all cases were Grade 1 or 2 in severity (Lee 2014 grading scale), with Grade 1 in 45% of patients and Grade 2 in 25% of patients. Grade 1 immune-effector cell associated neurotoxicity syndrome (ICANS) occurred in one patient (2.5%).

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

☒ GRANT:

Provide brief summary of rationale for granting:

MM is a serious condition, and ORR, supported by DOR data, is an acceptable endpoint for accelerated approval in this disease setting. The data submitted in support of the BTDR is sufficient to be considered as preliminary clinical evidence of improvement over available therapies for patients with triple-class refractory MM. The ORR of 60.6% with a median duration of response of 7.2 months observed with teclistamab in this refractory patient population suggests a substantial improvement in comparison to selinexor + dexamethasone. In addition, the depth of response (≥CR rate 33.3%) also represents a substantial improvement over available therapy.

Although the Division is not formally considering the BCMA-directed CAR T-cell product, idecabtagene vicleucel, as available therapy, the ORR and ≥CR rates observed with teclistamab are similar. Additionally, while teclistamab and idecabtagene vicleucel share some similarities in their mechanism of action, teclistamab has the advantage of being an off-the-shelf product, and the observed rates and severity of CRS and ICANS generally appear lower with teclistamab and other anti-BCMAxCD3 bispecific antibodies compared to BCMA-directed CAR T-cell products, including idecabtagene vicleucel.

Overall, teclistamab is a BCMA-directed bispecific antibody with a novel mechanism of action compared to other approved anti-myeloma therapies, an acceptable safety profile based on preliminary clinical experience, and preliminary clinical evidence that it may demonstrate substantial improvement on a clinically significant endpoint in MM over available therapies. Because the TCR population of patients with MM represents an area of unmet medical need, the Division recommends granting BTD for the revised indication: "For the treatment of adult patients with relapsed or refractory multiple myeloma, who have received at least (b) (4) prior lines of therapy and whose disease is refractory to a proteasome inhibitor (PI), an immunomodulatory agent (IMiD), and an anti-CD38 monoclonal antibody."

☐ DENY:

Provide brief summary of rationale for denial:

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

a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

The Sponsor plans to submit the results from the MajesTEC-1 trial from patients treated at the RP2D of teclistamab in phase 1 (N=40) and in Cohort A in phase 2 (N=110), with supportive data from the phase 1 dose escalation cohorts and phase 2 Cohort C (N=38), with an endpoint of ORR as the basis of an application for accelerated approval. The Sponsor's plans for a confirmatory phase 3 trial, MMY3001, comparing teclistamab-SC in combination with daratumumab-SC versus a control arm of physician's choice (DPd or DVd regimens) were recently discussed at an End-of-Phase 2 teleconference on May 4, 2021. A pre-BLA teleconference is scheduled on May 26, 2021 to further discuss the planned BLA submission. The Agency has concerns regarding the Sponsor's plan to seek accelerated approval based on data from the single-arm trial, MMY1001, in patients who are triple-class exposed, given the availability of multiple approved therapies for this population and has advised the Sponsor that they should include data from a more refractory population (i.e., triple-class refractory patients) in the application. The Agency also has concerns regarding the Sponsor's proposed control arm and proposed flat dosing regimen for the phase 3 confirmatory trial, MMY3001. The Division plans to continue to provide guidance to the Sponsor regarding the planned BLA submission and confirmatory trial.

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. National Cancer Institute Cancer Stat Facts: Multiple Myeloma. Retrieved from https://seer.cancer.gov/statfacts/html/mulmy.html
2. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood. 2014;124:188–195.

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}

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/

ANDREA C BAINES
05/25/2021 04:45:48 PM

BINDU N KANAPURU
05/26/2021 09:22:21 AM

NICOLE J GORMLEY
05/26/2021 09:28:04 AM

IND 131272

MEETING PRELIMINARY COMMENTS

Janssen Research & Development, LLC
Attention: Nancy V. Nair, PharmD, MBA
Director, Global Regulatory Affairs
920 US Highway Route 202 South
Raritan, NJ 08869-0602

Dear Dr. Nair:[1]

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for JNJ-64007957 (teclistamab).

We also refer to your April 5, 2021, correspondence, received April 5, 2021, requesting a meeting to discuss the proposed content and format of the Biologics License Application (BLA) submission for the treatment of adult patients with relapsed or refractory multiple myeloma who have previously received at least (b) (4) prior therapies, including a PI, an IMID, and an Anti-CD38 monoclonal antibody.

Our preliminary responses to your meeting questions are enclosed.

You should provide me an electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

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

If you have any questions, please contact me via email at denise.felluca@fda.hhs.gov or at 301-796-4574.

Sincerely,

{See appended electronic signature page}

Denise Felluca, PharmD, MBA
Regulatory Health Project Manager
Hematologic Malignancies II
Division of Regulatory Operations for Oncologic Diseases
Office of Regulatory Operations
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

U.S. FOOD & DRUG ADMINISTRATION

PRELIMINARY MEETING COMMENTS

Meeting Type:	B
Meeting Category:	Pre-BLA
Meeting Date and Time:	May 26, 2021; 12:00 PM – 1:00 PM (ET)
Meeting Location:	Teleconference
Application Number:	IND 131272
Product Name:	JNJ-64007957 (teclistamab)
Indication:	Teclistamab is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have previously received at least (b)(4) prior therapies, including a PI, an IMiD, and an anti-CD38 monoclonal antibody
Sponsor Name:	Janssen Research & Development, LLC.
Regulatory Pathway:	351(a) of the Public Health Service Act

Office of Oncologic Diseases/Division of Hematologic Malignancies II
Nicole Gormley, MD, *Director*
Bindu Kanapuru, MD, *Clinical Team Leader*
Andrea Baines, MD, PhD, *Clinical Reviewer*

Office of Biostatistics/Division of Biometrics IX
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Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for May 26, 2021, via teleconference between Janssen Research & Development and the Division of Hematologic Malignances II. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Janssen Research & Development, LLC (Janssen) is investigating teclistamab in adult patients with multiple myeloma. Teclistamab is a humanized immunoglobulin G-4 (IgG-4) bispecific antibody directed against the B lymphocyte (B cell) maturation antigen (BCMA) and cluster of differentiation 3 (CD3) receptors with proline, alanine, alanine (PAA) (b) (4)

Janssen requested a Type B Pre-Biologics License Application (BLA) meeting to discuss their proposed content and format of the BLA, planned efficacy and safety analyses, clinical pharmacology plan, and the CMC strategy to support the submission of teclistamab SC for the treatment of adult patients with relapsed or refractory multiple myeloma who have previously received at least (b) (4) prior therapies, including a PI, an IMiD, and an anti-CD38 monoclonal antibody. The BLA will present efficacy and safety data from Study 64007957MMY1001 (MajesTEC-1), titled "*A Phase 1/2, First-in-Human, Open-Label, Dose Escalation Study of Teclistamab, a Humanized BCMA×CD3 Bispecific Antibody, in Subjects with Relapsed or Refractory Multiple Myeloma*."

Janssen intends on submitting a BLA for teclistamab for the proposed indication in December 2021.

2.0 Discussion

2.1 Chemistry Manufacturing and Controls

Question 1: *Is the DS comparability package described for the DS process changes to be introduced into Part 3 of MajesTEC-1 sufficient for the marketing application?*

FDA Response to Question 1:
It appears that the proposed drug substance (DS) change will be implemented during the pivotal clinical study; therefore, a comprehensive analytical comparability data package is expected in the BLA submission. In addition to the quality attributes proposed in the comparability package described in the meeting package, include the following items in the analytical comparability study:

1. Binding activities to CD3 and BCMA.
2. Binding activity to the neonatal Fc receptor (FcRn).
3. Post-translational modifications (such as oxidation, deamidation, and isomerization).
4. Side-by-side comparison of degradation rates using stability indicating assays under forced degradation condition(s).

The DS comparability package submitted to IND amendment SN0113 on 4/6/2021 is still under review. We will communicate additional comments, if any, to you separately.

Question 2: *With regards to the proposed DP PPQ strategy in support of the BLA, does the Agency agree that the approach to include process data on 3 batches (1 representative clinical batch and 2 PPQ batches) for each strength in Section 3.2.P.3.5 Process Validation and/or Evaluation is acceptable?*

FDA Response to Question 2:
Yes, we agree with the proposed drug product (DP) PPQ strategy described in the meeting package.

Question 3: *The Sponsor proposes submission of a stability package with 12 months of real time data from the Part 3 DP clinical batches and 6 months real time data from the DP PPQ batches to support a commercial shelf-life of 12 months, with additional stability data being provided during the BLA review. Does the Agency agree with this proposal?*

FDA Response to Question 3:
In general, product expiries are based on real-time real-condition stability data from DP batches for which manufacture (both DS and DP) and storage are representative of the commercial production (per ICH Q5C). Stability data from earlier processes might be used as supporting data. The final determination of shelf-life will be made upon review

of all available stability data in the BLA. You may provide stability update within 30 calendar days after submission of the original BLA, and/or in response to the Agency's request during the BLA review. In the original submission, please inform the Agency when additional stability data will be available during the BLA review cycle.

Question 4: *The Sponsor is executing the clinical pharmacology plan that was agreed on by the Agency at the End-of-Phase 1 meeting. Does the Agency agree with the proposed plan for format of the Population PK and exposure-response datasets and Immunogenicity data?*

FDA Response to Question 4:
The proposed plan for population PK and exposure-response and immunogenicity appears acceptable to support the BLA submission. A final determination of the adequacy of the clinical pharmacology package will be determined at the time of BLA review. Refer to "Additional Clinical Pharmacology Comments" for more detailed information including the format of datasets.

In addition, we have the following recommendations:

a. Evaluate the effect of DP (i.e., 90 mg/mL or 10 mg/mL DP) on teclistamab PK. In addition, clarify which DP was administered by dose and cohort.

b. As part of the analysis (e.g., noncompartmental analysis, population PK analysis and exposure-response analysis), incorporate teclistamab free drug concentration (i.e., active form) to understand the impact of soluble BCMA on teclistamab PK and PD, efficacy, and safety.

c. Assess race and ethnicity in addition to other covariates known to affect teclistamab PK and PD to facilitate exposure-response analyses to inform safe and effective dosing regimens across the intended patient population. The adequacy of the assessment, which should include a sufficient number of patients reflective of the ethnic and racial diversity of the US patient population, will be a review issue.

2.2 Clinical

Question 5: *Does the Agency agree with the proposed efficacy and safety populations for the CSR for MajesTEC-1?*

FDA Response to Question 5:
No, we have significant concerns regarding your proposal to submit a BLA to support accelerated approval for teclistamab based on the results from Part 2 and Part 3 Cohort A of the MajesTEC-1 trial. As expressed at the EOP1 meeting there are multiple approved regimens available for the treatment of patients with relapsed MM who are triple-class exposed (i.e., exposed to a PI, an IMiD, and an anti-CD38 mAb).To support

accelerated approval based on a single arm trial evaluating an intermediate endpoint such as ORR, the results will need to demonstrate that teclistamab provides a meaningful advantage in the context of available therapies in the proposed patient population. Available therapies are determined at the time of regulatory action on the NDA. The definition of available therapy may change over time given the evolving treatment landscape for multiple myeloma.

Clarify your plans for submission of data from the more refractory population of patients in Cohort B.

If you decide to proceed with the submission, we have the following comments:

- It would not be appropriate to pool patients from phase 1 and phase 2 for the primary efficacy analysis due to the differences in response assessment (i.e., Investigator-assessed vs. IRC-assessed). We recommend that you base the primary efficacy population on patients with IRC-assessed responses from phase 2.
- It would be reasonable to pool patients treated at the RP2D from phase 1 and phase 2 for presentation in the summary of clinical efficacy to provide supportive evidence for efficacy. You should also submit integrated summary of efficacy datasets.
- You should ensure that the primary efficacy population includes patients with a minimum of 6 months of follow-up form the time of response to allow for an adequate assessment of durability of response.
- For the primary efficacy population, the CSR should address any differences between IRC-, algorithm-, and investigator-assessed responses.
- We strongly recommend that you provide efficacy results based on refractory status of patients to prior therapies in the CSR and include flags in the datasets to indicate this information.
- We recommend that you present data from the 80 and 240 mcg/kg SC dose escalation cohorts separately.
- For single-arm trials with the registrational intent, the study should have at least 90% power at 2-sided alpha of 0.05 to rule out the response rate under the null hypothesis in the proposed population.
- Your proposal for the primary safety data to include all patients treated at the RP2D in phase 1 and phase 2 Cohort A (approximately 165 to 175 patients) appears reasonable. Clarify your plans for presentation of the safety data for patients treated in the phase 1 dose escalation cohorts.

Question 6: *The Sponsor proposes to submit narratives and case report forms for all treated subjects in MajesTEC-1 who meet the following criteria:*

(b) (4)

Does the Division agree with the proposed criteria?

FDA Response to Question 6:
No, we do not agree with your proposal. For a single arm trial, FDA considers all treatment-emergent adverse events regardless of attribution relevant to assess safety of the product. You should submit narratives and CRFs for all deaths within 30 days of last dose, serious TEAEs, TEAEs leading to permanent discontinuation, and AEs of clinical interest regardless of "relatedness." In addition, you should also submit narratives and CRFs for patients who had Grade 1 or 2 CRS who received tocilizumab and narratives for patients with clinical evidence of disease progression.

The case narratives should be generated or reviewed/edited by trained personnel with medical knowledge and should include the following information: study day of onset (not calendar date), day from last dose of study drug, basic demographic information (age, sex, underlying diagnosis), predisposing risk factors/comorbidities, description of the event including signs, symptoms and relevant laboratory values/diagnostic tests leading to diagnosis, treatment for the event, information related to study drug action (interrupted, modified, discontinued, etc.), duration of the event, event outcomes, re-challenge/de-challenge information (if available), and investigator and sponsor assessment regarding the causality of the event to either the investigational drug or an alternative etiology.

To enhance retrieval of narratives, your submission should include a hyperlinked table tracking subject narratives by category, similar to the example below:

Subject ID	DLT	Death	SAE	Discontinuation	CRS	Neurotoxicity	…
0001	Y						
0002			Y	Y			
0003		Y			Y	Y	
…							

Additional narratives and/or CRFs may be requested during the review of your BLA submission.

Question 7: *Does the Division agree with our proposal regarding the summary level clinical site dataset for MajesTEC-1 to support inspection planning?*

FDA Response to Question 7:
Your proposal to provide summary level clinical site datasets, site level listings, and subject level data line listings by clinical site in accordance with the draft guidance appears reasonable.

Question 8: *Does the Agency agree with the proposed submission of the SCE and that a separate Integrated Summary of Efficacy is not warranted?*

FDA Response to Question 8:
Refer to the FDA Response to Question 5.

Question 9: Does the Agency agree with the proposed plan for the submission of the SCS and that a separate Integrated Summary of Safety is not warranted?

FDA Response to Question 9:
No, the primary safety dataset should include data from patients treated at the RP2D and you should include an integrated summary of safety dataset that includes the safety data from all cohorts with flags to indicate pooled populations based on dose and route of administration.

We also have concerns regarding the interpretability of the primary safety data for events of CRS and ICANS given the use of different grading systems for the phase 1 and phase 2 portions of the trial. You will need to address these differences in the CSR and SCS.

Question 10: *The Sponsor proposes to provide (1) Financial Certification and/or Disclosure information (Form FDA 3454/3455) and (2) the list of all investigators who participated in MajesTEC-1. The list of investigators will contain the investigator's name, address, phone number, and number of subjects enrolled. Does the Division agree this is acceptable?*

FDA Response to Question 10:
In general, your proposal appears acceptable. Financial certification and/or disclosure should be provided for any clinical study(s) which uses data to establish the product efficacy, or safety demonstration. You should submit financial disclosure information in a format that will ensure all required information is included. Provide the total number of investigators in the study and a table indicating, for each clinical investigator listed who is not identified as an employee, whether they are providing a Certification (FORM FDA 3454), a Disclosure Statement (FORM FDA 3455) or certification that they acted with

due diligence but were unable to obtain the information (option 3 on FORM FDA 3454). All proper forms should be submitted for investigators per the following *Guidance for Clinical Investigators, Industry, and FDA Staff – Financial Disclosure by Clinical Investigators*.

Question 11: *Does the Agency agree with the proposed plan to submit SAS codes for the generation of analysis data sets and key efficacy/safety results*?

FDA Response to Question 11:
Your proposed plan appears reasonable. Additionally, we recommend you provide the following information:

1. Provide executable SAS programs with adequate document(s) used to create all ADaM datasets along with the tables and figures associated with primary and secondary efficacy analyses
2. Provide the SAS programs as well as format library files used for efficacy data analysis. If the SAS programs use any SAS macro, please provide all necessary macro programs.

Additional Clinical Comments

1. Refer to the comment below regarding the Assessment Aid. The Agency recommends that you consider submitting an assessment aid document with your BLA submission.
2. Include a dataset that includes the following information for all responders:

Subject ID	Disease assessment at screening*	Disease assessment at baseline (prior to treatment)*	Adjudicated best response to teclistamab	Disease assessment at progression*	Study day of progression
0001					
0002					
…					

*Include results of serum and urine protein electrophoresis, immunofixation, free light chain analysis, imaging, bone marrow aspirate and biopsy

3. For assessment of neurologic adverse events, we recommend grouping of preferred terms using, but not necessarily limited to, the grouped terms below:
    a. Aphasia: aphasia, dysphasia
    b. Delirium: agitation, delirium, delusion, disorientation, hallucination, restlessness
    c. Encephalopathy: cognitive disorder, confusional state, depressed level of consciousness, disturbances in attention, encephalopathy, hypersomnia, leukoencephalopathy, memory impairment, mental status changes, paranoia, somnolence, stupor
    d. Tremor: head titubation, tremor

4. We request that you include Yes/No flags for cytokine release syndrome (CRS) and neurotoxicity (NT) in the ADAE and ADSL datasets. The CRS and NT Yes/No flags should be a subject level flag and not an adverse event (AE) level flag.
5. We request that you submit separate datasets for CRS and neurotoxicity, if applicable. The dataset(s) should incorporate the following:

   CRS Dataset:
   - Each row assigned to a unique subject with CRS diagnosis per investigator's assessment.
   - Key elements of CRS: fever, hypotension, hypoxia.
   - CRS treatment: oxygen, vasopressors, tocilizumab, corticosteroids, ventilator support, ICU stay, other interventions (e.g., other IL-6 inhibitors), if used.
   - Details of treatment: For example, number of vasopressors and type of oxygen delivery (e.g., low-flow nasal cannula, facemask, etc.), need to be captured to grade CRS accurately by the proposed ASTCT (American Society for Transplantation and Cellular Therapy) grading criteria. Other treatment details should also be provided – for example, dose of steroids and start/stop dates for each intervention.
   - Date and day of study treatment and start and end dates and study days for CRS to capture timing of CRS onset and duration.
   - Maximum CRS grade based on ASTCT consensus grading system
   - Organ dysfunction (SOC and PT) grade based on CTCAE version 5.0 seen in association with CRS.
   - CRS grading by Lee criteria to enable comparison of toxicity profile across products.
   - Flag for subjects in CRS dataset that develop neurotoxicity concurrently with CRS, with maximum grade.

   NT Dataset:
   - Each row assigned to a unique subject.
   - NT timing in relation to study treatment and in relation to CRS (e.g. preceding CRS, occurring concurrently with CRS, following CRS, or an isolated event).
   - Date and day of study treatment and start and end dates and study days for NT to capture timing of NT onset and duration.
   - Therapeutic intervention with details/outcome.
   - Outcome: e.g., resolution, worsening, unchanged but ongoing.
   - Maximum grade of NT based on ICANS (immune effector cell-associated neurotoxicity syndrome) ASTCT consensus grading system
   - NT symptoms/signs not included under ICANS, such as tremor and dysarthria should be graded with CTCAE version 5.0.
   - Both Neurologic and Psychiatric SOC adverse events should be captured in the NT dataset

Additional Clinical Pharmacology Comments

The content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support this application should be consistent with FDA Guidance for Industry, "*Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format*". Consider strategies to enhance clarity, readability, and comprehension of this information for health care providers through the use of text attributes, tables, and figures as outlined in the above guidance.

Address the following questions in the Summary of Clinical Pharmacology:

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

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

1. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.
2. Provide the final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with range as appropriate.
3. Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The subjects' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.
    - Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
    - Identify individual subjects with dosage modifications; the time to the first dose reduction, interruption or discontinuation; the reasons for dosage modifications in the datasets.
4. Submit the following for the population pharmacokinetic analysis reports:
    - Standard model diagnostic plots
    - Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line
    - Model parameter names and units in tables.
    - Summary of the report describing the clinical application of modeling results.

Refer to the pharmacometric data and models submission guidelines.

5. Submit the following information and data to support the population pharmacokinetic analysis:
   - SAS transport files (*.xpt) for all datasets used for model development and validation
   - A description of each data item provided in a Define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets
   - Model codes or control streams and output listings for all major model building steps, (e.g., base structural model, covariates models, final model, and validation model). Submit these files as ASCII text files with *.txt extension (e.g., myfile_ctl.txt, myfile_out.txt)
6. Submit a study report describing exploratory exposure-response (measures of effectiveness, biomarkers and safety) relationships in the targeted patient population. Refer to Guidance for Industry for population PK, and exposure-response relationships.
7. Complete and include the tables (Table 1 - bioanalytical method life cycle information, and Tables 2a-b - summary method performance of each bioanalytical method) in your 351(a) BLA submission to provide the information regarding the bioanalytical methods for pharmacokinetic and/or immunogenicity assessments used in pivotal clinical pharmacology studies and its life-cycle information pertaining to the submission. Do not delete any rows from the tables. We recommend that these tables be included as an Appendix in the Summary of Biopharmaceutics located in eCTD 2.7.1. In addition to including in the Appendix, we request you also submit both tables in docx format. Include any other additional bioanalytical information that might be relevant for review in your BLA submission.

Table 1. Summary life cycle information of bioanalytical method(s) used in submission of BLA xxxxxx to measure analyte X in matrix

	Method validation #1	**Method validation #2**	**Clinical Study x**	**Clinical Studies y-z**
Analyte	Drug name	Drug x, Drug y	Drug x, and Drug y	Drug x, Drug z
Validation type	Full	Partial validation of method xx	NA	NA
• CTD ref #	Ref # in eCTD	x0000.0xxxxxxx	x0000.0xxxxxxx	x0000.0xxxxxxx
• method ID • BA site	Method ID xx (version)	SOP xxxx or Method xxx (v 1.0)	SOP xxxx or Method xxx (v 1.0)	SOP xxxx or Method xxx (v 1.0)
	Name of BA test facility	US Lab 1	US lab 1	Other lab
• Matrix	Serum/ Plasma/Urine/ whole blood			
• Platform	LC/MS, ELISA, ECL			
• Format	A validated sandwich format using x as capture and y as detection, a bridging format using z as both capture and detection, competitive assay using x as a capture and b as a competitor			

Stock reference & lot (expiry)	Drug 1, lot 1	Drug 1, lot 2 Drug 2, lot 1		
Calibration range (LLOQ -ULOQ) and levels validated	x- x000 ng/mL (Eg. 2, 5, 50, 250, 1000, 1500, 2000 ng/mL)	x- x000 ng/mL	x- x000 ng/mL	x- x000 ng/mL
Matrix/ study population	Normal or x diseased serum	Normal serum	Normal serum	x Diseased population
Relevant reference and applicable report amendment (s) and links -Amendment 1 -Amendment 2				
Amendment history				

The bioanalytical method performance summary table (**Table 2a**) is recommended in describing PK and/or biomarker methods. Please use one method per analyte per table. This table is not applicable for anti-drug antibody methods. Do not delete any rows or columns from the table. State "not applicable" if certain rows or columns are not applicable. Include any additional bioanalytical data that may be relevant to the submission.

Table 2a. Summary method performance of a bioanalytical method to measure [analyte] in [matrix]

Bioanalytical method validation report name, amendments, and hyperlinks			
Method description			
Materials used for calibration curve & concentration			
Validated assay range			
Material used for QCs & concentration			
Minimum required dilutions (MRDs)			
Source & lot of reagents (LBA)			
Regression model & weighting			
Validation parameters	**Method validation summary**		**Source location**
Calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	x	
	Cumulative accuracy (%bias) from LLOQ to ULOQ Product A Product B and/or Product C	 x to y% x to y% x to y%	

	Cumulative precision (%CV) from LLOQ to ULOQ Product A Product B and/or Product C	 ≤ x% ≤ x% ≤ x%	
QCs performance during accuracy & precision	**<u>Cummulative accuracy (%bias) in 5 QCs</u>** QCs: Product A Product B and/or Product C	 x to y% x to y% x to y%	
	<u>Inter-batch %CV</u> QCs: Product A Product B and/or Product C	 ≤ x% ≤ x% ≤ x%	
	<u>Total error</u> QCs: Product A Product B and/or Product C	 ≤ x% ≤ x% ≤ x%	
Selectivity & matrix effect	Number of total lots tested. Range of observed bias. State any issue		
Interference & specificity	Number of total lots tested. Range of observed bias. State any issue		
Hemolysis effect	Number of total lots tested. Range of observed bias. State any issue		
Lipemic effect	Number of total lots tested. Range of observed bias. State any issue		
Dilution linearity & hook effect	Describe data here		
Bench-top/process stability	Describe data here Product A Product B and/or Product C		
Freeze-Thaw stability	Describe data here Product A Product B and/or Product C		
Long-term storage	Describe data here Product A Product B and/or Product C		
Parallelism	Describe data here		
Carry over	Describe data here		
Method performance in study number **(In addition to the report name, also provide hyperlink to the report)**			
Materials used for calibration curve & QC			
Assay passing rate	(including incurred sample reanalysis (ISR))		
Standard curve performance	• Cumulative bias range: x to y% • Cumulative precision: ≤ x% CV		
QC performance	• Cumulative bias range: x to y% • Cumulative precision: ≤ x% CV • TE: ≤ x% (LBA only)		

Method reproducibility	Incurred sample reanalysis was performed in x% of study samples and x % of samples met the pre-specified criteria	
Study sample analysis/ stability	Describe storage stability coverage for standard/QC and samples	

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

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

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

Additional CMC Comments

1. To facilitate the Agency's review of the manufacturing processes for the teclistamab drug substance (DS), and drug product (DP), we suggest you provide information for all attributes, parameters, or controls proposed for routine commercial manufacturing as well as those evaluated during development and validation, in the tabular format (see below as one possible example). Please provide a separate table for each unit operation. The tables should summarize information from Module 3 and may be submitted either to Module 1 or Module 3R. Note, this table does not replace other parts of Module 3 or impact the nature or amount of information included in those parts of Module 3.

Title: INSERT UNIT OPERATION

Process parameter/	Proposed Range for	Criticality classification[3]	Characterized Range from	Manufactured Range from	Justification of the proposed commercial	Comment[5]

operating parameter/In-process control (IPC)/In-process tests (IPT)[1]	Commercial Manufacturing[2]		process development[2]	process validation[2]	acceptable range[4] (or link to eCTD)	

[1] Terminology should be adapted to the one used by Janssen Research & Development, LLC.
[2] As applicable.
[3] For example, critical process parameter, non-critical process parameter, as described in Module 3.
[4] This could be a brief verbal description (e.g., "development range", "validation range", or "platform experience") or links to the appropriate section of the eCTD.
[5] Optional.

2. To facilitate the Agency's review of the control strategy for teclistamab, we suggest you provide information for critical quality attributes, process and product related impurities for the DS, and DP in a tabular format (see below for one possible example). The tables should summarize information from Module 3 and may be submitted either to module 1 or Module 3R. Note, this table does not replace other parts of Module 3 or impact the nature or amount of information included in those parts of Module 3.

Title: INSERT DRUG SUBSTANCE OR DRUG PRODUCT

Critical Quality Attributes (including Process and Product related impurities for DS and DP)	Impact[1]	Source[2]	Analytical method[3]	Proposed control strategy[4]	Justification of the proposed control strategy[5]	Comment[6]

[1] What is the impact of the attribute, e.g., contributes to potency, immunogenicity, safety, efficacy.
[2] What is the source of the attribute or impurity, e.g., intrinsic to the molecule, fermentation, protein A column.
[3] List the methods used as part of the control strategy to test an attribute in-process, at release, and on stability. For example, if two methods are used to test identity then list both methods for that attribute.
[4] List all the ways the attribute is controlled, e.g., in-process testing, validated removal, release testing, stability testing.
[5] This could be a brief verbal description or links to the appropriate section of the eCTD.
[6] Optional.

Additional CMC Microbiology Comments

The FDA is providing additional product quality microbiology comments for you to consider during development of your commercial manufacturing process and preparation of your 351(a) BLA submission.

All facilities should be registered with the FDA at the time of the 351(a) BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Include in the BLA submission a complete list of the manufacturing and testing sites with their

corresponding FEI numbers. A preliminary manufacturing schedule for the drug substance and drug product should be provided in the BLA submission to facilitate the planning of pre-license inspections during the review cycle. Manufacturing facilities should be in operation and manufacturing the product under review during the inspection.

Information and data for CMC product quality microbiology should be submitted in the specified sections indicated below.

The CMC Drug Substance section of the 351(a) BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control of the drug substance. The information should include, but not be limited to the following:

- Bioburden and endotoxin levels at critical manufacturing steps should be monitored using qualified bioburden and endotoxin tests. Bioburden sampling should occur prior to any 0.2 µm filtration step. The pre-established bioburden and endotoxin limits should be provided (3.2.S.2.4).
- Bioburden and endotoxin data obtained during manufacture of three process qualification (PPQ) lots (3.2.S.2.5).
- Microbial data from three successful product intermediate hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5).
- Chromatography resin and UF/DF membrane lifetime study protocols and acceptance criteria for bioburden and endotoxin samples. During the lifetime studies, bioburden and endotoxin samples should be taken at the end of storage prior to sanitization (3.2.S.2.5).
- Information and summary results from the shipping validation studies (3.2.S.2.5).
- Drug substance bioburden and endotoxin release specifications (3.2.S.4).
- Summary reports and results from bioburden and endotoxin test method qualification studies performed for in-process intermediates and the drug substance. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers (3.2.S.4).

The CMC Drug Product section of the 351(a) BLA (Section 3.2.P) should contain validation data summaries to support the aseptic processing operations. For guidance on the type of data and information that should be submitted, refer to the 1994 FDA Guidance for Industry *"Submission Documentation for Sterilization Process Validation in*

Applications for Human and Veterinary Drug Products" at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf.

The following information should be provided in Sections 3.2.P.3.3 and/or 3.2.P.3.4, as appropriate.

- Identification of the manufacturing areas and type of fill line (e.g. open, RABS, isolator), including area classifications.
- Description of the sterilizing filter (supplier, size, membrane material, membrane surface area, etc.); sterilizing filtration parameters (e.g., differential pressure if a pump is used) as validated by the microbial retention study; wetting agent used for post-use integrity testing of the sterilizing filter and post-use integrity test acceptance criteria.
- Parameters for filling and capping for the vials.
- A list of all equipment and components that contact the sterile drug product (i.e. the sterile-fluid pathway) with the corresponding method(s) of sterilization and depyrogenation, including process parameters. The list should include single-use equipment.
- Processing and hold time limits, including the time limit for sterilizing filtration and aseptic filling.
- Sampling points and in-process limits for bioburden and endotoxin. Bioburden samples should be taken at the end of the hold time prior to the subsequent filtration step. Pre-sterile filtration bioburden limits should not exceed 10 CFU/100 mL.

The following study protocols and validation data summaries should be included in Section 3.2.P.3.5, as appropriate:

- Bacterial filter retention study for the sterilizing filter. Include a comparison of validation test parameters with routine sterile filtration parameters.
- Sterilization and depyrogenation of equipment and components that contact the sterile drug product. Provide summary data for the three validation studies and describe the equipment and component revalidation program.
- In-process microbial controls and hold times. Three successful product intermediate hold time validation runs should be performed at manufacturing scale, unless an alternative approach can be scientifically justified. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided.

- Isolator decontamination summary data and information, if applicable.
- Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs. Describe the environmental and personnel monitoring procedures followed during media fills and compare them to the procedures followed during routine production.
- Information and summary results from shipping validation studies.
- Validation of capping parameters, using a container closure integrity test.

The following product testing and method validation information should be provided in the appropriate sections of Module 3.2.P:

- Container closure integrity testing. System integrity should be demonstrated initially and during stability. Container closure integrity method validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress (≤ 20 microns). Container closure integrity testing should be performed *in lieu* of sterility testing for stability samples every 12 months (annually) until expiry.
- Summary report and results for qualification of the bioburden, sterility, and endotoxin test methods performed for in-process intermediates (if applicable) and the finished drug product, as appropriate. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers. Provide full descriptions and validation of non-compendial rapid microbial methods.
- Summary report and results of the Rabbit Pyrogen Test conducted on three batches of drug product in accordance with 21 CFR610.13(b).
- Low endotoxin recovery studies. Certain product formulations have been reported to mask the detectability of endotoxin in the USP <85> *Bacterial Endotoxin Test* (BET). The effect of hold time on endotoxin detection should be assessed by spiking a known amount of standard endotoxin (RSE or purified CSE) into undiluted drug product and then testing for recoverable endotoxin over time.

3.0 IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our April 14, 2021, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

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

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

Information on the Program is available at FDA.gov.[2]

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create

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

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

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

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

For the latest version of the molecular target list, please refer to FDA.gov.[3]

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020 or sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant

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

to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided. Meetings requests should be sent to the appropriate review division with the cover letter clearly stating "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[4]

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[5] and Pregnancy and Lactation Labeling Final Rule[6] 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.

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

- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

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

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

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

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

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

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

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

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

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

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[7]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[8]

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sBLA meeting. Those applicants who do not wish to

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

participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

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

- Assessment Aid[10]

NONPROPRIETARY NAME

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

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

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

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

Advancing Oncology Decentralized Trials

FDA Oncology requests that applicants submitting data to support NDA/BLA applications to voluntarily add flags to datasets in order to discriminate between REMOTE assessments and TRIAL SITE assessments. The intent is to allow FDA to learn from trials conducted in the COVID-19 pandemic that permitted some aspects of trial conduct to be performed remote from trial sites to reduce potential COVID exposure. The FDA hopes to learn more about the opportunities and challenges of

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

these REMOTE modifications in order to foster use of “decentralize” aspects of clinical trials prospectively in the post-COVID era.

For details please refer to: https://www.fda.gov/about-fda/oncology-center-excellence/advancing-oncology-decentralized-trials.

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/

DENISE A FELLUCA
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IND 131272

MEETING MINUTES

Janssen Research & Development, LLC
Attention: Sara Bender, PharmD, MHS
Manager Global Regulatory Affairs
920 US Highway Route 202 South
Raritan, NJ 08869-0602

Dear Dr. Bender:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for JNJ-6400795.

We also refer to the telecon between representatives of your firm and the FDA on May 4, 2021. The purpose of the meeting was to discuss the proposed Phase 3 study 64007957MMY3001.

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

If you have any questions, call Denise Felluca, Regulatory Project Manager, at 301-796-4574.

Sincerely,

{See appended electronic signature page}

Bindu Kanapuru, MD
Clinical Team Leader
Division of Hematologic Malignancies II
Office of Oncologic Diseases
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

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

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	End-of-Phase 2
Meeting Date and Time:	May 4, 2021 1:00-2:00PM ET
Meeting Location:	Teleconference
Application Number:	IND 131272
Product Name:	teclistamab (JNJ-64007957)
Indication:	For the treatment of adult patients with relapsed or refractory multiple myeloma, who previously received a proteasome inhibitor (PI), an immunomodulatory agent (IMiD), and ananti-CD38 antibody
Sponsor Name:	Janssen Research & Development, Inc.
Regulatory Pathway:	351(a) of the Public Health Service Act
Meeting Chair:	Bindu Kanapuru, MD
Meeting Recorder:	Denise Felluca, PharmD, MBA

FDA ATTENDEES

Office of Oncologic Diseases/Division of Hematologic Malignancies II
Nicole Gormley, MD, *Director*
Bindu Kanapuru, MD, *Team Leader*
Andrea Baines, MD, PhD, *Reviewer*

Office of Biostatistics/Division of Biometrics IX
Yu-Te Wu, PhD, *Team Leader*
Wenjuan Gu, PhD, *Reviewer*

Office of Clinical Pharmacology/Division of Cancer Pharmacology I
Edwin Chow, PhD, *Team Leader*
Vicky Hsu, PhD, *Reviewer*

Office of Regulatory Operations for Oncologic Diseases
Theresa Carioti, MPH, *Chief, Project Management Staff*
Denise Felluca, PharmD, MBA, Regulatory Health Project Manage

Center for Devices and Radiological Health/Division of Molecular Genetics and Pathology
Zivana Tezak, PhD, Branch Chief
Karen Bijwaard, PhD, Team Lead
Christopher Trindade, MD, Clinical Reviewer

SPONSOR ATTENDEES

Arnob Banerjee, MD, PhD, Executive Medical Director, Early Development
Sara Bender, PharmD, MHS, North American Regulatory Leader
Veerle Brochez, PhD, Chemistry, Manufacturing, and Controls Regulatory Affairs
John Fastenau, RPh, MPH, PhD, Senior Director, Patient Reported Outcomes
Suzette Girgis, MS, PhD, Clinical Pharmacology Leader
Jenna Goldberg, MD, Global Medical Head, Clinical Development
Carrie A Grasmeder, MS, North American Regulatory Scientist
Brett Hanna, MS, Chemistry, Manufacturing, and Controls Leader
Christoph Heuck, MD, Senior Medical Director, Clinical Oncology
Rachel Kobos, MD, Executive Medical Director, Clinical Oncology
Baolian Liu, MD, PhD, Medical Safety Officer
Bethany Paxson, Vice President Global Regulatory Affairs, NA Oncology
Lixia Pei, PhD, Clinical Statistics Leader
Jennifer Smit, MBA, Compound Development Team Leader
Sudhakar Rao, PhD, Head of Biostatistics, Oncology
Laura Rubin, PhD, Study Statistician
Aaron Schetter, PhD, Director, Global Regulatory Affairs Diagnostics
Weili Sun, MD, PhD, Sr. Medical Director
Yu-Nien (Tom) Sun, PhD, Senior Director, Clinical Pharmacology Oncology Group Leader
Rian Van Rampelbergh, MD, Director, Clinical Project Physician
Hilde Vanneste, MSc, Chemistry, Manufacturing, and Controls Regulatory Affairs
Raluca Verona, PhD, Translational Research Leader
Darshan Wariabharaj, BS, Global Regulatory Leader
Sen Zhuang, MD, Vice President, Clinical Research Development

1.0 BACKGROUND

Janssen Research & Development, LLC is investigating teclistamab in adult patients with multiple myeloma. Teclistamab is a humanized immunoglobulin G-4 (IgG-4) bispecific antibody directed against the B lymphocyte (B cell) maturation antigen (BCMA) and cluster of differentiation 3 (CD3) receptors with proline, alanine, alanine (PAA) (b) (4)

The purpose of this End-of-Phase 2 meeting is to obtain the Agency's review and agreement on key aspects of the design and elements of the proposed Phase 3 study 64007957MMY3001, entitled "*A Phase 3 Randomized Study Comparing Teclistamab SC in Combination with Daratumumab SC (Tec-Dara) versus Daratumumab SC, Pomalidomide, and Dexamethasone (DPd) or Daratumumab SC, Bortezomib, and Dexamethasone (DVd) in Participants with Relapsed or Refractory Multiple Myeloma*."

2.0 DISCUSSION

2.1. Clinical Pharmacology

Question 1: *Does the Agency agree that the proposed clinical pharmacology plan is sufficient to support the supplemental BLA submission for an indication extension?*

FDA Response to Question 1:
Yes, the proposed clinical pharmacology plan appears adequate to support filing of a sBLA submission. A final determination of the adequacy of the clinical pharmacology plan will be determined at the time of sBLA review.

Meeting Discussion: No discussion occurred.

Question 2: *In Study 64007957MMY3001, daratumumab immunogenicity samples will be tested for ADA against daratumumab, and positive ADA titers will be further tested by a neutralizing ADA assay. The Sponsor does not plan to collect immunogenicity samples for rHuPH20. Does the Agency agree that this approach is acceptable?*

FDA Response to Question 2:
Yes, your immunogenicity sampling and testing plan appears acceptable.

Meeting Discussion: No discussion occurred.

Question 3: *Does the Agency agree with the proposed dosing regimen including a fixed dose for step up and treatment doses, and switching from weekly dosing to biweekly in cycles 3 and beyond for teclistamab in clinical development studies, including Study 64007957MMY3001?*

FDA Response to Question 3:
No. You have not provided adequate justification for the change in dose and dosing regimen of teclistamab from a safety perspective. The simulated PK results in Figure 9 showed higher exposures ($C_{max,ss}$, $AUC_{tau,ss}$, $C_{trough,ss}$) for the proposed intermediate setup dose of 150 mg QW when compared to 1500 µg/kg QW, especially in patients with lower body weight. In addition, the proposed full dose of 300 mg Q2W in Cycles 3+ may result in $C_{max,ss}$ exposures that exceed the $C_{max,ss}$ exposures observed following 3000 µg/kg dose (Figure 10). Given that there was 60% serious TEAEs and 100% cytokine release syndrome (CRS) rates in the 1800 mg daratumumab + 3000 µg/kg teclistamab SC cohort in Study TRiMM-2, provide further justification of the proposed 300 mg dose Q2W specifically on the potential risk for increased serious toxicity and CRS with expected higher $C_{max,ss}$ and $AUC_{tau,ss}$. Provide the following information to support your dose selection:

a) Additional PK simulation for 3000 µg/kg QW, and compare the simulated steady-state exposures following 150 mg QW, 300 mg Q2W, 1500 µg/kg QW and 3000 µg/kg QW in different body weight categories.

b) Exposure-response analysis for the incidence rate of CRS based on Study TRiMM-2.
c) A summary table of infusion-related reaction (IRR)/cytokine release syndrome (CRS) events, by dose and by Grade, after each dose in the first cycle of Study TRiMM-2 for the two SC dosing regimens. Clarify specifically the timing (e.g., Week 1) of CRS event for each case.

Population PK modeling report and E-R analyses for safety and efficacy based on available clinical data

Meeting Discussion:
The Sponsor provided updated simulation results of PK profiles and steady-state exposures across different body weight (BW) categories as well as provided some updated clinical safety data for teclistamab (see attached document).

The Agency reiterated their concerns regarding the proposed flat dosing of teclistamab SC for the Phase 3 trial. The Agency stated that there is a potential for serious overlapping toxicities between daratumumab and teclistamab (i.e., neutropenia, thrombocytopenia, anemia) and limited number of patients have received daratumumab + 3000 µg/kg teclistamab SC (n=5) or the new flat dosing regimen. Additionally, the Agency also expressed concerns regarding the anticipated higher exposures in patients with low BW with the flat dosing. The Agency did not agree with the Sponsor's justification for the proposed flat dose for the Phase 3 clinical trial *(MMY3001)*.

The Agency recommended that the Sponsor evaluate two or more flat dose regimens of teclistamab SC in combination with daratumumab SC in the ongoing trial and obtain adequate safety and efficacy data in a sufficient number of patients across multiple teclistamab SC doses in combination with daratumumab SC prior to initiating the Phase 3 study. The Agency recommended that the Sponsor conduct integrated dose- and exposure-response analyses to justify the flat dose selection for the Phase 3 trial.

2.2. Clinical

Question 4: *Does the Agency agree that the proposed patient population as defined by the key inclusion and exclusion criteria for the Phase 3 study, 64007957MMY3001, is appropriate and adequately represents the target population?*

FDA Response to Question 4:
No, we do not agree. You should provide justification for the inclusion of patients who have received prior anti-CD38 mAb treatment given that data regarding re-treatment is limited. Your proposal to exclude patients whose disease is considered refractory to an anti-CD38 monoclonal antibody (mAb) per IMWG consensus guidelines is acceptable.

We also note that you propose to enroll patients who have received 1 to 3 prior lines of anti-MM therapy. The final indication will reflect the patient population enrolled on the study, considering the number of patients receiving specific lines of therapy prior to study entry, as well as efficacy results within the subgroups based on prior therapies.

We may provide additional comments upon review of the eligibility criteria in the full protocol.

Meeting Discussion:
The Agency reiterated their concerns regarding the inclusion of patients who have received prior anti CD38 antibody and stated that patients with prior anti-CD38 mAb therapy should account for only a limited percentage of the trial population.

Question 5: *Does the Agency agree that PFS is appropriate as the primary endpoint in the randomized, controlled Phase 3 Study 64007957MMY3001 and may support a full approval of teclistamab?*

FDA Response to Question 5:
It is premature to answer this question. In general, PFS has been used as an endpoint to support regular approval for multiple myeloma.

Meeting Discussion: No discussion occurred.

Question 6: *Does the Agency agree that either daratumumab SC + pomalidomide + dexamethasone (DPd) or daratumumab SC + bortezomib + dexamethasone (DVd), chosen at the investigator's discretion, would be an appropriate comparator for the randomized, controlled Phase 3 Study 64007957MMY3001?*

FDA Response to Question 6:
The use of a triplet-drug comparator arm is reasonable; however, we have the following comments:

1. We note that the use of the DPd regimen in combination with daratumumab-IV is indicated in patients who have received at least 2 prior therapies including a PI and lenalidomide, whereas you propose to enroll patients who have previously received 1 to 3 prior lines of therapy including a PI and lenalidomide. We recommend that you consider evaluating a more refractory population (e.g., patients who have received at least 2 prior lines of therapy). Alternatively, provide additional justification for the proposed population.
2. We have concerns with your proposal to use DVd as a comparator. Given that patients may receive bortezomib, and possibly daratumumab, as part of their initial therapy, DVd and DPd may have differing efficacy in patients with relapsed/refractory MM who have been previously treated with a PI and daratumumab. Provide additional justification for including DVd as an option for the control arm.

Meeting Discussion:
The Agency stated that the Sponsor's proposal to include patients with 1 to 3 prior lines of therapies may be reasonable, but reiterated that the final indication would reflect the actual patient population enrolled on the study, considering the numbers of patients enrolled receiving specific lines of therapy and the efficacy results within those subgroups.

The Agency stated that the selection of a control arm is at the Sponsor's discretion. However, the Agency reiterated the concerns with the use of DVd as a comparator and noted that there is limited data to inform expected outcomes with DVd among those who have received prior daratumumab and possibly prior bortezomib. Differences in the efficacy and safety of the DPd and DVd regimens within the control arm may affect interpretability of the study results.

3. In addition, in the DVd arm, daratumumab alone is continued every 28 days after Cycle 8, as opposed to the DPd arm, in which all three agents are continued every 21 days after Cycle 8 until disease progression. Differences in the efficacy and safety of the DVd and DPd regimens within the control arm may affect the interpretability of the study results.
4. Your effect size estimation is based on no more than 60% of patients in the control arm receiving either DVd or DPd. It is unclear how you will ensure that the 60% ratio is maintained during the study conduct.
   Given these considerations and to minimize heterogeneity, we recommend that you consider selecting a single treatment regimen for the control arm.

Question 7: *Does the Agency agree with the selection of the PRO instruments to capture the patient-reported disease symptoms, treatment symptoms, and treatment effects, as well as the proposed schedule of administration of the PRO instruments during treatment and follow-up phase of Study 64007957MMY3001?*

FDA Response to Question 7:
Patient-reported outcomes from this trial will be considered as exploratory, descriptive data as part of the totality of submitted information, taking into consideration any factors that may affect the interpretability and reliability of the findings. Whether this is adequate for labeling will be a review issue and will depend on whether the PRO data are complete, robust, and clinical meaningful.

We have concerns about use of the MySImQ for assessment of disease related symptoms. You have not provided rationale for why the MySImQ is an improvement over established measures, and there is considerable overlap between the MySImQ and the other measures that are proposed for use in Study 64007957MMY3001.

You have not identified which PRO-CTCAE items you have selected nor the assessment frequency, therefore we cannot provide feedback whether the assessment of patient-reported treatment related symptoms is adequate to inform tolerability. Inclusion in Project Patient Voice will depend on the rationale for symptomatic adverse events selected, the frequency of assessment, and data quality.

Meeting Discussion: No discussion occurred.

Question 8: *Does the Agency agree with the Sponsor's proposed MRD analysis plan to pool NGF data for subjects from China and NGS data from the other subjects in Study 64007957MMY3001?*

FDA Response to Question 8:
Your proposal to pool MRD data between the clonoSEQ and the Covance EuroFlow based tests is problematic as the two tests are based on different methodologies and measure different biomarkers. The Adaptive Biotechnology ClonoSEQ Assay is an FDA approved medical device that identifies and quantifies rearranged IgH, IgK, and IgL gene sequences and translocated BCL1/IgH and BCL2/IgH from DNA isolated from bone marrow by PCR and NGS. The EuroFlow based assay identifies surface antigens and cytoplasmic kappa/lambda on lymphocytes isolated from bone marrow by flow cytometry. You have not provided data to demonstrate that the two tests are equivalent and identify the same patient populations at the same MRD levels. Therefore, we strongly recommend that you report each set of results separately.

In addition, we recommend the use of first pass bone marrow to minimize hemodilution, and to collect enough sample to have at least 2 million cells[1,2].

Whether the MRD results are robust and support inclusion in the label will be a review issue.

Refer to the following FDA Guidance for further information regarding assessment of MRD in clinical trials: "*Hematologic Malignancies: Regulatory Considerations for Use of Minimal Residual Disease in Development of Drug and Biological Products for Treatment*" https://www.fda.gov/regulatory-information/search-fda-guidance-documents/hematologic-malignancies-regulatory-considerations-use-minimal-residual-disease-development-drug-and

References

1. Landgren, O., Gormley, N., Turley, D., Owen, R. G., Rawstron, A., Paiva, B., ... & Marti, G. E. (2014). Flow cytometry detection of minimal residual disease in multiple myeloma: Lessons learned at FDA-NCI roundtable symposium. *American journal of hematology*, *89*(12), 1159-1160.
2. Costa, L. J., Derman, B. A., Bal, S., Sidana, S., Chhabra, S., Silbermann, R., ... & Paiva, B. (2020). International harmonization in performing and reporting minimal residual disease assessment in multiple myeloma trials. *Leukemia*, 1-13

Meeting Discussion: No discussion occurred.

2.3 Biostatistics

Question 9: *Does the Agency agree that the statistical assumptions, effect size, and proposed analyses for the registration Study 64007957MMY3001, including the sample size calculation, are adequate?*

FDA Response to Question 9:

1. The median PFS in the DPd arm is 12.4 months in APOLLO Study and the median PFS in the DVd group is 16.7 months in the CASTOR Study. In addition, given that your assumption of median PFS is also partly based on the EQUULEUS Study, which enrolled patients with at least 2 prior lines of therapy, your assumption may represent an underestimate since you propose to enroll patients who may have only received 1 prior line of therapy. Clarify the basis for the assumption of a median PFS of 13 months for Arm B used in the sample size calculation and provide further justification for your assumption.
2. We discourage seeking approval based on an interim analysis of PFS at 60% information level. An interim PFS analysis may not provide an accurate or reproducible estimate of the treatment effect size due to inadequate follow-up, missing assessments, disagreements between investigator and independent assessments. As documented in the literature, interim analysis results tend to overestimate the treatment effect. In addition, study accrual should be completed before an interim analysis of PFS is performed. If you decide to keep the interim analysis plan, we strongly recommend conducting an interim analysis at a later time point.
3. Specify if disease status and response will be assessed by independent review committee (IRC) or investigator. Given this is an open-label study, we recommend using IRC assessment for primary and key secondary endpoints.

   Meeting Discussion:
   Question 9.3. The Sponsor provided justification for the use of the computerized algorithm in the Phase 3 trial (see attached document). The Agency stated that it does not consider the computerized algorithm to be validated as stated by the Sponsor. The Agency stated that additional discussion will be needed to determine the appropriate use of the computerized algorithm in future clinical trials. The Agency recommended that the Sponsor include an audit plan to evaluate PFS using an IRC in the proposed phase 3 study.

4. You stated that key secondary objectives are to compare ORR, CRR, MRD-negativity rate, PFS2 and OS. Clarify if any of these endpoints will be the key secondary endpoint(s) and formally tested. If yes, specify the hierarchical testing

order and plan for multiplicity adjustment. Provide power calculations and estimated data maturity at both interim and final analysis of PFS for the key secondary endpoints in the protocol.

5. You propose 4 OS analyses: at interim analysis of PFS, at final analysis of PFS, at 268 OS events (80% information) and at the earlier of 335 OS events or end of survival follow up. Because OS is an important endpoint for evaluation of efficacy and safety, we recommend strict control for familywise Type I error. Provide estimated data maturity and power calculations at each time point in the protocol.

Additional Clinical Pharmacology Comments

We have the following recommendations regarding your proposed Protocol Synopsis 64007957MMY3001:

1. Ensure that appropriate DDI restrictions for pomalidomide, bortezomib, and dexamethasone (consistent with their respective labeling) are in your full protocol.
2. Ensure that appropriate sampling and analysis plans for pharmacokinetics, pharmacodynamics, immunogenicity as well as ECG monitoring are in your full protocol.

3.0 Other Important Information

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be "designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling" (section 505B(a)(3)). Applications for drugs or biological products for which

orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

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

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

For the latest version of the molecular target list, please refer to FDA.gov.[2]

FDARA REQUIREMENTS

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

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

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[3]

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog.[4]

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format - Standardized Study Data.* This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, *Study Data Technical Conformance Guide*, as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page[5] that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

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

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in

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

the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

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

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

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

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

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

[6] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber

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

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

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

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

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

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

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled Study Data Standards Resources[7] and the CDER/CBER Position on Use of SI Units for Lab Tests website.[8]

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard

[7] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[8] https://www.fda.gov/media/109533/download

format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[9]

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

SECURE EMAIL COMMUNICATIONS

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

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

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

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

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

Specifications.[11]

PATIENT-FOCUSED ENDPOINTS

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

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

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

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

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

UNITED STATES PATIENT POPULATION

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug.

[11] https://www.fda.gov/media/85061/download

Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the guidance for industry *Collection of Race and Ethnicity Data in Clinical Trials* for more information.

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

ONCOLOGY PILOT PROJECTS

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

- RTOR[12]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- Assessment Aid[13]

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were none identified during the meeting.

6.0 ATTACHMENTS AND HANDOUTS

Janssen's response to the Agency's Meeting Preliminary Comment received via email on May 3, 2021, is appended to these minutes.

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

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